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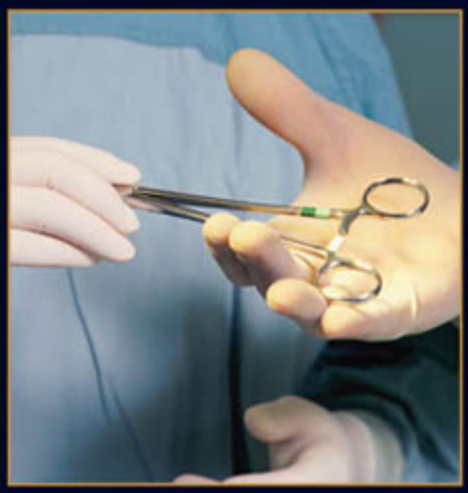

THIRD EDITION

Lawrence H. Cohn

CARDIAC SURGERY IN THE ADULT

Cardiac Surgery in the Adult

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Cardiac Surgery in the Adult

THIRD EDITION

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To the cardiac surgery team
at Brigham and Women's Hospital,
past, present, and future

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Stentless Aortic Valve Replacement: Porcine and Pericardial

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Myocardial Revascularization with Percutaneous Devices

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Myocardial Revascularization with Percutaneous Devices

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Transmyocardial Laser Revascularization and Extravascular Angiogenetic Techniques to Increase Myocardial Blood Flow

Foreword

Heart surgery, as we know it today did not exist when I graduated from medical school in 1944. During the last half of the twentieth century, however, cardiovascular surgery emerged as an important therapeutic discipline, and I am fortunate to have participated in the excitement of the specialty's formative years.

Probably the most stimulating advance in the treatment of congenital heart disease occurred in 1944, when Alfred Blalock and Helen Taussig introduced their technique of systemic-to-pulmonary artery shunting for tetralogy of Fallot. The success of the "blue-baby" operation was so dramatic and promising that cardiac surgery began to grow at a frenzied pace. The early operative procedures for congenital anomalies, including the blue-baby operation, proved that the circulatory system could be altered to improve blood flow and cardiopulmonary function.

With the introduction of temporary cardiopulmonary bypass, intracardiac procedures soon followed. Once open-heart operations became feasible, cardiac surgeons became active explorers of the cardiac chambers. Mechanical and biological prostheses were developed to repair and replace parts of the heart as well as the heart itself. In my opinion, the most exciting of those early years was cardiac transplantation. Although early transplant survival rates were often disappointing, the success of the procedure stimulated surgeons to tackle other difficult cardiovascular problems. Methods to treat coronary artery disease using coronary artery bypass grafts were developed. Surgeons began to use fabric grafts to repair aortic aneurysms, using specialized techniques to preserve cerebral and spinal cord function during surgery. Those investigators involved in device development brought mechanical circulatory support devices from the laboratories to clinical use. As the field of cardiac surgery expanded, so did that of diagnostic testing. Digital, computer-enhanced techniques provided more precise knowledge of cardiac anatomy and function, facilitating surgical treatment.

Even though many of the obstacles confronting surgeons in the past have been successfully overcome, numerous challenges remain, including the refinement of existing surgical techniques. *Cardiac Surgery in the Adult,* edited by L. Henry Edmunds, Jr., was first published in 1997 at a time when cardiovascular surgery was in a period of incredible growth. The original text was a major contribution to the treatment of adult patients, and it remains on my shelf as testament to how much our specialty has changed, yet remains the same. Dr. Larry Cohn became its co-editor for the second edition and is updating the text for the third time. The original chapters have been updated to reflect current thought and trends, and much more has been added. The new edition discusses refinements in less invasive techniques, such as minimally invasive valve repair and replacement, interventional therapy for atrial and ventricular arrhythmias, and use of the surgical robot. These techniques allow surgeons to attain the same therapeutic objectives with less trauma and discomfort for the patient. Also included are chapters that look to the future to describe, for example, the latest treatments for cardiac failure–a remaining challenge for scientists, cardiologists, and cardiac surgeons. Could the ultimate solution be a combination of therapies, for example, stem cells and mechanical cardiac assistance? Both are discussed within the pages of *Cardiac Surgery*.

Thus, this edition of *Cardiac Surgery in the Adult*, with its impressive list of contributors, provides an important progress report and treatment guide for our specialty. But there is an added bonus. Reading the text, which begins with an excellent history of the specialty, should stimulate its readers to think about how far cardiovascular surgery has come since its beginnings and about how each of us can contribute to insuring its continued, successful evolution.

Denton A. Cooley, MD
President and Surgeon-in-Chief
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Preface

The third edition of *Cardiac Surgery in the Adult* presents new knowledge and current experience by the world's leading cardiovascular surgeons and physicians for the treatment of adults with congenital, acquired, infectious, and traumatic diseases of the heart and great vessels. The third edition release date in 2007 celebrates the tenth anniversary of the publication of the first edition edited by L. Henry "Hank" Edmunds in 1997. In the short span of ten years there have been enormous changes in the cardiac surgical armamentarium, with new innovations in minimally invasive cardiac surgery, new percutaneous cardiovascular devices, and new approaches in the imaging, diagnosis, and treatment of all forms of cardiac disease. There have also been changes in cardiac surgical demographics, with increasing interest in percutaneous intervention, endovascular graft technology, and concomitant interest in the pursuit of cross-training for endovascular skills. For these reasons we have added six new chapters in areas related to these new technologies: percutaneous valve therapy, minimally invasive valve and coronary artery bypass surgery, updates in percutaneous treatment of coronary artery disease, and the latest data on stem cell technology. Every chapter has been updated with significant new information and a revamped bibliography. In addition to the updated chapters, this edition also includes 6 video-clip demonstrations of complex operative procedures, a totally new feature in this edition.

My goal as editor is to publish information as quickly as possible to maximize the educational aspect of new technology and developments in cardiac surgical expertise; thus, the turnaround time from receipt of chapters to publication was approximately 18 months.

As in any publication of this magnitude I am indebted to many people. First and foremost, thanks to Hank Edmunds for his inspiration and motivation to continue the good work he began, to the editorial staff at McGraw-Hill, especially Karen Edmonson, Marsha Loeb and Peter Boyle, who have been extremely helpful and supportive in every way possible to get this book to press, to Ann Maloney, my executive assistant in the Division of Cardiac Surgery at the Brigham and Women's Hospital, who was extremely helpful in organization and logistics, and a special thanks to Dr. Denton Cooley, cardiac surgical pioneer and innovator who has written a superb foreword to this third edition. To all the chapter authors, who are some of the busiest physicians in the world, profound thanks; their time and energy have produced a superb volume of surgical and perioperative expertise in a timely fashion.

On a sad note, our profound condolences to the University of Michigan transplant team who lost four members and two pilots on June 4, 2007. A member of this team, Martin Spoor coauthored Chapter 69 with Steven Bolling.

Finally and most importantly, thanks and love to my family, Roberta, Leslie, Jennifer, Stephen, Carly, and Rachel, who have again supported me during the production of another edition of *Cardiac Surgery in the Adult.*

Lawrence H. Cohn, MD
Boston, Massachusetts

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PART

I

Fundamentals

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CHAPTER 1

History of Cardiac Surgery

Larry W. Stephenson

The development of major surgery was retarded for centuries by a lack of knowledge and technology. Significantly, the general anesthetics, ether and chloroform, were not developed until the middle of the nineteenth century. These agents made major surgical operations possible, which created an interest in repairing wounds to the heart, leading some investigators in Europe to conduct studies in the animal laboratory on the repair of heart wounds. The first simple operations in humans for heart wounds soon were reported in the medical literature.

HEART WOUNDS

On July 10, 1893, Dr. Daniel Hale Williams (Fig. 1-1), a surgeon from Chicago, successfully operated on a 24-year-old man who had been stabbed in the heart during a fight. The patient was admitted to Chicago's Provident Hospital on July 9 at 7:30 P.M. The stab wound was slightly to the left of the sternum and dead center over the heart. Initially, the wound was thought to be superficial, but during the night, the patient experience persistent bleeding, pain, and pronounced symptoms of shock. Williams opened the patient's chest and tied off an artery and vein that had been injured inside the chest wall, likely causing the blood loss. Then he noticed a tear in the pericardium and a puncture wound to the heart, "about one-tenth of an inch in length."[1]

The wound in the right ventricle was not bleeding, so Williams did not place a stitch through the heart wound. He did, however, stitch closed the hole in the pericardium. The patient recovered. Williams reported this case 4 years later.[1] This operation, which is referred to frequently, is probably the first successful surgery involving a documented stab wound to the heart. At the time, Williams' surgery was considered bold and daring, and although he did not actually place a stitch through the wound in the heart, his treatment seems to have been appropriate. Under the circumstances, he most likely saved the patient's life.

A few years after Williams' case, a couple of other surgeons actually sutured heart wounds, but the patients did not survive. Dr. Ludwig Rehn (Fig. 1-2), a surgeon in Frankfurt, Germany, performed what many consider the first successful heart operation.[2] On September 7, 1896, a 22-year-old man was stabbed in the heart and collapsed. The police found him pale, covered with cold sweat, and extremely short of breath. His pulse was irregular, and his clothes were soaked with blood. By September 9, his condition was worsening, as shown in Dr. Rehn's case notes:

> Pulse weaker, increasing cardiac dullness on percussion, respiration 76, further deterioration during the day, diagnostic tap reveals dark blood. Patient appears moribund. Diagnosis: increasing hemothorax. I decided to operate entering the chest through the left fourth intercostal space, there is massive blood in the pleural cavity. The mammary artery is not injured. There is continuous bleeding from a hole in the pericardium. This opening is enlarged. The heart is exposed. Old blood and clots are emptied. There is a 1.5 cm gaping right ventricular wound. Bleeding is controlled with finger pressure. . . .
>
> I decided to suture the heart wound. I used a small intestinal needle and silk suture. The suture was tied in diastole. Bleeding diminished remarkably with the third suture, all bleeding was controlled. The pulse improved. The pleural cavity was irrigated. Pleura and pericardium were drained with iodoform gauze. The incision was approximated, heart rate and respiratory rate decreased and pulse improved postoperatively.
>
> . . . Today the patient is cured. He looks very good. His heart action is regular. I have not allowed him to work physically hard. This proves the feasibility of cardiac suture repair without a doubt! *I hope this will lead*

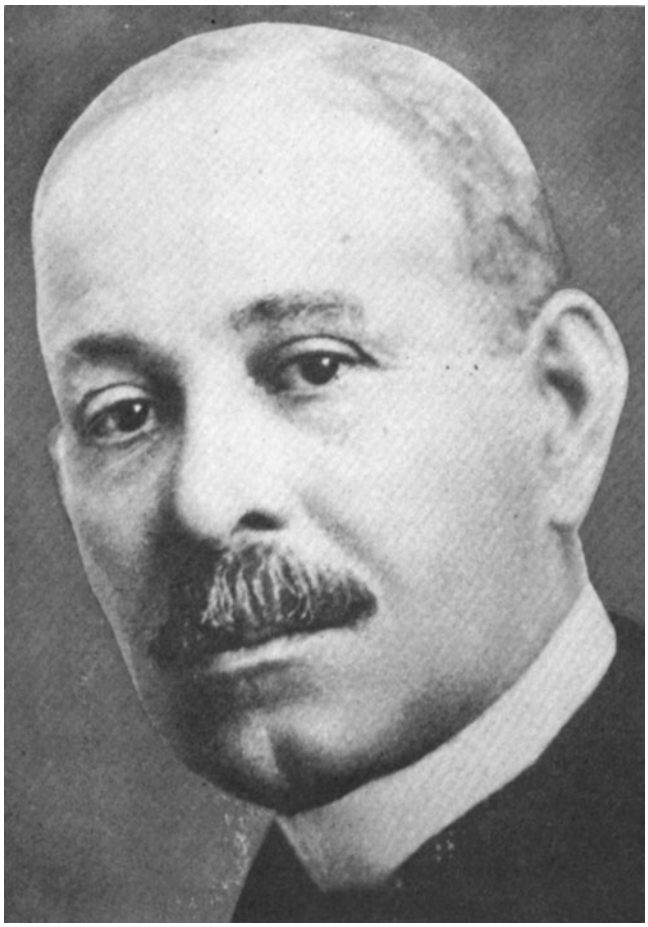

Figure 1-1. Dr. Daniel Hale Williams, a surgeon from Chicago who successfully operated on a patient with a wound to the chest involving the pericardium and the heart. *(Reproduced with permission from Organ CH Jr, Kosiba MM: The Century of the Black Surgeons: A USA Experience. Norman, OK, Transcript Press, 1987; p 312.)*

Figure 1-2. Dr. Ludwig Rehn, a surgeon from Frankfurt, Germany, who performed the first successful suture of a human heart wound. *(Reproduced with permission from Mead R: A History of Thoracic Surgery. Springfield, IL, Charles C Thomas, 1961; p 887.)*

> *to more investigation regarding surgery of the heart. This may save many lives.*

Ten years after Rehn's initial repair, he had accumulated a series of 124 cases with a mortality of only 60%, quite a feat at that time.[3]

Dr. Luther Hill was the first American to report the successful repair of a cardiac wound, in a 13-year-old boy who was a victim of multiple stab wounds.[4] When the first doctor arrived, the boy was in profound shock. The doctor remembered that Dr. Luther Hill had spoken on the subject of repair of cardiac wounds at a local medical society meeting in Montgomery, Alabama. With the consent of the boy's parents, Dr. Hill was sent for. He arrived sometime after midnight with six other physicians. One was his brother. The surgery took place on the patient's kitchen table in a run-down shack. Lighting was provided by two kerosene lamps borrowed from neighbors. One physician administered chloroform anesthesia. The boy was suffering from cardiac tamponade as a result of a stab wound to the left ventricle. The stab wound to the ventricle was repaired with two catgut sutures. Although the early postoperative course was stormy, the boy made a complete recovery. That patient, Henry Myrick, eventually moved to Chicago, where, in 1942, at the age of 53, he got into a heated argument and was stabbed in the heart again, very close to the original stab wound. This time, Henry was not as lucky and died from the wound.

Another milestone in cardiac surgery for trauma occurred during World War II when Dwight Harken, then a U.S. Army surgeon, removed 134 missiles from the mediastinum, including 55 from the pericardium and 13 from cardiac chambers, without a death.[5] It is hard to imagine this type of elective (and semielective) surgery taking place without sophisticated indwelling pulmonary artery catheters, blood banks, and electronic monitoring equipment. Rapid blood infusion consisted of pumping air into glass bottles of blood.

OPERATIVE MANAGEMENT OF PULMONARY EMBOLI

Friedrich Trendelenburg was the first to attempt a pulmonary embolectomy. In his classic paper that appeared in 1908,[6]

he stated that the clinical picture is characteristic: rapid collapse, frequently accompanied by substernal pain that often causes the patient to suddenly scream wildly. He reported on animal studies in 1907; following rapid exposure of the heart, he quickly incised the conus pulmonalis, inserted a cannula, advanced it into the pulmonary artery, and removed emboli using suction. Further experimentation revealed that a direct incision in the artery with removal of the emboli using forceps (those designed for removal of polyps) was much easier. He describes his first unsuccessful pulmonary embolectomy in a human. That operation became famous and is known as the *Trendelenburg operation.*

Trendelenburg subsequently reported two more cases, both fatal.[7] The first of those two patients died 15 hours postoperatively of cardiac failure; the second, 37 hours postoperatively. Kirschner, Trendelenburg's student, reported the first patient who recovered fully after undergoing pulmonary embolectomy in 1924.[8] In 1937, John Gibbon estimated that nine of 142 patients who had undergone the Trendelenburg procedure worldwide left the hospital alive.[9] These dismal results were a stimulus for Gibbon to start work on a pump oxygenator that could maintain the circulation during pulmonary embolectomy. Sharp was the first to perform pulmonary embolectomy using cardiopulmonary bypass, in 1962.[10]

SURGERY OF THE PERICARDIUM

Morgagni reported seven cases of constrictive pericarditis in 1761 and described the dangers of cardiac compression by stating that the heart was "so constricted and confined that it could not receive a proper quantity of blood to pass through it."[11] Pick presented a paper in 1896 in which he described the course of chronic pericarditis under the guise of cirrhosis of the liver.[12] Weill in 1895 and Delorme in 1898 proposed excision of the thickened fibrous pericardium in constrictive pericarditis.[13,14] Pericardial resection was introduced independently by Rehn[15] and Sauerbruch.[16] Since Rehn's report, there have been few advances in the surgical treatment of constrictive pericarditis. Some operations are now performed with the aid of cardiopulmonary bypass. In certain situations, radical pericardiectomy that removes most of the pericardium posterior to the phrenic nerves is done.

CATHETERIZATION OF THE RIGHT SIDE OF THE HEART

Although cardiac catheterization is not considered heart surgery, it is an invasive procedure, and some catheter procedures have replaced heart operations. Werner Forssmann is credited with the first heart catheterization. He performed the procedure on himself and reported it in *Klrinische Wochenschrift.*[17] In 1956, Forssmann shared the Nobel Prize in Physiology or Medicine with Andre F. Cournand and Dickenson W. Richards, Jr. His 1929 paper states, "One often hesitates to use intercardiac injections promptly, and often, time is wasted with other measures. This is why I kept looking for a different, safer access to the cardiac chambers: the catheterization of the right heart via the venous system." He goes on to say:

> I confirmed these facts by studies on a cadaver, catheterizing any vein near the elbow, the catheter would pass easily into the right ventricle. . . .
>
> After these successful preliminary studies, I attempted the first experiment on a living human, performing the experiment on myself. In a preliminary experiment, I had asked a colleague to puncture my right brachial vein with a large-bore needle. Then I advanced a well-lubricated No. 4 ureteral catheter through the cannula into the vein. . . . One week later I tried it again without assistance this time. I proceeded with vena puncture in my left antebrachial vein and introduced the catheter to its full length of 65 cm. . . .
>
> I checked the catheter position radiologically, after having climbed stairs from the OR to the radiology department. A nurse was holding a mirror in front of the x-ray screen for me to observe the catheter advance in position. The length of the catheter did not allow further advancement than into the right atrium. I paid particular attention to the possible effects on the cardiac conduction system, but I could not detect any effect.

In this report by Forssmann, a photograph of the x-ray taken of Forssmann with the catheter in his heart is presented. Forssmann, in that same report, goes on to present the first clinical application of the central venous catheter for a patient in shock with generalized peritonitis. Forssmann concludes his paper by stating, "I also want to mention that this method allows new options for metabolic studies and studies about cardiac physiology."

In a 1951 lecture, Forssmann discussed the tremendous resistance he faced during his initial experiments.[18] "Such methods are good for a circus, but not for a respected hospital" was the answer to his request to pursue physiologic studies using cardiac catheterization. His progressive ideas pushed him into the position of an outsider with ideas too crazy to give him a clinical position. Klein applied cardiac catheterization for cardiac output determinations using the Fick method a half year after Forssmann's first report.[19] In 1930, Forssmann described his experiments with catheter cardiac angiography.[20] Further use of this new methodology had to wait until Cournand's work in the 1940s.

HEART VALVE SURGERY BEFORE THE ERA OF CARDIOPULMONARY BYPASS

The first clinical attempt to open a stenotic valve was carried out by Theodore Tuffier on July 13, 1912.[21] Alexis Carrel was present at the operation.[22] Tuffier used his finger to reach the stenotic aortic valve. He was able to dilate the valve supposedly by pushing the invaginated aortic wall through the stenotic valve. The 26-year-old patient recovered and

returned to his home in Belgium. One must be skeptical as to what was accomplished. Russell Brock attempted to dilate calcified aortic valves in humans in the late 1940s by passing an instrument through the valve from the innominate or another artery.[23] His results were poor, and he abandoned the approach. During the next several years, Brock[24] and Bailey and colleagues[25] used different dilators and various approaches to dilate stenotic aortic valves in patients. Mortality for these procedures that often were done in conjunction with mitral commissurotomy was high.

Harvey Cushing attempted to create mitral stenoses in dogs but was not successful.[26] He encouraged Elliott Cutler, a young surgeon working with him, to continue. In collaboration with a Boston cardiologist, Samuel Levine, Cutler worked 2 years on a mitral valvulotomy procedure in the laboratory.[27] Their first patient was a desperately ill 12-year-old girl who was confined to bed for 6 months before operation. She underwent successful valvulotomy on May 20, 1923, using a teratomy knife. Unfortunately, most of Cutler's subsequent patients died because he created too much regurgitation with his valvulotome, and he soon gave up the operation. In 1925, Mr. Souttar, an English surgeon, successfully performed a mitral valvulotomy using his finger to fracture the commissures in a young girl who had been bedridden for 6 months.[28] His case was successful, but he did not do more operations.

In 1961, Dr. Dwight Harken wrote Henry Suttar a letter and asked him why he did not continue with his mitral valvuloplasty. He replied: "Thank you so much for your very kind letter. I did not repeat the operation because I could not get another case. Although my patient made an uninterrupted recovery, the physicians declared that it was all nonsense and in fact the operation was unjustifiable. In fact, it is of no use to be ahead of one's time. . . ."[29] Two decades passed before there was a resurgence of interest in valvular surgery.

In Charles Bailey's 1949 paper entitled, "The Surgical Treatment of Mitral Stenosis," he states: "After 1929 no more surgical attempts [on mitral stenosis] were made until 1945. Dr. Dwight Harken, Dr. Horace Smithy, and the author recently made operative attempts to improve mitral stenosis. Our clinical experience with the surgery of the mitral valves has been five cases to date. During the past 8 years, the author and his associates have performed operations on the mitral valves of 60 mongrel dogs."[30] Bailey goes on to state several conclusions from their animal research. He then describes his five patients, four of whom died and only one of whom lived a long life.

Bailey's home base, Hahnemann Hospital, refused to allow him to attempt any more mitral commissurotomies after two deaths. He became known as the "butcher of Hahnemann Hospital."[29] However, his cardiologist, Dr. Durant, continued to support him. On June 10, 1948, Bailey scheduled cases 4 and 5. The patient operated on at Philadelphia General Hospital in the morning died (case 4). The surgical team regrouped and rushed to Episcopal Hospital, where the second operation was started promptly before the bad morning news was known and before the hospital administration forbade the procedure. The surgery was completed, and 1 week later Bailey brought the patient by train 1000 miles to Chicago, where he presented the woman to the American College of Chest Physicians.[31] A few days after Bailey's success, on June 16 in Boston, Dr. Dwight Harken successfully performed his first valvulotomy for mitral stenosis. Three months later, Russell Brock in England did his first successful clinical case. He did not report this, however, until 1950, when he described success with six patients.[32]

The first successful pulmonary valvulotomy was performed by Thomas Holmes Sellers on December 4, 1947. A systemic pulmonary artery shunt was planned on the left side, but the attempt was abandoned in this patient with severe tetralogy of Fallot and advanced bilateral pulmonary tuberculosis.[33] The pericardium was opened. Dr. Sellers could feel the stenotic valve each time it pushed through the pulmonary trunk during ventricular systole. Sellers used a tenotomy knife, which he passed through the right ventricle to perform the valvulotomy. The patient made a good recovery and was markedly improved.

Russell Brock also attempted pulmonary valvulotomies in a number of patients during the same period using various techniques. Brock's first three patients died, but he eventually developed a successful procedure similar to that of Sellers.[34]

In the early 1950s, Charles Hufnagel, in Washington, DC, and J. M. Campbell, in Oklahoma, independently developed and implanted artificial valves in the descending aorta of dogs. The valves consisted of a mobile ball inside a Lucite case.[35,36] After presenting this first model of a mechanical prosthesis at the American College of Surgeons meeting in 1949, Hufnagel applied this concept clinically for the treatment of aortic valvular insufficiency. In his first clinical paper published in *Surgery* in 1954,[37] Hufnagel reported a series of 23 patients starting September 1952 who had this operation for aortic insufficiency. There were four deaths among the first 10 patients and two deaths among the next 13. Hufnagel's caged-ball valve, which used multiple-point fixation rings to secure the apparatus to the aorta, was the only surgical treatment for aortic valvular incompetence until the advent of cardiopulmonary bypass and the development of heart valves that could be sewn into the aortic annulus position.

The first surgical treatment of multiple valvular disease was by Trace and colleagues.[38] After closed mitral commissurotomy on May 2, 1952, in a 24-year-old woman, the surgeon noted that the right auricular appendage was gravely distended and pointed directly toward the left. Its pulsation was noticed, and it was quite blue-purple in color. The purse-string suture was being placed around the appendage in order to explore it when the patient's heart became arrhythmic. It was deemed advisable to terminate the surgical procedure at this point. The patient did poorly postoperatively. In the 2 weeks after the first operation, a tricuspid commissurotomy was performed. The patient made a good recovery and at 1-year follow-up remained improved.

Combined mitral and tricuspid commissurotomy was performed by Brofman in 1953.[39] Likoff and colleagues[40] reported a series of 74 patients who had combined aortic and mitral valve commissurotomies in 1955 with up to a 2-year follow-up. C. Walton Lillehei was the first to report repair of

multiple valvular lesions using cardiopulmonary bypass. On May 23, 1956, he successfully performed an open mitral commissurotomy and aortic valvuloplasty in a 52-year-old man with mitral stenosis and combined aortic stenosis and incompetence.[41] Borman performed a quadruple-valve commissurotomy in October 1973 in a 12-year-old Israeli girl with stenosis of all four valves.[42]

CONGENITAL CARDIAC SURGERY BEFORE THE HEART-LUNG MACHINE ERA

Congenital cardiac surgery began when John Streider at Massachusetts General Hospital first successfully interrupted a ductus on March 6, 1937. The patient was septic and died on the fourth postoperative day. At autopsy, vegetations filled the pulmonary artery down to the valve.[43] On August 16, 1938, Robert Gross, at Boston Children's Hospital, operated on a 7-year-old girl with dyspnea after moderate exercise.[44] Dr. Gross described the ductus as 7 to 8 mm in diameter and 5 to 6 mm in length. A no. 8 braided silk tie was placed around the ductus with an aneurysm needle, and the vessel was occluded temporarily for 3 minutes of observation. During this time, blood pressure rose from 100/35 to 125/90 mm Hg. According to Dr. Gross, "Since there was no embarrassment of the circulation, it was decided to ligate the ductus permanently." The patient made an uneventful recovery.

Modifications of the ductus operation soon followed. In 1944, Dr. Gross reported a technique for dividing the ductus successfully. The next major congenital lesion to be overcome was coarctation of the aorta. Dr. Clarence Crafoord, in Stockholm, Sweden, successfully resected a coarctation of the aorta in a 12-year-old boy on October 19, 1944.[45] Twelve days later he successfully resected the coarctation of a 27-year-old patient. Dr. Gross, in Boston, who had been working on a coarctation model in the laboratory, first operated on a 5-year-old boy with this condition on June 28, 1945.[46] After he excised the coarctation and rejoined the aorta, the patient's heart stopped suddenly. The patient died in the operating room. One week later, however, Dr. Gross operated on a second patient, a 12-year-old girl. This patient's operation was successful. Dr. Gross had been unaware of Dr. Crafoord's successful surgery several months previously, probably because of World War II.

In 1945, Dr. Gross reported the first successful case of surgical relief for tracheal obstruction from a vascular ring.[47] In the 5 years that followed Gross's first successful operation, he reported 40 more cases.[48]

The famous Blalock-Taussig operation also was first reported in 1945. The first patient was a 15-month-old girl with a clinical diagnosis of tetralogy of Fallot with a severe pulmonary stenosis.[49] At age 8 months, the baby had her first cyanotic spell, which occurred after eating. Dr. Helen Taussig, the cardiologist, followed the child for 3 months, and during that time, cyanosis increased, and the child failed to gain weight. She was readmitted and during the next 6 weeks refused most of her feedings, lost weight, and weighed only 4 kg at operation. The operation was performed by Dr. Alfred Blalock at Johns Hopkins University on November 29, 1944. The left subclavian artery was anastomosed to the left pulmonary artery in an end-to-side fashion. The postoperative course was described as stormy; the patient was discharged 2 months postoperatively. Two additional successful cases were done within 3 months of that first patient.

Thus, within a 7-year period, three congenital cardiovascular defects, patent ductus arteriosus, coarctation of the aorta, and vascular ring, were attacked surgically and treated successfully. However, the introduction of the Blalock-Taussig shunt probably was the most powerful stimulus to the development of cardiac surgery because this operation palliated a complex intracardiac lesion and focused attention on the pathophysiology of cardiac disease.

Anomalous coronary artery in which the left coronary artery communicates with the pulmonary artery was the next surgical conquest. The surgery was performed on July 22, 1946, and was reported by Gunnar Biorck and Clarence Crafoord.[50] The patient was a 15-year-old boy who was unable to do gymnastics or play football because of dyspnea shortly after beginning exercise. At operation, the ductus arteriosus was found to be a cord, but there was a thrill over the pericardium. When the pericardium was opened, the anomalous coronary artery was identified and doubly ligated. The patient made an uneventful recovery.

Muller[51] reported successful surgical treatment of transposition of the pulmonary veins in 1951, but the operation addressed a partial form of the anomaly. Later in the 1950s, Gott, Varco, Lillehei, and Cooley reported successful operative variations for anomalous pulmonary veins.

Another of Gross's pioneering surgical procedures was surgical closure of an aortopulmonary window in a 4-year-old girl who had dyspnea with slight exertion and a cardiac murmur that was consistent with a patent ductus.[52] The operation was carried out on May 22, 1948. After dissecting the posterior aspect of the great vessels, a similar plane was developed between the vessels above the shunt, and an aneurysm needle was passed completely around the shunt.[52] A piece of linen tape 1 cm wide was drawn around the vessel so that it encircled the shunt. At this point, arterial blood began to escape from the depths of the wound so that it was evident that the thin posterior wall of the shunt had been torn slightly. Believing that the one hope of controlling the situation might be to quickly tie the tape that had been placed previously, this was now rapidly and tightly drawn down. Fortunately, all bleeding stopped. All the thrill in the pulmonary artery disappeared. The chest was closed, and the patient made a satisfactory convalescence.

Gross stated: "After successfully treating the child, it is felt that the fortunate outcome had been attended by a high degree of luck and that simple ligature might lead to disaster if attempted in all cases of aortopulmonary artery fenestration. As far as is known, this is the first instance of successful surgical correction of this congenital abnormality." Others were soon to follow using various techniques to interrupt the aortopulmonary window. Cooley and colleagues[53] were the first to report on the use of cardiopulmonary bypass to

repair this defect and converted a difficult and hazardous procedure into a relatively straightforward one.

The cavopulmonary anastomosis has had several variations by different designers. Carlon and colleagues[54] are credited with first proposing the anastomosis in 1951. Glenn[55] reported the first successful clinical application in the United States in 1958 for what has been termed the *Glenn shunt.* Similar work was done in Russia during the 1950s by several investigators. On January 3, 1957, Galankin,[56] a Russian surgeon, performed a cavopulmonary anastomosis in a 16-year-old patient with tetralogy of Fallot. The patient made a good recovery with significant improvement in exercise tolerance and cyanosis.

THE DEVELOPMENT OF CARDIOPULMONARY BYPASS

The development of the heart-lung machine made repair of intracardiac lesions possible. To bypass the heart, one needs a basic understanding of the physiology of the circulation, a method of preventing the blood from clotting, a mechanism to pump blood, and finally, a method to ventilate the blood.[57]

Before 1900, physiologists already were interested in isolated organ perfusion and therefore needed a method to oxygenate blood. Von Frey and Gruber[58] described a blood pump in 1885 in which gas exchange occurred as blood flowed into a thin film over the inner surface of a slanted rotating cylinder. In 1895, Jacobi passed blood through an excised animal's lung that was aerated by artificial respiration.[59] In 1926, Professors S. S. Brukhonenko and S. Terebinsky[60] in Russia designed a machine that used an excised lung from a donor animal as an oxygenator and two mechanically actuated blood pumps. Their machine was used initially to perfuse isolated organs but later was used to perfuse entire animals.

Alexis Carrel, a Nobel laureate, and Charles Lindbergh, the famous aviator, developed a device that successfully perfused the thyroid gland of a cat for 18 days, beginning April 5, 1935.[61] A picture of the two investigators with their perfusion apparatus appeared on the June 13, 1938, cover of *Time* magazine.[62] At the end of that time, much of the tissue was partially preserved, and pieces grew epithelial cells in tissue culture. According to Edwards and Edwards,[61] many other organs were perfused over the next few years by Carrel and Lindbergh. Hearts were kept beating for several days. Although perfused organs survived surprisingly well, all showed progressive degenerative changes in a few days. Edema fluid filled tissue spaces, arteries became calcified, and connective tissue cells outgrew the more specialized cells.

One of the key requirements of the heart-lung machine was anticoagulation. Heparin was discovered by a medical student, Jay McLean, working in the laboratory of Dr. William Howell, a physiologist at Johns Hopkins.[63] In 1915, Howell gave McLean the task of studying a crude brain extract known to be a powerful thromboplastin. Howell believed that the thromboplastic activity was caused by cephalin contained in the extract. McLean's job was to fractionate the extract and purify the cephalin. McLean also studied extracts prepared from heart and liver. McLean discovered that a substance in the extract was retarding coagulation. McLean wrote[64]:

> I went one morning to the door of Dr. Howell's office, and standing there (he was seated at his desk), I said, Dr. Howell, I have discovered antithrombin. He smiled and said, "Antithrombin is a protein and you are working with phospholipids. Are you sure that salt is not contaminating your substance?". . . I told him that I was not sure of that, but it was a powerful anticoagulant. He was most skeptical, so I had the diener, John Schweinhand, bleed a cat. Into a small beaker full of its blood, I stirred all of the proven batch of heparphosphotides, and placed this on Dr. Howell's laboratory table and asked him to tell when it clotted. It never did.

McLean described his finding in February 1916 at a medical society meeting in Philadelphia and later reported it in an article entitled, "The Thromboplastic Action of Cephalin."[64,65] Howell and Holt[66] reported their work on heparin in 1918. In the 1920s, animal experiments confirmed that heparin was an effective anticoagulant.[67]

John Gibbon contributed more to the success of the development of the heart-lung machine than anyone else. His interest began as a young doctor one night in 1930 in Boston "during an all-night vigil by the side of a patient with a massive embolus. . . ."[68] Unfortunately, the patient did not survive, but Gibbon thought that if he had a machine that could take over for the heart and lungs while the blood clot was removed surgically from the pulmonary arteries, the patient could have been saved.

Gibbon's work on the heart-lung machine took place over the next 20 years in laboratories at Massachusetts General Hospital, the University of Pennsylvania, and Thomas Jefferson University. In 1937, Gibbon reported the first successful demonstration that life could be maintained by an artificial heart and lung and that the native heart and lungs could resume function. Unfortunately, only three animals recovered adequate cardiorespiratory function after total pulmonary artery occlusion and bypass, and even they died a few hours later.[69] Gibbon's work was interrupted by World War II; afterward, he resumed his work at Thomas Jefferson Medical College in Philadelphia. Meanwhile, other groups, including Clarence Crafoord in Stockholm, Sweden, J. Jongbloed at the University of Utrecht in Holland, Clarence Dennis at the University of Minnesota, Mario Digliotti and coworkers at the University of Turino in Italy, and Forest Dodrill at Harper Hospital in Detroit, also worked on a heart-lung machine.[70]

Clarence Dennis's first clinical attempt at open-heart surgery was in a 5-year-old girl with end-stage cardiac disease.[71] Her heart was already massive, and her only hope was surgical closure of an atrial septal defect. At operation on April 6, 1951, her circulation was supported by a heart-lung machine that Dennis and his coworkers had developed.[72] The atrial septal defect (ASD) was very difficult to close. Although the heart-lung machine functioned well, the patient did not survive, probably because of a combination of blood loss and surgically induced tricuspid stenosis (Table 1-1).

Table 1–1.

Twilight Zone: Clinical Status of Open-Heart Surgery, 1951–1955

1951	*April 6*: Clarence Dennis at the University of Minnesota used a heart-lung machine to repair an ostium primum or AV canal defect in a 5-year-old girl. Patient could not be weaned from cardiopulmonary bypass.[72]
	May 31: Dennis attempted to close an atrial septal defect using heart-lung machine in a 2-year-old girl who died intraoperatively of a massive air embolus. [72] Although unsuccessful, these were probably the first two surgeries where a heart-lung machine was used while the surgeon attempted to correct a human heart defect.
1951	*August 7:* Achille Mario Digliotti, professor of surgery at the University of Turino, Italy, used a heart-lung machine of his own design to partially support the circulation (flow at 1 L/min for 20 minutes) while he resected a large mediastinal tumor compressing the right side of the heart.[74] The cannulation was through the right axillary vein and artery. The patient survived. This was the first successful clinical use of a heart-lung machine, but the machine was not used as an adjunct to heart surgery.
1952	*February* (1952 or 1953 John Gibbon; see February 1953)
	March: John Gibbon used his heart-lung machine for right-sided heart bypass only while surgeon Frank Allbritten at Pennsylvania Hospital, Philadelphia, operated to remove a large clot or myxomatous tumor suspected by angiography.[75] The right atrium and tricuspid valve were very dilated. No tumor or clot was found. The patient died of heart failure in the operating room shortly after discontinuing right-sided heart bypass.
1952	*July 3*: Dodrill used the Dodrill-GMR pump to bypass the left side of the heart while he repaired a mitral valve.[76] The patient survived. This was the first successful use of a mechanical pump for total substitution of the left ventricle in a human being.
	September 2: John Lewis, at the University of Minnesota, closed an atrial septal defect under direct vision in a 5-year-old girl. The patient survived. This was the first successful clinical heart surgery procedure using total-body hypothermia. A mechanical pump and oxygenator were not used. Others, including Dodrill, soon followed, using total-body hypothermia techniques to close atrial septal defects (ASDs) and perform pulmonary valvulotomies. By 1954, Lewis reported on 11 ASD closures using hypothermia with two hospital deaths.[77] He also operated on two patients with ventricular septal defect (VSD) in early 1954 using this technique. Both resulted in intraoperative deaths.
	October 21: Dodrill performed pulmonary valvulotomy under direct vision using Dodrill-GMR pump to bypass the right atrium, ventricle, and main pulmonary artery.[78] The patient survived.
	Although Dr. William Mustard in Toronto would describe a type of "corrective" surgical procedure for transposition of the great arteries (TGA) in 1964, which, in fact, for many years, would become the most popular form of surgical correction of TGA, his early results with this lesion were not good. In 1952 he used a mechanical pump coupled to the lung that had just been removed from a monkey to oxygenate the blood in seven children while attempts were made to correct their TGA defect.[79] There were no survivors.
1953	*February* (or 1952): Gibbon at Jefferson Hospital in Philadelphia operated to close an ASD in a very sick 15-month-old girl weighing 11 lb.[80] He used his heart-lung machine. No ASD was found. The patient died intraoperatively. Autopsy showed a large patent ductus arteriosus.
	May 6: Gibbon used his heart-lung machine to close an ASD in an 18-year-old woman with symptoms of heart failure.[80] The patient survived the operation and became the first patient to undergo successful open-heart surgery using a heart-lung machine.
	July: Gibbon used the heart-lung machine on two 5-year-old girls to close atrial septal defects.[80] Cardiac arrest occurred after the chest was opened in the first patient. The heart and great vessels were cannulated during CPR. Cardiopulmonary bypass was commenced. The patient died intraoperatively. The second patient was found at operation to have AV canal and a small patent ductus arteriosus. The AV canal was partially closed. She died intraoperatively. Gibbon was extremely distressed and declared a moratorium on further cardiac surgery at Jefferson Medical School until more work could be done to solve problems related to heart-lung bypass. This was probably the last heart operation he performed using the heart-lung machine.

(continued)

Table 1–1.

Twilight Zone: Clinical Status of Open-Heart Surgery, 1951–1955 (*continued*)

1954	*March 26*: C. Walton Lillehei and associates at the University of Minnesota closed a VSD under direct vision in a 15-month-old boy using a technique to support the circulation that they called *controlled cross-circulation*. An adult (usually a parent) with the same blood type was used more or less as the heart-lung machine. The adult's femoral artery and vein were connected with tubing and a pump to the patient's circulation. The adult's heart and lungs oxygenated and supported the circulation while the child's heart defect was corrected. The first patient died 11 days postoperatively from pneumonia, but six of their next seven patients survived.[81] Between March 1954 and the end of 1955, 45 heart operations were performed by Lillehei on children using this technique before it was phased out. Although controlled cross-circulation was a short-lived technique, it was an important stepping stone in the development of open-heart surgery. *July*: Clarence Crafoord and associates at the Karolinska Institute in Stockholm, Sweden, used a heart-lung machine of their own design coupled with total-body hypothermia (patient was initially submerged in an ice-water bath) to remove a large atrial myxoma in a 40-year-old woman.[82] She survived.
1955	*March 22*: John Kirklin at the Mayo Clinic used a heart-lung machine similar to Gibbon's, but with modifications his team had worked out over 2 years in the research laboratory, to successfully close a VSD in a 5-year-old patient. By May of 1955, they had operated on eight children with various types of VSDs, and four were hospital survivors. This was the first successful series of patients (i.e., more than one) to undergo heart surgery using a heart-lung machine.[83] Although their mortality was 50% Kirklin continued on in 1955, his open-heart mortality rates dropped.[84] *May 13*: Lillehei and colleagues began using a heart-lung machine of their own design to correct intracardiac defects. By May of 1956, their series included 80 patients.[81] Initially they used their heart-lung machine for lower-risk patients and used controlled cross-circulation, with which they were more familiar, for the higher-risk patients. Starting in March 1955, they also tried other techniques in patients to oxygenate blood during heart surgery, such as canine lung, but with generally poor results.[81] Dodrill had been performing heart operations with the GM heart pump since 1952 and used the patient's own lungs to oxygenate the blood. Early in the year 1955, he attempted repairs of VSDs in two patients using the heart pump, but with a mechanical oxygenator of his team's design. The first patient died day one after surgery when the endotracheal tube became obstructed, which was undetected for several minutes. The other patient had a common ventricle (no ventricular septum), which Dodrill attempted to repair. This patient died on the second postoperative day. On December 1, he closed a VSD in a 3-year-old girl using his heart-lung machine. She survived. In May 1956 at the annual meeting of the American Association for Thoracic Surgery, he reported on six children with VSDs, including one with tetralogy of Fallot, who had undergone open-heart surgery using his heart-lung machine. All survived at least 48 hours postoperatively.[85] Three were hospital survivors, including the patient with tetralogy of Fallot. *June 30*: Clarence Dennis, who had moved from the University of Minnesota to the State University of New York, successfully closed an ASD in a girl using a heart-lung machine of his own design.[86] Mustard successfully repaired a VSD and dilated the pulmonary valve in a 9-month-old with a diagnosis of tetralogy of Fallot using a mechanical pump and a monkey lung to oxygenate the blood.[87] He did not give the date in 1955, but the patient is listed as Human Case 7. Unfortunately, in the same report, cases 1–6 and 8–15 operated on between 1951 and the end of 1955 with various congenital heart defects did not survive the surgery using the pump and monkey lung, nor did another seven children in 1952, all with TGA (see timeline for 1952) using the same bypass technique.

Note: This list is not all-inclusive but likely includes most of the historically significant clinical open-heart events where a blood pump was used to support the circulation during this period. (A twilight zone can mean an ill-defined area between two distinct conditions, such as the area between darkness and light.)

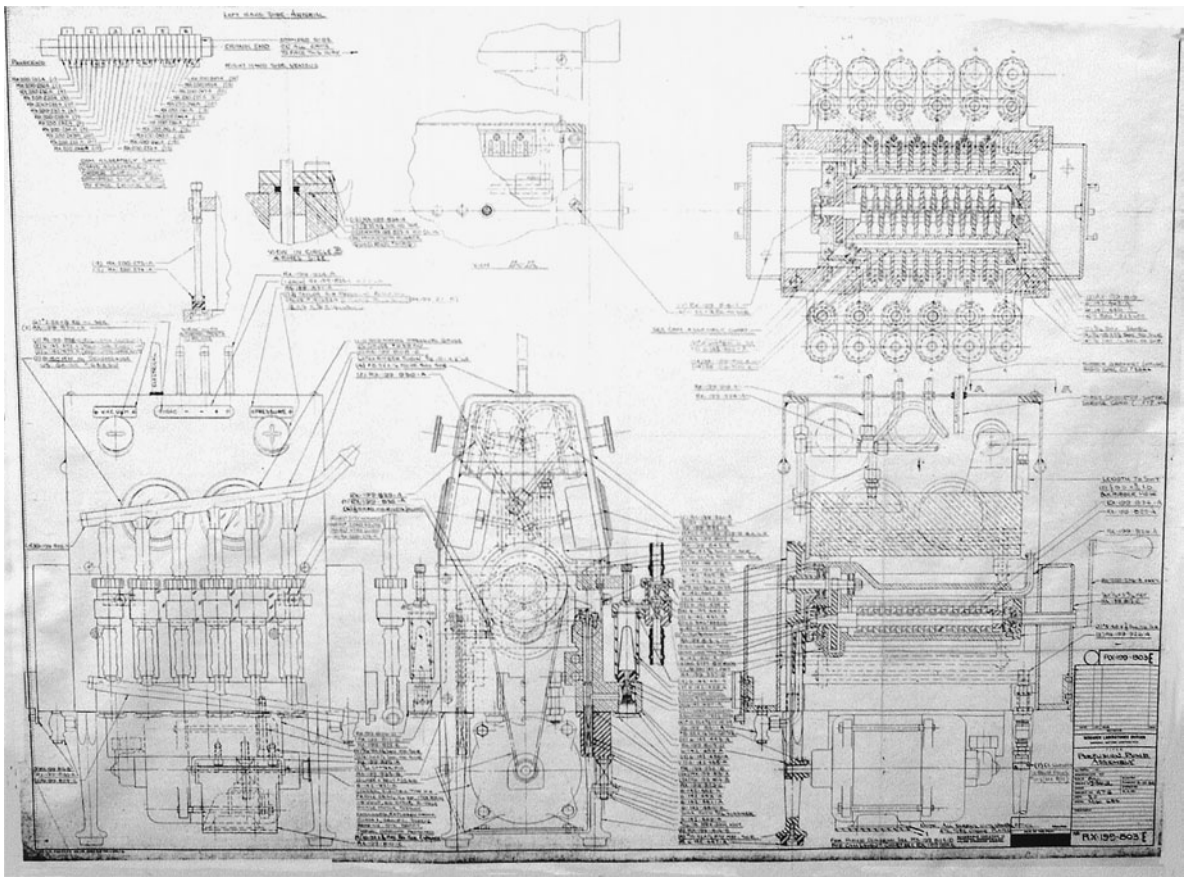

Figure 1-3. Blueprints by General Motors engineers of the Dodrill-GMR mechanical heart. *(Courtesy of Calvin Hughes, M.D.)*

In August of 1951, Mario Digliotti used his heart-lung machine to partially support the circulation of a 49-year-old patient during resection of a large mediastinal tumor.[74] During the operation, the patient developed hypotension and cyanosis. He therefore was placed on partial bypass at 1 L/min for 20 minutes. Although the mass was resected successfully, the Italian machine was never used for open-heart surgery in humans.

Forest Dodrill and colleagues used the mechanical blood pump they developed with General Motors on a 41-year-old man[76] (Fig. 1-3). The machine was used to substitute for the left ventricle for 50 minutes while a surgical procedure was carried out to repair the mitral valve; the patient's own lungs were used to oxygenate the blood. This, the first clinically successful total left-sided heart bypass in a human, was performed on July 3, 1952, and followed from Dodrill's experimental work with a mechanical pump for univentricular, biventricular, or cardiopulmonary bypass. Although Dodrill and colleagues had used their pump with an oxygenator for total heart bypass in animals,[88] they felt that left-sided heart bypass was the most practical method for their first clinical case.

Later, on October 21, 1952, Dodrill and colleagues used their machine in a 16-year-old boy with congenital pulmonary stenosis to perform a pulmonary valvuloplasty under direct vision; this was the first successful right-sided heart bypass.[78] Between July 1952 and December 1954, Dodrill performed approximately 13 clinical operations on the heart and thoracic aorta using the Dodrill–General Motors machine, with at least five hospital survivors.[89] While he used this machine with an oxygenator in the animal laboratory, he did not start using an oxygenator with the Dodrill–General Motors mechanical heart clinically until early 1955.

Hypothermia was another method to stop the heart and allow it to be opened. In 1950, Bigelow and colleagues[90] reported on 20 dogs that had been cooled to 20°C with 15 minutes of circulatory arrest; 11 animals also had a cardiotomy. Only six animals survived after rewarming. Bigelow and colleagues continued to study hypothermia.[91–93]

John Lewis closed an atrial septal defect in a 5-year-old girl on September 2, 1952, using a hypothermic technique[77]:

> She was wrapped in refrigerated blankets until after a period of 2 hours and 10 minutes her rectal temperature had fallen to 28°C. At this point the chest was entered through the bed of the right fifth rib. The cardiac inflow was occluded for a total of 5½ minutes and during this time the septal defect was closed under direct vision. The patient was rewarmed by placing her in hot water kept at 45°C, and after 35 minutes her

> rectal temperature had risen to 36°C, at which time she was removed from the bath. Recovery from the anesthesia was prompt and her subsequent postoperative convalescence was uneventful.

Shortly thereafter, Swan and colleagues[94] reported successful results in 13 clinical cases using a similar technique. But the use of systemic hypothermia for open intracardiac surgery was relatively short-lived; after the heart-lung machine was introduced clinically, it appeared that deep hypothermia was obsolete. However, during the 1960s, it became apparent that operative results in infants under 1 year of age using cardiopulmonary bypass were poor. In 1967, Hikasa and colleagues,[95] from Kyoto, Japan, published an article that reintroduced profound hypothermia for cardiac surgery in infants and used the heart-lung machine for rewarming. Their technique involved surface cooling to 20°C, cardiac surgery during circulatory arrest for 15 to 75 minutes, and rewarming with cardiopulmonary bypass. At the same time, other groups reported using profound hypothermia with circulatory arrest in infants with the heart-lung machine for cooling and rewarming.[96–99] Results were much improved, and subsequently, the technique also was applied for resection of aortic arch aneurysms.

After World War II, John Gibbon resumed his research. He eventually met Thomas Watson, chairman of the board of the International Business Machines (IBM) Corporation. Watson was fascinated by Gibbon's research and promised help. Soon afterward, six IBM engineers arrived and built a machine that was similar to Gibbon's earlier machine, which contained a rotating vertical cylinder oxygenator and a modified DeBakey rotary pump. Gibbon used this new machine successfully for intercardiac surgery on small dogs and had several long-term survivors, but the blood oxygenator was too small for human patients. Eventually, the team developed a larger oxygenator that the IBM engineers incorporated into a new machine.[100]

In 1949, Gibbon's early mortality in dogs was 80%, but it improved gradually.[101] Gibbon operated on a 15-month-old girl with severe congestive heart failure (CHF). The preoperative diagnosis was ASD, but at operation, none was found. She died, and a huge patent ductus was found at autopsy. The next patient was an 18-year-old girl with CHF owing to an ASD. This defect was closed successfully on May 6, 1953, with the Gibbon-IBM heart-lung machine. The patient recovered, and several months later the defect was confirmed closed at cardiac catheterization.[101] Unfortunately, Gibbon's next two patients did not survive intracardiac procedures when the heart-lung machine was used. These failures distressed Dr. Gibbon, who declared a 1-year moratorium for the heart-lung machine until more work could be done to solve the problems causing the deaths.

During this period, C. Walton Lillehei and colleagues at the University of Minnesota studied a technique called *controlled cross-circulation.*[57] With this technique, the circulation of one dog was used temporarily to support that of a second dog while the second dog's heart was stopped temporarily and opened. After a simulated repair in the second dog, the animals were disconnected and allowed to recover.

Lillehei and colleagues[102] used their technique at the University of Minnesota to correct a VSD in a 12-month-old infant on March 26, 1954 (Fig. 1-4). Either a parent or a close relative with the same blood type was connected to the child's circulation. In Lillehei's first clinical case, it was the child's father. The patient had been hospitalized 10 months for uncontrollable heart failure and pneumonitis. The patient made an uneventful recovery until death on the eleventh postoperative day from a rapidly progressing tracheal bronchitis. At autopsy, the VSD was closed, and the respiratory infection was confirmed as the cause of death. Two weeks later, the second and third patients had VSDs closed by the same technique 3 days apart. Both remained long-term survivors with normal hemodynamics confirmed by cardiac catheterization.

In 1955, Lillehei and colleagues[103] published a report of 32 patients that included repairs of VSDs, tetralogy of Fallot, and atrioventricularis communis defects. By May of 1955, the blood pump used for systemic cross-circulation by Lillehei and colleagues was coupled with a bubble oxygenator developed by Drs. DeWall and Lillehei, and cross-circulation was soon abandoned after use in 45 patients during 1954 and 1955. Although its clinical use was short-lived, cross-circulation was an important steppingstone in the development of cardiac surgery.[57]

Meanwhile, at the Mayo Clinic only 90 miles away, John W. Kirklin and colleagues launched their open-heart program on March 5, 1955.[83] They used a heart-lung machine based on the Gibbon-IBM machine but with their own modifications. Dr. Kirklin wrote[104]:

> We investigated and visited the groups working intensively with the mechanical pump oxygenators. We visited Dr. Gibbon in his laboratories in Philadelphia, and Dr. Forest Dodrill in Detroit, among others. The Gibbon pump oxygenator had been developed and made by the International Business Machine Corporation and looked quite a bit like a computer. Dr. Dodrill's heart-lung machine had been developed and built for him by General Motors and it looked a great deal like a car engine. We came home, reflected and decided to try to persuade the Mayo Clinic to let us build a pump oxygenator similar to the Gibbon machine, but somewhat different. We already had had about a year's experience in the animal laboratory with David Donald using a simple pump and bubble oxygenator when we set about very early in 1953, the laborious task of building a Mayo-Gibbon pump oxygenator and continuing the laboratory research.
>
> Most people were very discouraged with the laboratory progress. The American Heart Association and the National Institutes of Health had stopped funding any projects for the study of heart-lung machines, because

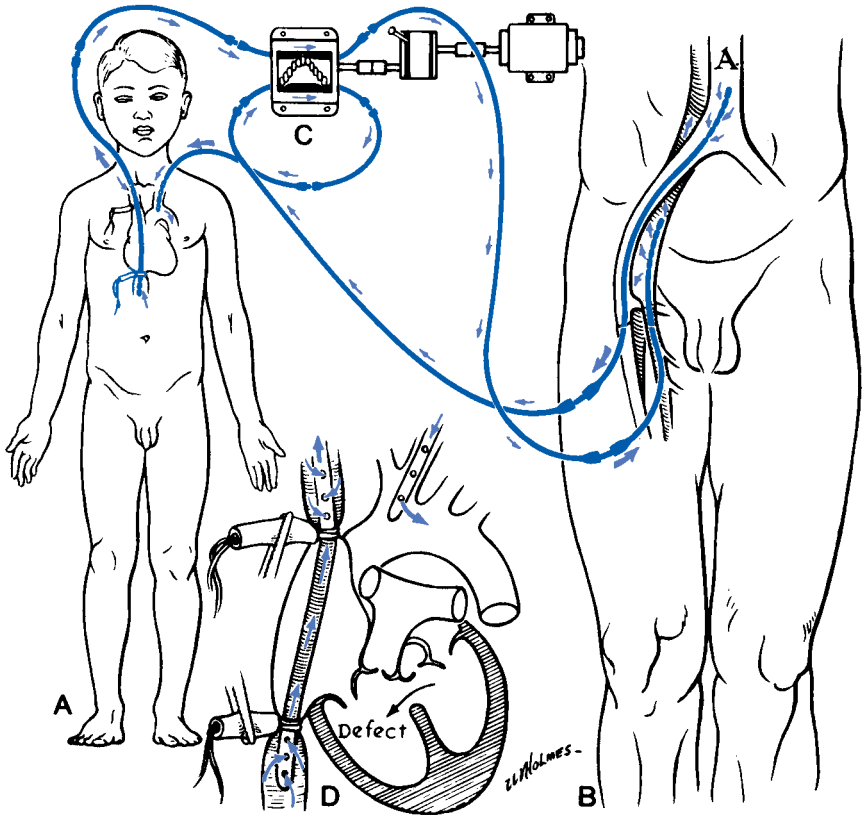

Figure 1-4. A depiction of the method of direct-vision intracardiac surgery using extracorporeal circulation by means of controlled cross-circulation. (*A*) The patient, showing sites of arterial and venous cannulations. (*B*) The donor, showing sites of arterial and venous (superficial femoral and great saphenous) cannulations. (*C*) The Sigma motor pump controlling precisely the reciprocal exchange of blood between the patient and donor. (*D*) Close-up of the patient's heart, showing the vena caval catheter positioned to draw venous blood from both the superior and inferior venae cavae during the cardiac bypass interval. The arterial blood from the donor circulated to the patient's body through the catheter that was inserted into the left subclavian artery. *(Reproduced with permission from Lillehei CW, Cohen M, Warden HE, et al: The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. Surg Gynecol Obstet 1955; 101:446. Copyright American College of Surgeons.)*

it was felt that the problem was physiologically insurmountable. David Donald and I undertook a series of laboratory experiments lasting about 1½ years during which time the engineering shops at the Mayo Clinic constructed a pump oxygenator based on the Gibbon model.[105]

. . . The electrifying day came in the spring of 1954 when the newspapers carried an account of Walt Lillehei's successful open-heart operation on a small child. Of course, I was terribly envious and yet I was terribly admiring at the same moment. That admiration increased exponentially when a short time later, a few of my colleagues and I visited Minneapolis and observed one of what was now a series of successful open-heart operations with control cross-circulation.

. . . In the winters of 1954 and 1955 we had nine surviving dogs out of 10 cardiopulmonary bypass runs. With my wonderful colleague and pediatric cardiologist, Jim DuShane, we had earlier selected eight patients for intracardiac repair. Two had to be put off because two babies with very serious congenital heart disease came along and we decided to fit them into the schedule. We had determined to do all eight patients even if the first seven died. All of this was planned with the knowledge and approval of the governance of the Mayo Clinic. Our plan was then to return to the laboratory and spend the next 6 to 12 months solving the problems that had arisen in the first planned clinical trial of a pump oxygenator. . . . We did our first open-heart operation on a Tuesday in March 1955.

Kirklin continued[104]:

> Four of our first eight patients survived, but the press of the clinical work prevented our ever being able to return to the laboratory with the force that we had planned. By now, Walt Lillehei and I were on parallel, but intertwined paths.

By the end of 1956, many university groups around the world had launched into open-heart programs. Currently, it is estimated that more than 1 million cardiac operations are performed each year worldwide with use of the heart-lung machine. In most cases, the operative mortality is quite low, approaching 1% for some operations. Little thought is given to the courageous pioneers in the 1950s whose monumental contributions made all this possible.

Extracorporeal Life Support

Extracorporeal life support is an extension of cardiopulmonary bypass. Cardiopulmonary bypass was limited initially to no more than 6 hours. The development of membrane oxygenators in the 1960s permitted longer support. Donald Hill and colleagues in 1972 treated a 24-year-old man who developed shock lung after blunt trauma.[106] The patient was supported for 75 hours using a heart-lung machine with a membrane oxygenator, cannulated via the femoral vein and artery. The patient was weaned and

recovered. Hill's second patient was supported for 5 days and recovered. This led to a randomized trial supported by the National Institutes of Health to determine the efficacy of this therapy for adults with respiratory failure. The study was conducted from 1972 to 1975 and showed no significant difference in survival between patients managed by extracorporeal life support (9.5%) and those who received conventional ventilatory therapy (8.3%).[107] Because of these results, most U.S. centers abandoned efforts to support adult patients using extracorporeal life support (ECLS), also known as *extracorporeal membrane oxygenation* (ECMO).

One participant in the adult trial decided to study neonates. The usual causes of neonatal respiratory failure have in common abnormal postnatal blood shunts known as *persistent fetal circulation* (PFC).[108–111] This is a temporary, reversible phenomenon. In 1976, Bartlett and colleagues at the University of Michigan were the first to treat a neonate successfully using ECLS. Since that time, two prospective studies have shown the efficacy of ECLS for the management of neonatal respiratory failure.[112,113] More than 8000 neonatal patients have been treated using ECLS worldwide with a survival rate of 82% (ELSO registry data).

MYOCARDIAL PROTECTION

Alexis Carrel reported in 1914 that "The arresting of the circulation of the heart has already been performed in many ways by various experimenters. We ourselves have used all known methods of stopping the circulation through the heart."[114] He also referred to work of Borrel and others, who had experimented with different forms of myocardial preservation. Carrel goes on to state: "When the above-mentioned precautions were taken, it was possible to clamp the pedicle of the heart (aorta and pulmonary artery) for 2½ or 3 minutes without any subsequent trouble. As soon as the clamp was removed, the heart resumed its pulsations, and after a very short time, the pulsations were again normal."

Melrose and colleagues[115] in 1955 presented the first experimental study describing induced arrest by potassium-based cardioplegia. Blood cardioplegia was used "to preserve myocardial energy stores at the onset of cardiac ischemia." These authors state, "Ringer drew attention in 1883 to the effect of the differentiations on the heartbeat and Hooker in 1929 suggested that potassium inhibition induced by an excess of potassium chloride could be used to stop the heart when its beat was disorganized by ventricular fibrillation." Melrose goes on to state that ". . . they have succeeded in evolving a reliable method of stopping and restarting the heart at both normal and reduced body temperatures." Unfortunately, the Melrose solution proved to be toxic to the myocardium, and as a result, cardioplegia was not used widely for several years.

Gay and Ebert[116] and Tyres and colleagues[117] demonstrated that cardioplegia with lower potassium concentrations was safe. Studies by Kirsch and colleagues,[118] Bretschneider and colleagues,[119] and Hearse and colleagues[120] demonstrated the effectiveness of cardioplegia with other constituents and renewed interest in this technique. Gay and Ebert in 1973 demonstrated a significant reduction in myocardial oxygen consumption during potassium-induced arrest when compared with that of the fibrillating heart.[116] They also showed that the problems in the use of the Melrose solution in the early days of cardiac surgery probably were due to its hyperosmolar properties and perhaps not to the high potassium concentration.

In a 1978 publication by Follette and colleagues,[121] the technique of blood cardioplegia was reintroduced. In experimental and clinical studies, these authors demonstrated that hypothermic, intermittent blood cardioplegia provided better myocardial protection than normothermic, continuous coronary perfusion and/or hypothermic, intermittent blood perfusion without cardioplegia solution. The composition of the best cardioplegia solution remains controversial, and new formulations, methods of delivery, and recommended temperatures continue to evolve.

EVOLUTION OF CONGENITAL CARDIAC SURGERY DURING THE ERA OF CARDIOPULMONARY BYPASS

With the advent of cardiopulmonary bypass using either the cross-circulation technique of Lillehei and colleagues or the version of the mechanical heart-lung machine used by Kirklin and colleagues, the two groups led the way for intracardiac repairs for many of the commonly occurring congenital heart defects. Because of the morbidity associated with the heart-lung machine, palliative operations also were developed to improve circulatory physiology without directly addressing the anatomic pathology. These palliative operations included the Blalock-Taussig subclavian–pulmonary arterial shunt[49] with modifications by Potts and colleagues[122] and Waterston and colleagues,[123] the Blalock-Hanlon operation to create an atrial septal defect,[124] and the Galankin-Glenn superior vena cava–right pulmonary arterial shunt.[55]

As the safety of cardiopulmonary bypass improved steadily, surgeons addressed more and more complex abnormalities of the heart in younger and younger patients. Some of the milestones in the development of operations to correct congenital heart defects using cardiopulmonary bypass appear in Table 1-2. These advances coincided with simultaneous advances in the surgery of adult heart disease, and the same surgeons operated on both children and adults. In the 1970s, although depending on the same technology and basic knowledge, pediatric and adult cardiac surgery began to separate. Operations for more complex congenital lesions in younger and younger patients required new techniques, and likewise, the advent of direct operations for ischemic heart disease required new technology and methods to deal with damaged ventricles and acute complications of

Table 1–2.

First Successful Intracardiac Repairs Using Cardiopulmonary Bypass or Cross-Circulation

Lesion	Year	Reference	Comment
Atrial septal defect	1953	Gibbon[101]	May 6, 1953
Ventricular septal defect	1953	Lillehei[102]	Cross-circulation
Complete atrioventricular canal	1954	Lillehei[103]	Cross-circulation
Tetralogy of Fallot	1954	Lillehei[102]	Cross-circulation
Tetralogy of Fallot	1955	Kirklin[83]	Cardiopulmonary bypass (CPB)
Total anomalous pulmonary veins	1956	Kirklin[125]	
Congenital aneurysm sinus of Valsalva	1956	Kirklin[126]	
Congenital aortic stenosis	1956	Kirklin[127]	First direct visual correction
Aortopulmonary window	1957	Cooley[128]	First closure using CPB
Double outlet right ventricle	1957	Kirklin[129]	Extemporarily devised correction
Corrected transposition great arteries	1957	Lillehei[130]	
Transposition of great arteries: atrial switch	1959	Senning[131]	Physiologic total correction
Coronary arteriovenous fistula	1959	Swan[132]	
Ebstein's anomaly	1964	Hardy[133]	Repair of atrialized tricuspid valve
Tetralogy with pulmonary atresia	1966	Ross[134]	Used aortic allograft
Truncus arteriosus	1967	McGoon[135]	Used aortic allograft
Tricuspid atresia	1968	Fontan[136]	Physiologic correction
Single ventricle	1970	Horiuchi[137]	
Subaortic tunnel stenosis	1975	Konno[138]	
Transposition of great arteries: arterial switch	1975	Jatene[139]	Anatomic correction
Hypoplastic left heart syndrome	1983	Norwood[140]	Two-stage operation
Pediatric heart transplantation	1985	Bailey[141]	

ischemia. With the exception of sporadic patients who reached adult life with uncorrected or partially corrected congenital heart defects, cardiac surgery in the adult represents the surgery of acquired heart disease. Nevertheless, a close connection continues because the advances in one subspecialty usually are applicable in the other, and this kinship and interdependence probably will remain for the foreseeable future.

VALVULAR SURGERY: CARDIOPULMONARY BYPASS ERA

Cardiac valve repair or replacement under direct vision awaited the development of the heart-lung machine. The first successful aortic valve replacement (AVR) in the subcoronary position was performed by Dr. Dwight Harken and associates.[142] A caged-ball valve was used. Many of the techniques described in Harken's 1960 report are similar to those used today for AVR.

That same year, Starr and Edwards[143] successfully replaced the mitral valve using a caged-ball valve of their own design. Starr later wrote[144]:

> In 1958, Lowell Edwards presented himself in my office with a proposal to develop an implantable artificial heart. I learned that he was a retired engineer with considerable financial resources. His visit was fortuitous, because just about that time, I had become interested in valvular prostheses. . . . Edwards agreed to begin the project by working on one valve at a time. . . . The obvious direction then was toward the ball valve prosthesis. I drew out for Edwards the general configuration of the Hufnagel valve. He then drew out for me how he thought that particular valve could be adapted for intracardiac use using an open cage. The first animal to have this implant survived for more than a year, but all other subsequent animals died of thrombosis. . . . The big breakthrough came at the end of 1958 when we developed the Silastic shield for the ball valve, which allowed an 80% long-term survival. . . . A Silastic shield over the area where thrombus formed on the valve would give us a chance to have long-term survivors.

The first successful operation was done in September 1960 on a woman in her mid-twenties. The patient was in pulmonary edema on oxygen prior to operation and in excellent condition and wide awake on the evening of the day of the surgery.

By 1967, nearly 2000 Starr-Edwards valves had been implanted, and the caged-ball-valve prosthesis was established as the standard against which all other mechanical prostheses would be compared.

In 1964, Starr and colleagues reported 13 patients who had undergone multiple valve replacement.[145] One patient had the aortic, mitral, and tricuspid valves replaced on February 21, 1963. Cartwright and colleagues, however, on November 1, 1961, were the first to replace both the aortic and mitral valves successfully with ball-valve prostheses that they had developed.[146] Knott-Craig and colleagues,[147] from the Mayo Clinic, successfully replaced all four heart valves in a patient with carcinoid involvement.

In 1961, Andrew Morrow and Edwin Brockenbrough[148] reported a treatment for idiopathic hypertrophic subaortic stenosis by resecting a portion of the thickened ventricular septum. They referred to this as *subaortic ventriculomyotomy.* They gave credit to William Cleland and H. H. Bentall in London, who had encountered this condition unexpectedly at operation and resected a small portion of the ventricular mass. The patient improved, but no postoperative hemodynamic studies had been reported. The subaortic ventriculomyotomy became the standard surgical treatment for this cardiac anomaly, although in some patients systolic anterior motion (SAM) of the anterior leaflet of the mitral valve necessitates mitral valve replacement with a low-profile mechanical valve.

An aortic homograft valve was used clinically for the first time by Heimbecker and colleagues in Toronto for replacement of the mitral valve in one patient and an aortic valve in another.[149] Survival was short, 1 day in one patient and 1 month in the other. Donald Ross reported on the first successful aortic valve placement with an aortic valve homograft.[150] He used a technique of subcoronary implantation developed in the laboratory by Carlos Duran and Alfred Gunning in Oxford.

The technique of AVR with a pulmonary autograft described initially by Ross in 1967 is advocated by some groups for younger patients who require AVR.[151,152] An aortic or pulmonary valve homograft is used to replace the pulmonary valve that has been transferred to the aortic position.

Other autogenous materials that have been used to manufacture valve prostheses include pericardium, fasciae latae, and dura mater. In the 1960s, Binet and colleagues[153] began to develop and test tissue valves. In 1964, Duran and Gunning in England replaced an aortic valve in a patient using a xenograft porcine aortic valve. Early results with formaldehyde-fixed xenografts were good,[153] but in a few years these valves began to fail because of tissue degeneration and calcification.[154] Carpentier and colleagues revitalized interest in xenograft valves by fixating porcine valves with gluteraldehyde. Carpentier also mounted his valves on a stent to produce a bioprosthesis. Carpentier-Edwards porcine valves and Hancock and Angell-Shiley bioprostheses became popular and were implanted in large numbers of patients.[155,156]

Carpentier later wrote: "In 1964 as a young resident in thoracic surgery, I was asked by J. P. Binet, chief of the service, to collect homograft valves from cadavers. Studies of the anatomy of the valves in various animal species showed that the valves from the pigs were the closest to those of humans."[157] Carpentier described the first successful xenograft valve replacement in 1965, followed by 12 other operations,

but within 5 years, all the heterograft valves had to be replaced. Carpentier goes on to state:

> The use of formalin proposed by O'Brien did not significantly improve the results. I began mounting the valves on a stent in 1966, which permitted the use of heterograft valves in the mitral position. It became obvious that the future of tissue valves would depend upon the development of methods of preparation capable of preventing inflammatory cell reaction, and penetration into the tissue. My background in chemistry is obviously insufficient. I decided to abandon surgery for two days a week to follow the teaching program in chemistry at the Faculty of Sciences and prepare a Ph.D. It is certainly not easy to become a student in chemistry when you are 35 and an associate professor of surgery.
>
> I began to investigate numerous cross-linking inducing factors and found that gluteraldehyde was able to almost eliminate inflammatory reaction. . . .

With the development of cardiopulmonary bypass, valves could be approached under direct vision, and for the first time, mitral insufficiency could be attacked by reparative techniques. Techniques for mitral annuloplasty were described by Wooler and colleagues,[158] Reed and colleagues,[159] and Kay and colleagues.[160] The next step forward was development of annuloplasty rings by Carpentier and Duran. In the 1970s, few groups were involved in valve repairs. Slowly, techniques evolved, were tested clinically, and were followed over the years. Carpentier led the field by establishing the importance of careful analysis of valve pathology, described in detail several techniques of valve repair, and reported good results after early and late follow-up, especially with concomitant use of annuloplasty rings.[161]

From 1966 to 1968, a small epidemic of infective endocarditis in Detroit among heroin addicts broke out. Patients were dying of intractable gram-negative tricuspid valve endocarditis, often owing to *Pseudomonas aeruginosa.* Long-term antibiotic administration in combination with tricuspid valve replacement was 100% fatal. These results prompted Agustin Arbulu and colleagues to remove the tricuspid valve entirely without replacing it in seven dogs in 1969. Six survived with satisfactory hemodynamic performance. Starting in 1970, Arbulu operated on 55 patients; in 53, the tricuspid valve was removed without replacing it.[162,163] At 25 years, the actuarial survival is 61%.

CORONARY ARTERY SURGERY

Alexis Carrel remarked in 1910[164]:

> I attempted to perform an indirect anastomosis between descending aorta and the left coronary artery. It was for many reasons a difficult operation. On account of the continuous motion of the heart, it was not easy to dissect and to suture the artery. In one case, I implanted one end of a long carotid artery, preserved in a cold storage, on the descending aorta. The other end was passed through the pericardium and anastomosed to the pericardial end of the coronary near the pulmonary artery. Unfortunately, the operation was too slow. Three minutes after the interruption of the circulation fibrillary contractions appeared, but the anastomosis took five minutes. By massage of the heart, the dog was kept alive, but he died less than two hours afterwards. It shows that the anastomosis must be done in less than three minutes.

In 1930, Claude Beck, a Cleveland surgeon, developed methods to indirectly revascularize the hearts of animals by attaching adjacent tissues in hopes of forming collateral blood flow to ischemic myocardium.[165] These tissues included pericardium, pericardial fat, pectoralis muscle, and omentum. Postmortem examination showed that anastomotic vessels did develop between these tissues and the myocardium. In the first patient, Beck roughened the outer surface of the heart with a burr and then sutured a pedicle graft of pectoralis muscle to the left ventricular wall.[166] The patient made an uneventful recovery and was angina-free after the operation. Beck subsequently performed this operation with modifications on 16 patients.[167]

Arthur Vineberg, a Canadian surgeon, in 1946 reported implanting the internal mammary artery through a tunnel in the myocardium, but he did not actually anastomose the left internal mammary artery to a coronary artery.[168] He showed in animals that communications developed between the internal mammary and the coronary arteries. Contemporary surgeons, however, remained skeptical, but Mason Sones validated Vineberg's concept by demonstrating communications between the graft in the myocardium and the coronary system by angiography in two patients operated on 5 and 6 years earlier. In the middle 1960s, the Vineberg operation with many variations was performed at many institutions in the United States and Canada.[169]

At the same time, other surgeons performed coronary arterial endarterectomies. Longmire and colleagues[170] were the first to report endarterectomy of the coronary arteries for the treatment of ischemic coronary disease. In 1958, they reported five patients, with four hospital survivors. Although the operation was used subsequently by other groups, mortality was high, and the procedure was abandoned as an isolated operation.

Selective coronary angiography was developed by Sones and Shirey at the Cleveland Clinic and reported in their 1962 classic paper entitled, "Cine Coronary Arteriography."[171] They used a catheter to inject contrast material directly into the coronary artery ostia. This technique gave a major impetus to direct revascularization of obstructed coronary arteries.

From 1960 to 1967, several sporadic instances of coronary grafting were reported. All were isolated cases and, for uncertain reasons, were not reproduced. None had an impact on the development of coronary surgery. Dr. Robert H. Goetz performed what appears to be the first

clearly documented coronary artery bypass operation in a human, which was successful. The surgery took place at Van Etten Hospital in New York City on May 2, 1960.[172] He operated on a 38-year-old man who was severely symptomatic and used a nonsuture technique to connect the right internal mammary artery to a right coronary artery. It took him 17 seconds to join the two arteries using a hollow metal tube. The right internal mammary artery–coronary artery connection was confirmed patent by angiography performed on the 14th postoperative day. The patient remained asymptomatic for about a year and then developed recurrent angina and died of a myocardial infarction on June 23, 1961. Goetz was severely criticized by his medical and surgical colleagues for this procedure, although he had performed it successfully many times in the animal laboratory. He never attempted another coronary bypass operation in a human.

Another example involved a case of autogenous saphenous vein bypass grafting performed on November 23, 1964, in a 42-year-old man who was scheduled to have endarterectomy of his left coronary artery.[173] Since the lesion involved the entire bifurcation, endarterectomy with venous patch graft was abandoned as too hazardous. The anterior descending coronary artery was softer distal to the bifurcation. An autogenous saphenous vein graft therefore was placed from the aorta to the left anterior descending. This was probably the first clinical case of successful coronary artery bypass surgery using saphenous vein. The authors, Garrett, Dennis, and DeBakey, however, did not report this case until 1973. The patient was alive at that time, and angiograms showed the vein graft to be patent.

Shumaker[174] credits Longmire with the first internal mammary–coronary artery anastomosis. "It was almost surely Longmire, long-time chairman at UCLA, and his associate, Jack Cannon, who first performed an anastomosis between the internal mammary artery and a coronary branch, probably in early 1958." Longmire wrote:

> At that time we were doing the coronary thromboendarterectomy procedure, we also, I think, performed a couple of the earliest internal mammary–coronary anastomoses. . . . We were forced into it when the coronary artery we were endarterectomizing disintegrated, and in desperation we anastomosed the internal mammary artery to the distal end of the right coronary artery—and later decided it was a good operation.

The reference that Shumaker gives for this quotation from Longmire is a personal communication to Shumaker in 1990, which is 32 years after the fact!

As early as 1952, Vladimir Demikhov, the renowned Soviet surgeon, was anastomosing the internal mammary artery to the left coronary artery in dogs.[175] In 1967, at the height of the Cold War, a Soviet surgeon from Leningrad, V. I. Kolessov, reported his experience with mammary artery–coronary artery anastomoses for the treatment of angina pectoris in six patients in an American surgical journal.[176] The first patient in that series was done in 1964. Operations were performed through a left thoracotomy without extracorporeal circulation or preoperative coronary angiography. The following year, Green and colleagues[177] and Bailey and Hirose[178] separately published reports in which the internal mammary artery was used for coronary artery bypass in patients. Bailey and Hirose carried out the anastomosis on the beating heart and advocated using loupes for magnification. Green and colleagues advocated using cardiopulmonary bypass, fibrillating the vented heart, cross-clamping the aorta, and washing all blood from the coronary system while performing the anastomosis.

Rene Favalaro from the Cleveland Clinic used saphenous vein for bypassing coronary obstructions.[179] Favalaro's 1968 article focused on 15 patients, who were part of a larger series of 180 patients who had undergone the Vineberg procedure. In these 15 patients with occlusion of the proximal right coronary artery, an interpositional graft of saphenous vein also was placed between the ascending aorta and the right coronary artery distal to the blockage. The right coronary artery was divided, and the vein graft was anastomosed end to end. Favalaro states that this procedure was done because of the unfavorable results with pericardial patch reconstruction of the coronary artery. In an addendum to that paper, 55 patients were added, 52 for segmental occlusion of the right coronary and 3 others for circumflex disease.

The contributions by Favalaro, Kolessov, Green and colleagues, and Bailey and Hirose all were important, but arguably, the official start of coronary bypass surgery as we know it today happened in 1969 when W. Dudley Johnson and coworkers from Milwaukee reported their series of 301 patients who had undergone various operations for coronary artery disease (CAD) since February of 1967.[180] In that report, the authors presented their results with direct coronary artery surgery during a 19-month period. They state:

> After two initial and successful patch grafts, the vein bypass technique has been used exclusively. Early results were so encouraging that last summer the vein graft technique was expanded and used to all major branches. Vein grafts to the left side of the arteries run from the aorta over the pulmonary artery and down to the appropriate coronary vessel. Right-sided grafts run along the atrioventricular groove and also attach directly to the aorta. There is almost no limit of potential (coronary) arteries to use. Veins can be sutured to the distal anterior descending or even to posterior marginal branches. Double vein grafts are now used in over 40% of patients and can be used to any combination of arteries.

Johnson goes on to say:

> Our experience indicates that five factors are important to direct surgery. One: Do not limit grafts to proximal portions of large arteries. . . . Two: Do not work with diseased arteries. Vein grafts can be made as long as necessary and should be inserted into distal normal

> arteries. Three: Always do end-to-side anastomoses. . . . Four: Always work on a dry, quiet field. Consistently successful fine vessel anastomoses cannot be done on a moving, bloody target. . . . Five: Do not allow the hematocrit to fall below 35.

In discussing Dr. Johnson's presentation, Dr. Frank Spencer commented: "I would like to congratulate Dr. Johnson very heartily. We may have heard a milestone in cardiac surgery today. Because for years, pathologists, cardiologists, and many surgeons have repeatedly stated that the pattern of coronary artery disease is so extensive that direct anastomosis can be done in only 5 to 7% of patients. If the exciting data by Dr. Johnson remain valid and the grafts remain patent over a long period of time, a total revision of thinking will be required regarding the feasibility of direct arterial surgery for CAD." [180]

The direct anastomosis between the internal mammary artery and the coronary artery was not as popular initially as the vein-graft technique; however, owing to the persistence of Drs. Green, Loop, Grondin, and others, internal mammary artery grafts eventually became the conduit of choice when their superior long-term patency became known.[181]

Denton Cooley and colleagues made two important contributions to the surgery for ischemic heart disease.[182] In 1956, with the use of cardiopulmonary bypass, they were the first to repair a ruptured interventricular septum following acute myocardial infarction. The patient did well initially but died of complications 6 weeks after operation. Cooley and colleagues also were the first to report the resection of a left ventricular aneurysm with the use of cardiopulmonary bypass.[183]

Beck[184] in 1944 was the first to excise a left ventricular aneurysm successfully, and Bailey and colleagues[185] in 1951 had five survivors of six attempts with a clamp and oversew technique.

ARRHYTHMIC SURGERY

Sealy and colleagues at Duke University developed the first successful surgical treatment for cardiac arrhythmias.[186,187] A 32-year-old fisherman was referred for symptomatic episodes of atrial tachycardia that caused CHF. On May 2, 1968, after epicardial mapping, a 5- to 6-cm cut was made extending from the base of the right atrial appendage to the right border of the right atrium during cardiopulmonary bypass. The incision transsected the conduction pathway between the atrium and ventricle. Subsequent epicardial mapping indicated eradication of the pathway. Six weeks after the operation, heart size had decreased and lung fields had cleared. The patient eventually returned to work.

A year earlier, Dr. Dwight McGoon at the Mayo Clinic closed an ASD in a patient who also had the Wolf-Parkinson-White (WPW) syndrome.[187] At operation, Dr. Birchell mapped the epicardium of the heart and localized the accessory pathway to the right atrioventricular groove. Lidocaine was injected into the site, and the delta wave disappeared immediately. Unfortunately, conduction across the pathway reappeared a few hours later. This probably was the first attempt to treat the WPW syndrome surgically. As a result of knowledge gained from the surgical treatment for WPW syndrome, over 95% of all refractory clinical cases now are treated successfully by nonsurgical means.[187]

Ross and colleagues[188] in Sydney, Australia, and Cox and colleagues[189] in St. Louis, Missouri, used cryosurgical treatment of atrial ventricular node reentry tachycardia. Subsequently, James L. Cox, after years of laboratory research, developed the Maze operation for atrial fibrillation.[190] Cox spent years in the animal laboratory at Duke University in Durham, North Carolina, and subsequently Washington University School of Medicine in St. Louis, Missouri, developing a surgical technique for the treatment of atrial fibrillation.[187] That technique, with his subsequent modifications, is now known as the *Cox Maze procedure* and has become the world standard with which other techniques used to treat atrial fibrillation, either surgically or with catheters, are compared.[190]

Guiraudon and colleagues[191] from Paris, France, reported their results with an encircling endomyocardial ventriculotomy for the treatment of malignant ventricular arrhythmias. The following year, in 1979, Josephson and colleagues[192] described a more specific procedure for treatment of malignant ventricular arrhythmias. After endocardial mapping, the endocardial source of the arrhythmia was excised. Although the Guiraudon technique usually isolated the source of the arrhythmia, the incision also devascularized healthy myocardium and was associated with high mortality. Endocardial resection was safer and more efficacious and became the basis of all approaches for the treatment of ischemic ventricular tachycardia.[187]

Stimulated by the death of a close personal friend from ventricular arrhythmias, Dr. Mirowski developed a prototype defibrillator over a 3-month period in 1969. In 1980, Mirowski and colleagues described three successful cases using their implantable myocardial stimulator at Johns Hopkins.[193]

PACEMAKERS

Lidwill and Booth in Australia supposedly revived a stillborn infant with electrical pacing in the 1920s.[194] Hyman temporarily paced the heart using two needle electrodes that were passed through the ribs and an electrical device of his own design. In the early 1950s, Bigelow and colleagues reported controlling the heart rate in dogs using external pacemakers.[90]

Paul Zoll is given credit for ushering in the clinical era of pacemaking. In 1952, he reported on two patients suffering from recurring prolonged ventricular standstill whom he treated with an external pacemaker.[195] The first patient was a 75-year-old man with complete heart block who had been revived with 34 intracardiac injections of epinephrine over a 4-hour period. Zoll applied electric shocks 2 ms in duration that were transmitted through the

chest wall at frequencies from 25 to 60 per minute and increased the intensity of the shock until ventricular responses were observed. After 25 minutes of intermittent stimulation, however, the patient died. Many subsequent patients, however, recovered.

The next step came when Lillehei and colleagues reported a series of patients who had external pacing after open-heart surgery during the 1950s.[196] The field of open-heart surgery gave a major impetus to the development of pacemakers because there was a high incidence of heart block following many intracardiac repairs. The major difference between Zoll's pacing and that of Lillehei and colleagues was that Zoll used external electrodes placed on the chest wall, whereas Lillehei and colleagues attached electrodes directly to the heart at operation. Lillehei and colleagues used a relatively small external pacemaker to stimulate the heart and much less electric current. This form of heart pacing was better tolerated by the patient and was a more efficient way to stimulate the heart. The survival rate of Lillehei's patients with surgically induced heart block was improved significantly.

During this period, progress was made toward a totally implantable pacemaker. Elmquist and Senning[197] developed a pacer battery that was small enough for an epigastric pocket with electrodes connected to the heart. They implanted the unit in a patient with atrioventricular block in 1958. Just before implantation, the patient had 20 to 30 cardiac arrests a day. To avoid publicity, the implantation was done in the evening when the operating rooms were empty. The first pacemaker that was implanted functioned only 8 hours; the second pacemaker implanted in the same patient had better success. The patient survived until January 2002 and had many additional pacemakers. Chardack, Gage, and Greatbatch are perhaps better known for their development of the totally implantable pacemaker.[198] In 1961 they reported a series of 15 patients who had pacemakers that they had developed implanted. The technique for inserting permanent transvenous bipolar pacemaker electrodes was developed in 1962 by Parsonnet and colleagues[199] in the United States and Ekestrom and colleagues[200] in Sweden.

Early implantable pacemakers were fixed-rate, asynchronous devices that delivered an impulse independent of the underlying cardiac rhythm. During the past 35 years, enormous progress has been made in the field of pacing technology. The number of individuals with artificial pacemakers is unknown; however, estimates indicate that approximately 500,000 Americans are living with a pacemaker and that each year another 100,000 or more patients require permanent pacemakers in the United States.

HEART, HEART-LUNG, AND LUNG TRANSPLANTATION

Alexis Carrel and Charles Guthrie reported transplantation of the heart and lungs while at the University of Chicago in 1905.[201] The heart of a small dog was transplanted into the neck of a larger one by anastomosing the caudad ends of the jugular vein and carotid artery to the aorta and pulmonary artery. The animal was not anticoagulated, and the experiment ended about 2 hours after circulation was established because of blood clot in the cavities of the transplanted heart. Carrel also reported in 1906 that he had transplanted the heart and lungs of a 1-week-old cat into the neck of a larger cat.[202] The coronary circulation was reestablished immediately, and the "auricles began to beat. The lungs became red and after a few minutes effective pulsation of the ventricles appeared." Carrel stated that a phlegmon of the neck terminated this observation 2 days later.

Vladimir Demikhov, the great Soviet investigator, described more than 20 different techniques for heart transplantation in 1950.[203] He also published various techniques for heart and lung transplantation. He was even able to perform an orthotopic heart transplant in a dog before the heart-lung machine was developed. This was accomplished by placing the donor heart above the dog's own heart, and then with a series of tubes and connections, he rerouted the blood from one heart to the other until he had the donor heart functioning in the appropriate position and the native heart removed. One of his dogs climbed the steps of the Kremlin on the sixth postoperative day but died shortly afterward of rejection.

Richard Lower and Norman Shumway established the technique for heart transplantation as it is performed today.[204] Preservation of the cuff of recipient left and right atria with part of the atrial septum was described earlier by Brock[205] in England and Demikhov[175] in the Soviet Union, but it became popular only after Shumway and Lower reported it in their 1960 paper. Shumway stated[206]:

> In 1958 when I started work at Stanford, the idea [cardiac transplantation] grew out of our local cooling experiments, since we had one hour of aortic cross-clamping during cardiopulmonary bypass. Accordingly we decided to remove the heart at the atrial level and then to suture it back into position. After several of these experiments, we found it would be easier to remove the heart of another dog and to do the actual allotransplant. Something like 20 to 30 experiments were performed before we had a survivor. All of this was done before chemical immune suppression was available.

The first attempt at a human heart transplantation was made by Hardy and colleagues[207] at the University of Mississippi. Since no human donor organ was available at the time, a large chimpanzee's heart was used; however, it was unable to support the circulation because of hyperacute rejection.

The first human-to-human heart transplant occurred December 3, 1967, at the Groote Schuur Hospital in Capetown, South Africa.[209] The surgical team, headed by Christiaan Barnard, transplanted the heart of a donor who had been certified dead after the electrocardiogram showed no activity for 5 minutes into a 54-year-old man whose heart

was irreparably damaged by repeated myocardial infarctions. The second human heart transplant using a human donor was performed on a child 3 days after the first on December 6, 1967, by Adrian Kantrowitz in Brooklyn, New York. Dr. Kantrowitz's patient died of a bleeding complication within the first 24 hours.[209] Barnard's patient, Lewis Washkansky, died on the eighteenth postoperative day. At autopsy, the heart appeared normal, and there was no evidence of chronic liver congestion, but bilateral pneumonia, possibly owing to severe myloid depression from immunosuppression, was present.[210]

On January 2, 1968, Barnard performed a second heart transplant on Phillip Blaiberg, 12 days after Washkansky's death.[211] Blaiberg was discharged from the hospital and became a celebrity during the several months he lived after the transplant. Blaiberg's procedure indicated that a heart transplant was an option for humans suffering from end-stage heart disease. Within a year of Barnard's first heart transplant, 99 heart transplants had been performed by cardiac surgeons around the world. However, by the end of 1968, most groups abandoned heart transplantation because of the extremely high mortality related to rejection. Shumway and Lower, Barnard, and a few others persevered both clinically and in the laboratory. Their efforts in discovering better drugs for immunosuppression eventually established heart transplantation as we know it today.

A clinical trial of heart-lung transplantation was commenced at Stanford University in 1981 by Reitz and colleagues.[212] Their first patient was treated with a combination of cyclosporine and azathioprine. The patient was discharged from the hospital in good condition and was well more than 5 years after the transplant. Reitz's clinical success was based on earlier experiments with primates using allografts.[213,214] These primate recipients survived for more than 140 days when cyclosporine A was used for immune suppression. Several of these animals lived for more than 5 years after allotransplantation.[215]

The current success with heart, heart-lung, and lung transplantation is related in part to the discovery of cyclosporine by workers at the Sandoz Laboratory in Basel, Switzerland, in 1970. In December of 1980, cyclosporine was introduced at Stanford for cardiac transplantation. The incidence of rejection was not reduced, nor was the incidence of infection. However, these two major complications of cardiac transplantation were less severe when cyclosporine was used. Availability of cyclosporine stimulated many new programs across the United States in the mid-1980s.

Andre Juvenelle showed that animals could survive autologous lung transplantation for many years.[216] Lung transplantation from dog to dog was fatal when attempted in the early 1950s.[217] Some animals, however, survived with an autotransplant up to 29 days before succumbing to rejection.[218] The first human lung transplant was performed by Hardy and colleagues[219] at the University of Mississippi on June 11, 1964. A pneumonectomy for carcinoma with pleural adhesions had to be performed first. The patient died on the seventeenth postoperative day. In 1971, a Belgian surgeon, Fritz Derom, achieved a 10-month survival in a patient with pulmonary silicosis.[220]

Much of the credit, however, for the success of lung transplantation belongs to the Toronto group whose efforts were headed by Joel Cooper. Their successes were based on laboratory experimentation and the discovery of cyclosporine. After losing an early patient to bronchial anastomotic dehiscence in 1978, the group substituted cyclosporine for cortisone and wrapped the bronchial suture line with a pedicle of omentum. They also developed a comprehensive preoperative preparation program that increased the strength and nutritional status of the recipients. In 1986, Cooper and associates presented their first two successful patients, who had returned to normal activities and were alive 14 and 26 months after operation.[221] This success was the culmination of more than 40 previous attempts throughout the world made after Derom's case.

HEART ASSIST AND ARTIFICIAL HEARTS

The concept of intra-aortic counterpulsation was first described by Harken[222] in 1958 and reported by Clauss and colleagues[223] in 1961. This idea proposed removal of blood via the femoral artery during systole and rapid reinfusion of the same blood during diastole to increase coronary perfusion. Technical difficulties and complications secondary to hemolysis delayed clinical use until 1962, when Moulopoulos and colleagues introduced a balloon catheter placed in the thoracic aorta.[224] In 1963, Kantrowitz and colleagues reported the first use of the intra-aortic balloon pump (IABP) in three patients.[225] All were in cardiogenic shock but improved during balloon pumping. One survived to leave the hospital.

Akutsu and Kolff reported the development and first application of a totally artificial heart in an animal model at the Cleveland Clinic in 1957.[226] The authors implanted a totally artificial heart in a living dog that survived for 90 minutes with the mechanical heart.

In 1963, Liotta and colleagues reported a 42-year-old man who had a stenotic aortic valve replaced but suffered a cardiac arrest the following morning.[227] The patient was resuscitated but developed severe ventricular failure. An artificial intrathoracic circulatory pump was implanted. The patient's pulmonary edema cleared, but he died 4 days later with the pump working continuously. In 1966, the same group used a newer intrathoracic pump to support another patient who could not be weaned from cardiopulmonary bypass. This pump maintained the circulation. The patient eventually died before the pump could be removed.[228] Later that year, the same group used a left ventricular assist device (LVAD) in a woman who could not be weaned from cardiopulmonary bypass after double valve replacement.[229] After 10 days of circulatory assistance, the patient was weaned successfully from the device and recovered. This woman was probably the first patient to be weaned from an assist device and to leave the hospital.

The first human application of a totally artificial heart was by Denton Cooley and colleagues as a "bridge" to transplantation.[230] They implanted a totally artificial heart in a patient who could not be weaned from cardiopulmonary bypass. After 64 hours of artificial heart support, heart transplantation was performed, but the patient died of *Pseudomonas* pneumonia 32 hours after transplantation. The first two patients bridged successfully to transplantation were reported at almost the same time and in the same location by different groups. On September 5, 1984, in San Francisco,[231] Donald Hill implanted a Pierce-Donachy LVAD in a patient in cardiogenic shock. The patient received a successful transplant 2 days later and was discharged subsequently. The assist device used by Hill was developed at Pennsylvania State University by Pierce and Donachy. Phillip Oyer and colleagues at Stanford University placed an electrically driven Novacor LVAD in a patient in cardiogenic shock on September 7, 1984.[232] The patient was transplanted successfully and survived beyond 3 years. The device used by the Stanford group was developed by Peer Portner.

The first implantation of a permanent totally artificial heart (Jarvik-7) was performed by DeVries and colleagues at the University of Utah in 1982.[233] By 1985, they had implanted the Jarvik in four patients, and one survived for 620 days after implantation. This initial clinical experience was based heavily on the work of Kolff and colleagues.

THORACIC AORTA SURGERY

Alexis Carrel was responsible for one of the great surgical advances of the twentieth century: techniques for suturing and transplanting blood vessels.[234] Although Carrel initially developed his methods of blood vessel anastomosis in Lyon, France, his work with Charles Guthrie in Chicago led to many major advances in vascular, cardiac, and transplantation surgery. In a short period of time, these investigators perfected techniques for blood vessel anastomoses and transposition of arterial and venous segments using both fresh and frozen grafts. After leaving Chicago, Carrel continued to expand his work on blood vessels and organ transplantation and in 1912 received the Nobel Prize. Interestingly, Carrel's work did not receive immediate clinical application.

Rudolph Matas pioneered clinical vascular surgery. Matas's work took place before drugs were available to prevent blood clotting, before antibiotics, and without reliable blood vessel substitutes.[235] Matas performed 620 vascular operations between 1888 and 1940. Only 101 of these were attempts to repair arteries; most involved ligation. Matas developed three variations of his well-known endoaneurysmorrhaphy procedure. The most advanced was to reconstruct the wall of the blood vessel from within while using a rubber tube as a stent.

Vascular surgery advanced tentatively during World War II as traumatic injuries to major blood vessels were repaired in some soldiers with results significantly better than with the standard treatment of ligation.[236] The successful treatment of coarctation of the aorta by Crafoord and Gross added a major boost to the reconstructive surgery of arteries.

Shumaker reported the excision of a small descending thoracic aortic aneurysm with reanastomosis of the aorta in 1948.[237] Swan and colleagues[238] repaired a complex aneurysmal coarctation and used aortic homograft for reconstruction in 1950. Gross[239] reported a series of similar cases using homograft replacement. In 1951, DuBost and colleagues[240] in Paris resected an intra-abdominal aortic aneurysm with homograft replacement.

In 1953, Henry Bahnson,[241] from Johns Hopkins, successfully resected six saccular aneurysms of the aorta in eight patients. In the same year, DeBakey and Cooley[242] reported a 46-year-old man who had resection of a huge aneurysm of the descending thoracic aorta that measured approximately 20 cm in length and in greatest diameter. The aneurysm was resected and replaced with an aortic homograft approximately 15 cm in length.

During the Korean War, the arterial homograft and autogenous vein graft were used to reconstruct battlefield arterial injuries and reduce the overall amputation rate to 11.1%,[243] compared with the rate of 49.6% reported in World War II. Although the vein autograft remains the first-choice peripheral vascular conduit today, the arterial homograft was superseded by the development of synthetic vascular grafts by Arthur Voorhees at Columbia University in 1952. Voorhees and colleagues developed Vinyon-N cloth tubes to substitute for diseased arterial segments,[244] but because of kinking, these smooth-lined tubes could not be used across joints. Development of the crimped graft by Edwards and Tapp[245] and introduction of the Dacron graft by DeBakey[240] were important milestones. DeBakey's account of his discovery of Dacron reflects the resourcefulness and innovation of these pioneering surgeons[247]:

> We were greatly impressed with the report of Voorhees on the use of a fabric woven of Vinyon-N. On my first trip to obtain some of these fabrics from a department store here, I found that they only had some sheets of Dacron. I purchased several yards and cut them in different sizes to make tubes by sewing on my wife's sewing machine. I had been taught by my mother as a boy to sew and I became an expert not only in the use of the sewing machine, but also on the other aspects of sewing. These tubes proved highly successful in animals, and although we later obtained sheets of Orlon, Teflon, nylon and Ivalon, none of these were as good as the original Dacron fabric. It was rather interesting and an example of serendipity that the first material we obtained (Dacron), the only one available at the store at the time, proved later to be the best. One of these Dacron grafts that I had fabricated as a bifurcation graft was used to replace an aneurysm of the abdominal aorta in September 1954.

Another advance in aortic surgery appeared in 1955 when DeBakey and colleagues[247] reported six cases of aortic

dissection treated by aggressive surgery. This paper included a description of pathologic and hemodynamic factors associated with the dissections and led to a more logical approach to treatment of these lesions. Because mortality of operation for acute dissections remained high, Myron Wheat, Jr., introduced medical therapy for the disease.[248]

During the late 1950s, the Houston group, consisting of Michael DeBakey, Denton Cooley, Stanley Crawford, and their other associates, systematically developed operations for resection and graft replacement of the ascending aorta,[249] descending aorta, and thoracoabdominal aorta.[250] Cardiopulmonary bypass was used for the ascending aortic resections. The high risk of paraplegia highlighted a major complication of thoracoabdominal aortic resections. The Houston group was the first to resect an aortic arch with the use of cardiopulmonary bypass in 1957[251] and replace the arch with a reconstituted aortic arch homograph. More interesting is that Cooley and colleagues, using great ingenuity, resected a large aortic arch aneurysm that also involved a portion of the descending aorta in a 49-year-old patient on June 24, 1955. The surgery was done, without the use of cardiopulmonary bypass, by first sewing in a temporary graft from the ascending aorta to the distal descending aorta and sewing in two more temporary limbs off that graft, which were anastomosed to the left and right carotid arteries, while the aneurysm was resected and a permanent graft was placed.[252]

In 1968, Bentall and De Bono[253] introduced replacement of the ascending aorta and aortic valve with reanastomoses of the coronary ostia to the replacement graft. They described the composite-graft technique for replacement of the ascending aorta with reimplantation of the coronary arteries into the composite Dacron graft containing the prosthetic aortic valve. As mentioned previously, Cooley and DeBakey were first to replace the supracoronary ascending aorta in 1956. In 1963, Starr and colleagues[254] reported replacing the supracoronary ascending aorta and the aortic valve at the same sitting. The technique of fashioning "buttons" of aortic tissue adjacent to the coronary ostia and then incorporating these buttons into the aortic graft along with the aortic valve replacement was described by Wheat and colleagues[255] in 1964. Bentall and De Bono incorporated the aortic prosthesis into the tube graft and used the Wheat technique for implanting the coronary arteries into the composite graft.

Since the early 1990s, stents also have been used for the treatment of aneurysms in both the descending aorta and abdominal aorta.[256,257] The progress in this field is moving rapidly.

SUMMARY

The history of adult cardiac surgery continues to be written and will continue to evolve as long as acquired heart disease shortens lives. In the early days after the introduction of cardiopulmonary bypass, the pace of advance was torrid but, in a way, narrowly focused. Now hundreds of thousands of clinicians, scientists, and engineers are involved in a broad and deep effort to develop new and safer operations and procedures, new valves, new revascularization techniques, new biomaterials, new heart substitutes, new life-support systems, and new methods to control cardiac arrhythmias and ventricular remodeling after injury. This research and development is supported by a vigorous infrastructure of basic science in biology and medicine, chemistry and pharmacology, and engineering and computer technology. The history of cardiac surgery is only a prelude; the moving finger writes and having writ moves on to a bright, exciting future.

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CHAPTER 2

Surgical Anatomy of the Heart

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A thorough knowledge of the anatomy of the heart is a prerequisite for the successful completion of the myriad procedures performed by the cardiothoracic surgeon. In this chapter we describe the normal anatomy of the heart, including its position and relationship to other thoracic organs. We describe the incisions used to expose the heart for various operations and discuss in detail the cardiac chambers and valves, coronary arteries and veins, and the important but surgically invisible conduction tissues.

OVERVIEW

Location of the Heart Relative to Surrounding Structures

The overall shape of the heart is that of a three-sided pyramid located in the middle mediastinum (Fig. 2-1). When viewed from the heart's apex, the three sides of the ventricular mass are readily apparent (Fig. 2-2). Two of the edges are named. The *acute margin* lies inferiorly and describes a sharp angle between the sternocostal and diaphragmatic surfaces. The *obtuse margin* lies superiorly and is much more diffuse. The posterior margin is unnamed but is also diffuse in its transition.

One-third of the cardiac mass lies to the right of the midline and two-thirds to the left. The long axis of the heart is oriented from the left epigastrium to the right shoulder. The short axis, which corresponds to the plane of the atrioventricular groove, is oblique and is oriented closer to the vertical than to the horizontal plane (see Fig. 2-1).

Anteriorly, the heart is covered by the sternum and the costal cartilages of the third, fourth, and fifth ribs. The lungs contact the lateral surfaces of the heart, whereas the heart abuts onto the pulmonary hila posteriorly. The right lung overlies the right surface of the heart and reaches to the midline. In contrast, the left lung retracts from the midline in the area of the cardiac notch. The heart has an extensive diaphragmatic surface inferiorly. Posteriorly, the heart lies on the esophagus and the tracheal bifurcation and bronchi that extend into the lung. The sternum lies anteriorly and provides rigid protection to the heart during blunt trauma and is aided by the cushioning effects of the lungs.

The Pericardium and Its Reflections

The heart lies within the pericardium, which is attached to the walls of the great vessels and to the diaphragm. The pericardium can be visualized best as a bag into which the heart has been placed apex first. The inner layer, in direct contact with the heart, is the *visceral epicardium,* which encases the heart and extends several centimeters back onto the walls of the great vessels. The outer layer forms the *parietal pericardium,* which lines the inner surface of the tough fibrous pericardial sack. A thin film of lubricating fluid lies within the pericardial cavity between the two serous layers. Two identifiable recesses lie within the pericardium and are lined by the serous layer. The first is the *transverse sinus,* which is delineated anteriorly by the posterior surface of the aorta and pulmonary trunk and posteriorly by the anterior surface of the interatrial groove. The second is the *oblique sinus,* a cul-de-sac located behind the left atrium, delineated by serous pericardial reflections from the pulmonary veins and the inferior vena cava.

Mediastinal Nerves and Their Relationships to the Heart

The vagus and phrenic nerves descend through the mediastinum in close relationship to the heart (Fig. 2-3). They enter through the thoracic inlet, with the phrenic nerve located anteriorly on the surface of the anterior scalene muscle and lying just posterior to the internal thoracic artery (internal mammary artery) at the thoracic inlet. In this position, the phrenic nerve is vulnerable to injury during dissection

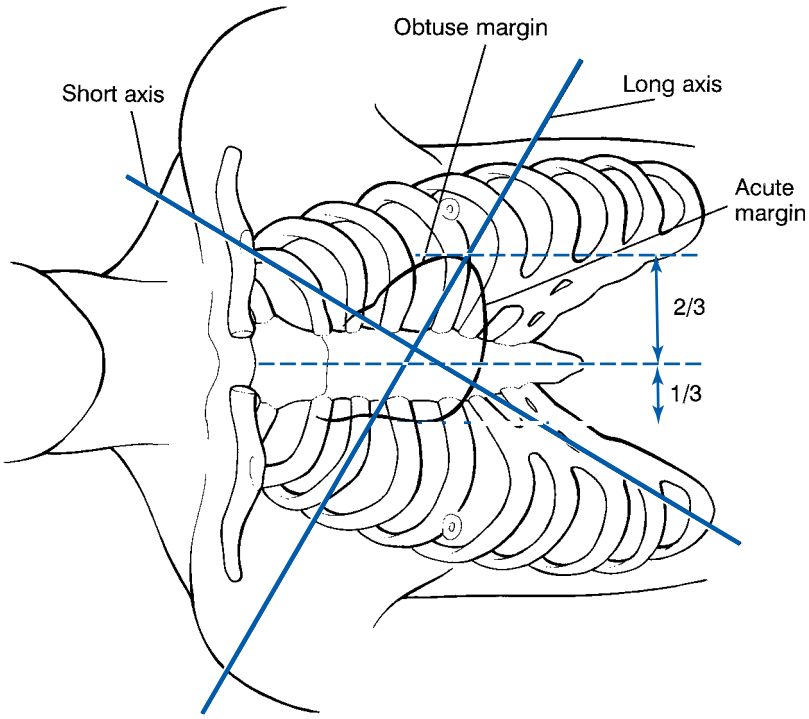

Figure 2-1. This diagram shows the heart within the middle mediastinum with the patient supine on the operating table. The long axis lies parallel to the interventricular septum, whereas the short axis is perpendicular to the long axis at the level of the atrioventricular valves.

and preparation of the internal thoracic artery for use in coronary arterial bypass grafting. On the right side, the phrenic nerve courses on the lateral surface of the superior vena cava, again in harm's way during dissection for venous cannulation for cardiopulmonary bypass. The nerve then descends anterior to the pulmonary hilum before reflecting onto the right diaphragm, where it branches to provide its innervation. In the presence of a left-sided superior vena cava, the left phrenic nerve is applied directly to its lateral surface. The nerve passes anterior to the pulmonary hilum and eventually branches on the surface of the diaphragm. The vagus nerves enter the thorax posterior to the phrenic nerves and course along the carotid arteries. On the right side, the vagus gives off the recurrent laryngeal nerve that

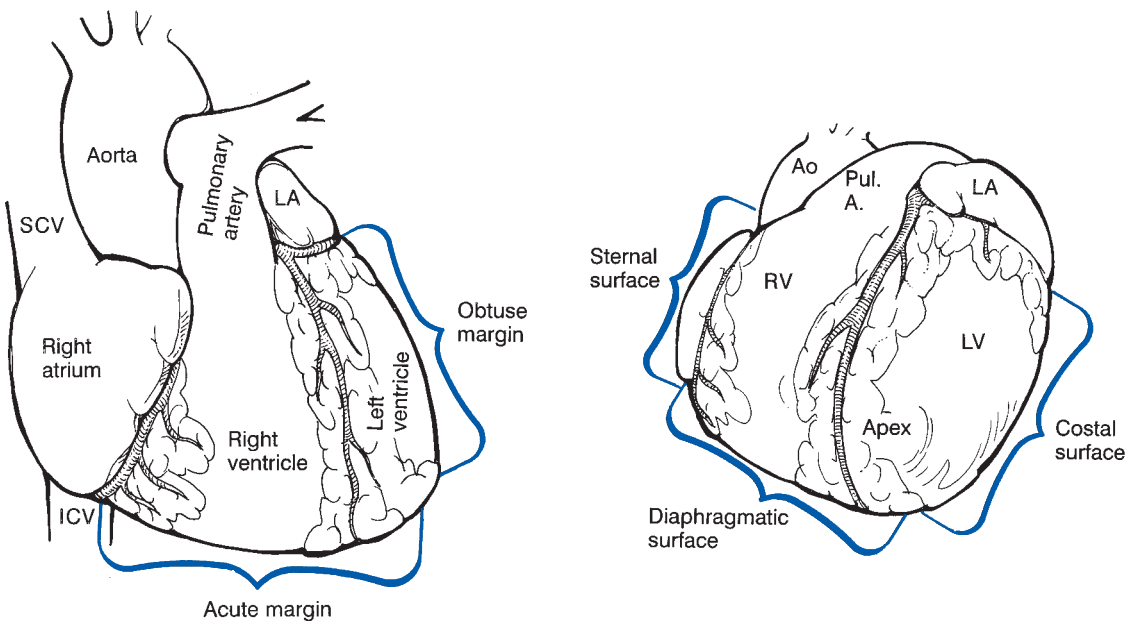

Figure 2-2. This diagram shows the surfaces and margins of the heart as viewed anteriorly with the patient supine on the operating table (*left*) and as viewed from the cardiac apex (*right*).

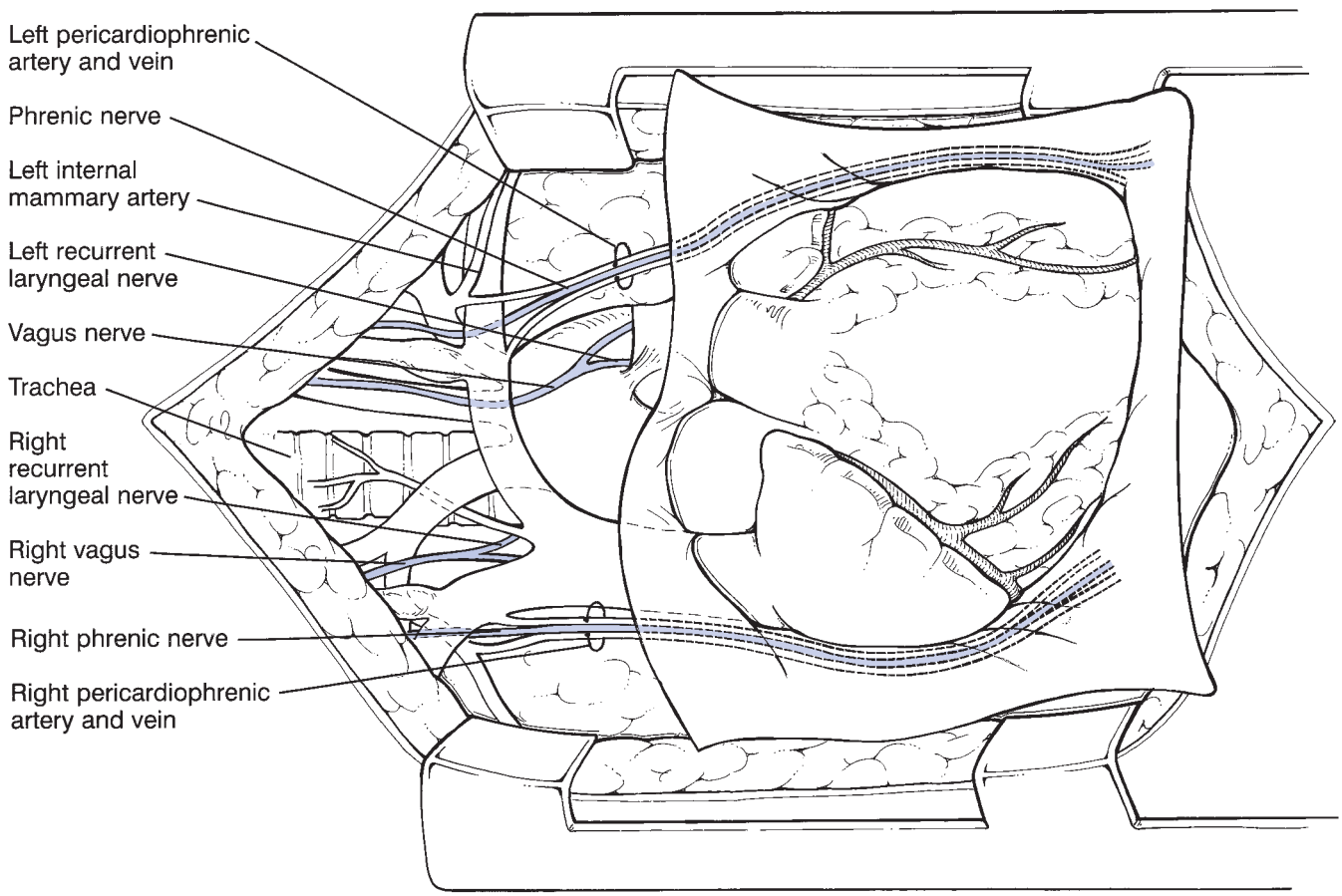

Figure 2-3. Diagram of the heart in relation to the vagus and phrenic nerves as viewed through a median sternotomy.

passes around the right subclavian artery before ascending out of the thoracic cavity. The right vagus nerve continues posterior to the pulmonary hilum, gives off branches of the right pulmonary plexus, and exits the thorax along the esophagus. On the left, the vagus nerve crosses the aortic arch, where it gives off the recurrent laryngeal branch. The recurrent nerve passes around the arterial ligament before ascending in the tracheoesophageal groove. The vagus nerve continues posterior to the pulmonary hilum, gives rise to the left pulmonary plexus, and then continues inferiorly out of the thorax along the esophagus. A delicate nerve trunk known as the *subclavian loop* carries fibers from the stellate ganglion to the eye and head. This branch is located adjacent to the subclavian arteries bilaterally. Excessive dissection of the subclavian artery during shunt procedures may injure these nerve roots and cause Horner syndrome.

SURGICAL INCISIONS

Median Sternotomy

The most common approach for operations on the heart and aortic arch is the median sternotomy. The skin incision is made from the jugular notch to just below the xiphoid process. The subcutaneous tissues and presternal fascia are incised to expose the periostium of the sternum. The sternum is divided longitudinally in the midline. After placement of a sternal spreader, the thymic fat pad is divided up to the level of the brachiocephalic vein. An avascular midline plane is identified easily but is crossed by a few thymic veins that are divided between fine silk ties or hemoclips. Either the left or right or, occasionally, both lobes of the thymus gland are removed in infants and young children to improve exposure and to minimize compression on extracardiac conduits. If a portion of the thymus gland is removed, excessive traction may result in injury to the phrenic nerve. The pericardium is opened anteriorly to expose the heart. Through this incision, operations within any chamber of the heart or on the surface of the heart and operations involving the proximal aorta, pulmonary trunk, and their primary branches can be performed. Extension of the superior extent of the incision into the neck along the anterior border of the right sternocleidomastoid muscle provides further exposure of the aortic arch and its branches for procedures involving these structures. Exposure of the proximal descending thoracic aorta is facilitated by a perpendicular extension of the incision through the third intercostal space.

Bilateral Transverse Thoracosternotomy (Clamshell Incision)

The bilateral transverse thoracosternotomy (clamshell incision) is an alternative incision for exposure of the pleural spaces and heart. This incision may be made through either the fourth or fifth intercostal space, depending on the intended procedure. After identifying the appropriate interspace, a bilateral submammary incision is made. The incision is extended down through the pectoralis major muscles to enter the hemithoraces through the appropriate intercostal space. The right and left internal thoracic arteries are dissected and ligated proximally and distally prior to transverse division of the sternum. Electrocautery dissection of the pleural reflections behind the sternum allows full exposure of both hemithoraces and the entire mediastinum. Bilateral chest spreaders are placed to maintain exposure. Morse or Haight retractors are particularly suitable with this incision. The pericardium may be opened anteriorly to allow access to the heart for intracardiac procedures. When required, standard cannulation for cardiopulmonary bypass is achieved easily. This incision is popular for bilateral sequential double-lung transplants and heart-lung transplants because of enhanced exposure of the apical pleural spaces. When made in the fourth intercostal space, the incision is useful for access to the ascending aorta, the aortic arch, and descending thoracic aorta.

Anterolateral Thoracotomy

The right side of the heart can be exposed through a right anterolateral thoracotomy. The patient is positioned supine, with the right chest elevated to approximately 30 degrees by a roll beneath the shoulder. An anterolateral thoracotomy incision can be made that can be extended across the midline by transversely dividing the sternum if necessary. With the lung retracted posteriorly, the pericardium can be opened just anterior to the right phrenic nerve and pulmonary hilum to expose the right and left atria. The incision provides access to both the tricuspid and mitral valves and the right coronary artery. Cannulation may be performed in the ascending aorta and the superior and inferior venae cavae. Aortic cross-clamping, administration of cardioplegia, and removal of air from the heart after cardiotomy are difficult with this approach. This incision is particularly useful nonetheless for performance of the Blalock-Hanlon atrial septectomy or for valve replacement after a previous procedure through a median sternotomy. A left anterolateral thoracotomy performed in a similar fashion to that on the right side may be used for isolated bypass grafting of the circumflex coronary artery or for left-sided exposure of the mitral valve.

Posterolateral Thoracotomy

A left posterolateral thoracotomy is used for procedures involving the distal aortic arch and descending thoracic aorta. With left thoracotomy, cannulation for cardiopulmonary bypass must be done through the femoral vessels. A number of variations of these incisions have been used for minimally invasive cardiac surgical procedures. These include partial sternotomies, parasternal incisions, and limited thoracotomies.

RELATIONSHIP OF THE CARDIAC CHAMBERS AND GREAT ARTERIES

The surgical anatomy of the heart is best understood when the position of the cardiac chambers and great vessels is known in relation to the cardiac silhouette. The atrioventricular junction is oriented obliquely, lying much closer to the vertical than to the horizontal plane. This plane can be viewed from its atrial aspect (Fig. 2-4) if the atrial mass and great arteries are removed by a parallel cut just above the

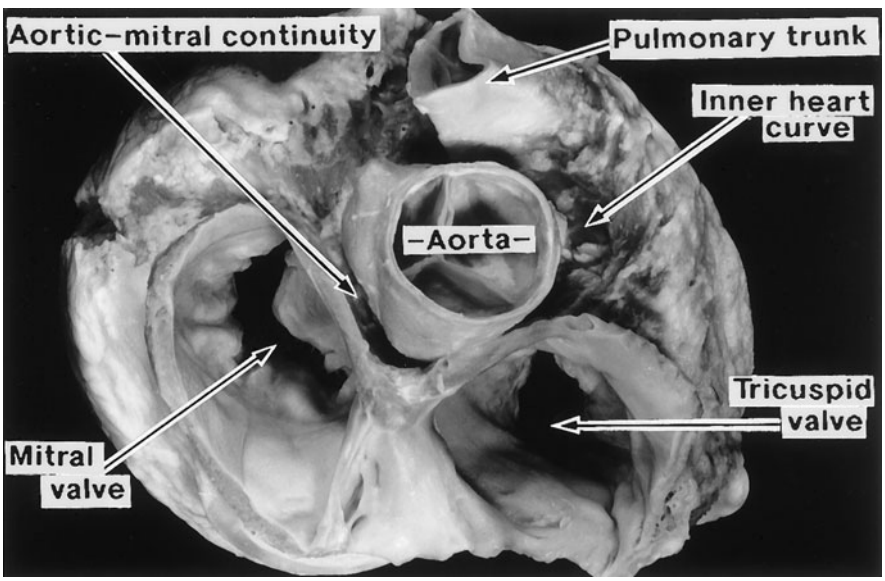

Figure 2-4. This dissection of the cardiac short axis, seen from its atrial aspect, reveals the relationships of the cardiac valves.

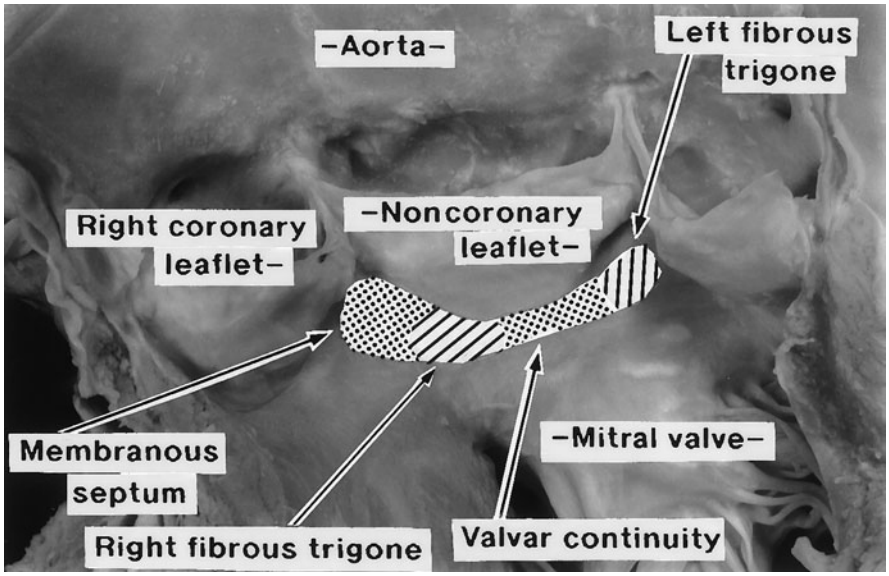

Figure 2-5. This view of the left ventricular outflow tract, as seen from the front in anatomic orientation, shows the limited extent of the fibrous skeleton of the heart.

junction. The tricuspid and pulmonary valves are widely separated by the inner curvature of the heart lined by the transverse sinus. Conversely, the mitral and aortic valves lie adjacent to one another, with fibrous continuity of their leaflets. The aortic valve occupies a central position, wedged between the tricuspid and pulmonary valves. Indeed, there is fibrous continuity between the leaflets of the aortic and tricuspid valves through the central fibrous body.

With careful study of this short axis, several basic rules of cardiac anatomy become apparent. First, the atrial chambers lie to the right of their corresponding ventricles. Second, the right atrium and ventricle lie anterior to their left-sided counterparts. The septal structures between them are obliquely oriented. Third, by virtue of its wedged position, the aortic valve is directly related to all the cardiac chambers. Several other significant features of cardiac anatomy can be learned from the short-axis section. The position of the aortic valve minimizes the area of septum where the mitral and tricuspid valves attach opposite each other. Because the tricuspid valve is attached to the septum further toward the ventricular apex than the mitral valve, a part of the septum is interposed between the right atrium and the left ventricle to produce the muscular atrioventricular septum. The central fibrous body, where the leaflets of the aortic, mitral, and tricuspid valves all converge, lies cephalad and anterior to the muscular atrioventricular septum. The central fibrous body is the main component of the fibrous skeleton of the heart and is made up in part by the right fibrous trigone, a thickening of the right side of the area of fibrous continuity between the aortic and mitral valves, and in part by the membranous septum, the fibrous partition between the left ventricular outflow tract and the right-sided heart chambers (Fig. 2-5). The membranous septum itself is divided into two parts by the septal leaflet of the tricuspid valve, which is directly attached across it (Fig. 2-6). Thus the membranous septum has an atrioventricular component between the right

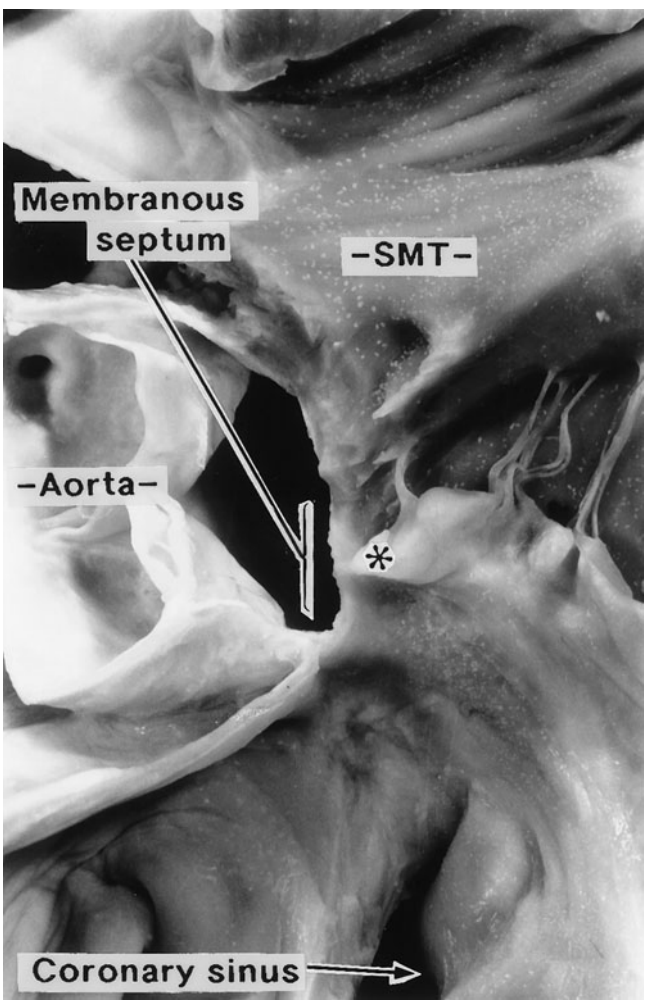

Figure 2-6. This dissection, made by removing the right coronary sinus of the aortic valve, shows how the septal leaflet of the tricuspid valve (*asterisk*) divides the membranous septum into its atrioventricular and interventricular components. SMT = septomarginal trabeculation.

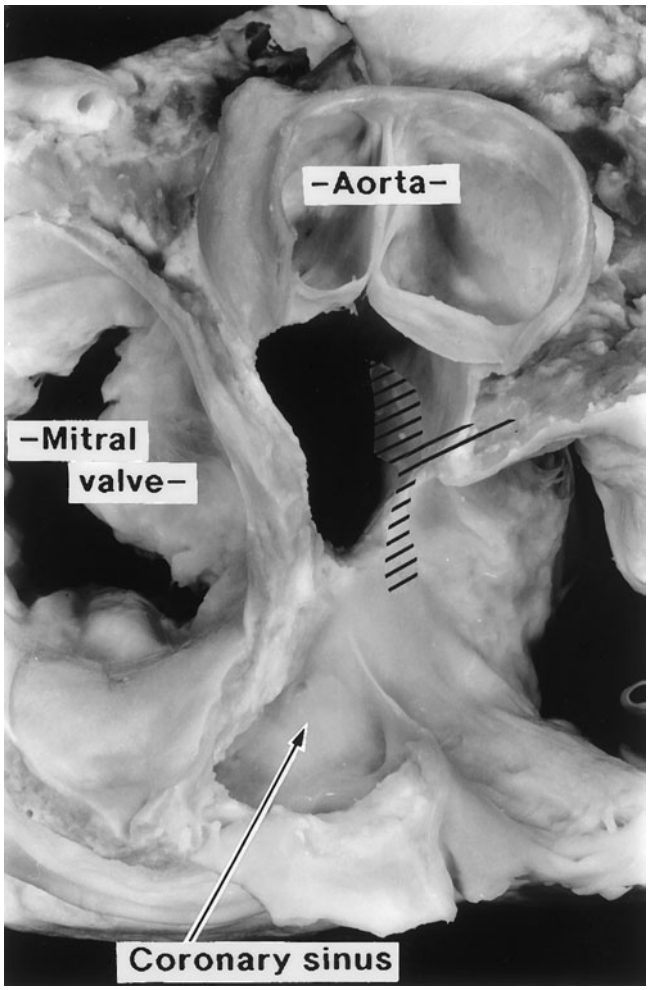

Figure 2-7. This dissection, made by removing the noncoronary aortic sinus (compare with Figs. 2-4 and 2-6), shows the approximate location of the atrioventricular conduction axis (*hatched area*) and the relationship of the mitral valve to the ventricular septum.

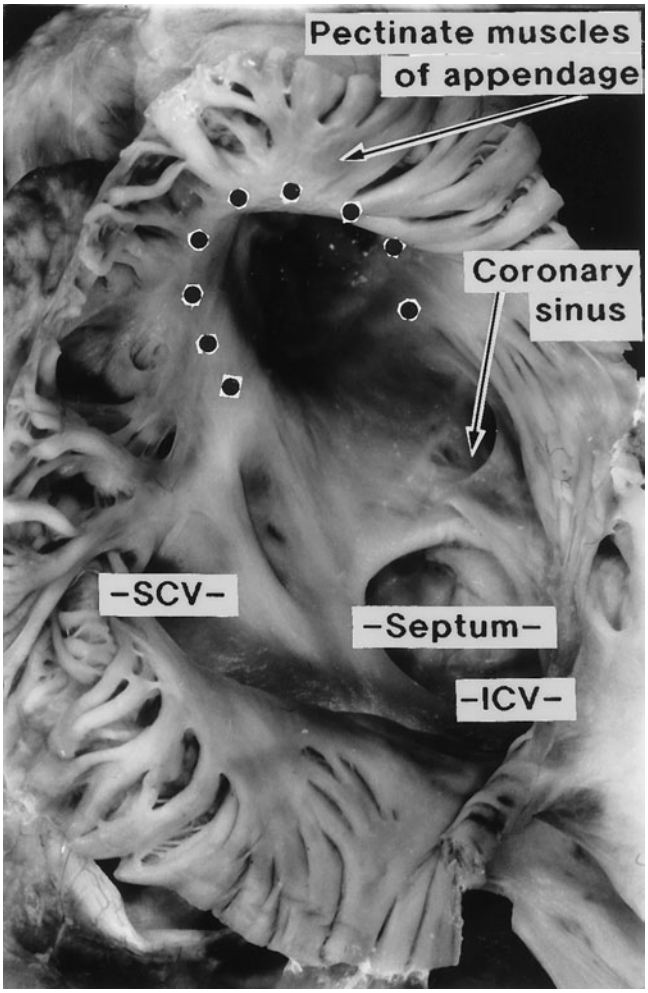

Figure 2-8. This view of the right atrium, seen in surgical orientation, shows the pectinate muscles lining the appendage, the smooth vestibule (*circles*) surrounding the orifice of the tricuspid valve, and the superior vena cava (SCV), inferior vena cava (ICV), and coronary sinus joining the smooth-walled venous component. Note the prominent rim enclosing the oval fossa, which is the true atrial septum (see Fig. 2-11).

atrium and left ventricle, as well as an interventricular component. Removal of the noncoronary leaflet of the aortic valve demonstrates the significance of the wedged position of the left ventricular outflow tract in relation to the other cardiac chambers. The subaortic region separates the mitral orifice from the ventricular septum; this separation influences the position of the atrioventricular conduction tissues and the position of the leaflets and tension apparatus of the mitral valve (Fig. 2-7).

THE RIGHT ATRIUM AND TRICUSPID VALVE

Appendage, Vestibule, and Venous Component

The right atrium has three basic parts: the appendage, the vestibule, and the venous component (Fig. 2-8). Externally, the right atrium is divided into the appendage and the venous component, which receives the systemic venous return. The junction of the appendage and the venous component is identified by a prominent groove, the *terminal groove*. This corresponds internally to the location of the terminal crest. The right atrial appendage has the shape of a blunt triangle, with a wide junction to the venous component across the terminal groove. The appendage also has an extensive junction with the vestibule of the right atrium; the latter structure is the smooth-walled atrial myocardium that inserts into the leaflets of the tricuspid valve. The most characteristic and constant feature of the morphology of the right atrium is that the pectinate muscles within the appendage extend around the entire parietal margin of the atrioventricular junction (Fig. 2-9). These muscles originate as parallel fibers that course at right angles from the

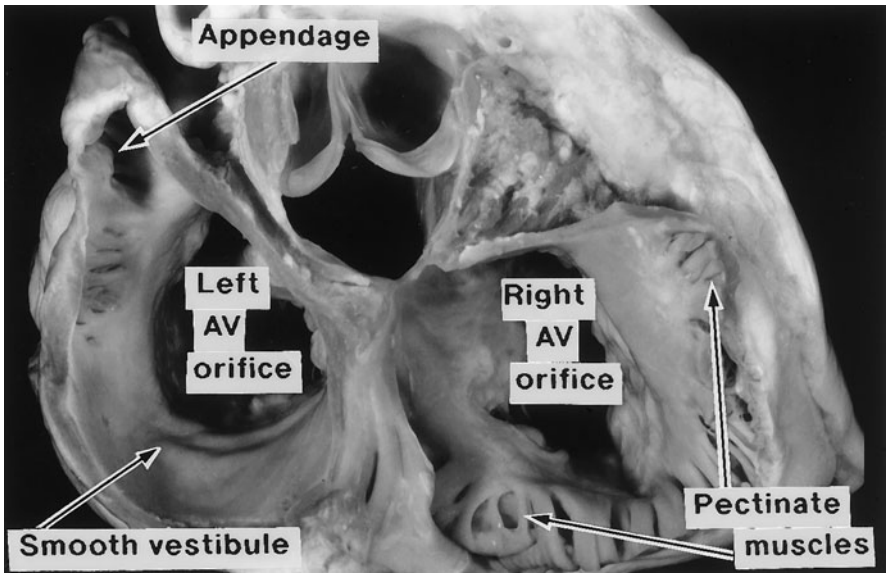

Figure 2-9. This dissection of the short axis of the heart (compare with Fig. 2-4) shows how the pectinate muscles extend around the parietal margin of the tricuspid valve. In the left atrium, the pectinate muscles are confined within the tubular left atrial appendage, leaving the smooth vestibule around the mitral valve confluent with the pulmonary venous component of the left atrium.

terminal crest. The venous component of the right atrium extends between the terminal groove and the interatrial groove. It receives the superior and inferior venae cavae and the coronary sinus.

Sinus Node

The sinus node lies at the anterior and superior extent of the terminal groove, where the atrial appendage and the superior vena cava are juxtaposed. The node is a spindle-shaped structure that usually lies to the right or lateral to the superior cavoatrial junction (Fig. 2-10). In approximately 10% of cases, the node is draped across the cavoatrial junction in horseshoe fashion.[1]

The blood supply to the sinus node is from a prominent nodal artery that is a branch of the right coronary artery in approximately 55% of individuals and a branch of the circumflex artery in the remainder. Regardless of its artery of origin, the nodal artery usually courses along the anterior interatrial groove toward the superior cavoatrial junction, frequently within the atrial myocardium. At the cavoatrial junction, its course becomes variable and may circle either anteriorly or posteriorly or, rarely, both anteriorly and posteriorly around the cavoatrial junction to enter the node. Uncommonly, the artery arises more distally from the right coronary artery and courses laterally across the atrial appendage. This places it at risk of injury during a standard right atriotomy. The artery also may arise distally from the circumflex artery to cross the dome of the left atrium, where it is at risk of injury when using a superior approach to the mitral valve. Incisions in either the right or left atrial chambers always should be made with this anatomic variability in mind. In our experience, these vessels can be identified by careful gross inspection, and prompt modification of surgical incisions can be made accordingly.

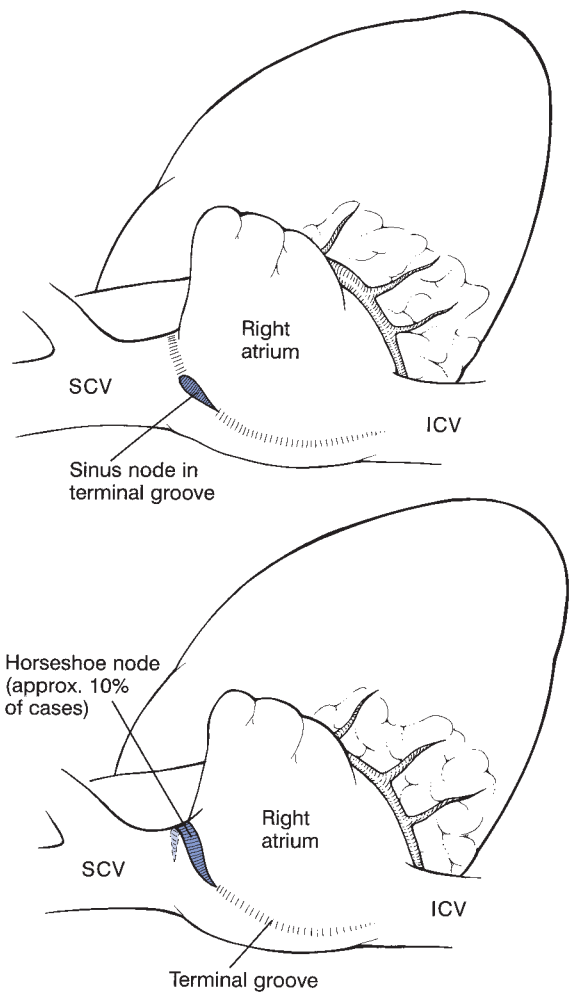

Figure 2-10. This diagram shows the location of the sinus node at the superior cavoatrial junction. The node usually lies to the right (lateral) side of the junction but may be draped in horseshoe fashion across the anterior aspect of the junction. SCV = superior vena cava; ICV = inferior vena cava.

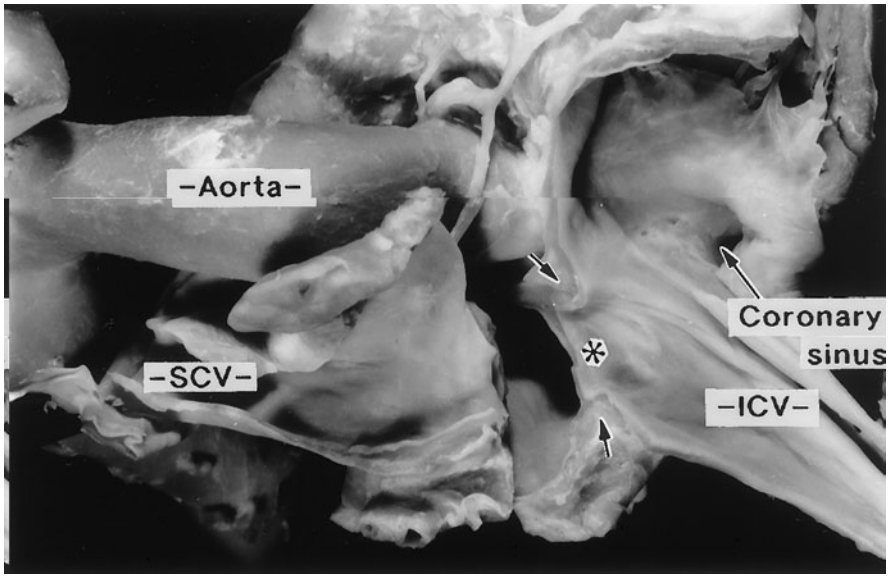

Figure 2-11. This transection across the middle of the oval fossa (*asterisk*) shows how the so-called septum secundum, the rim of the fossa, is made up of the infolded atrial walls (arrows). SCV = superior vena cava; ICV = inferior vena cava.

Atrial Septum

The most common incision into the right atrium is made into the atrial appendage parallel and anterior to the terminal groove. Opening the atrium through this incision confirms that the terminal groove is the external marking of the prominent terminal crest. Anteriorly and superiorly, the crest curves in front of the orifice of the superior vena cava to become continuous with the so-called septum secundum, which, in reality, is the superior rim of the oval fossa. When the right atrium is inspected through this incision, there appears to be an extensive septal surface between the tricuspid valve and the orifices of the venae cavae. This septal surface includes the opening of the oval fossa and the orifice of the coronary sinus. The apparent extent of the septum is spurious because the true septum between the atrial chambers is virtually confined to the oval fossa[2,3] (Fig. 2-11). The superior rim of the fossa, although often referred to as the *septum secundum,* is an extensive infolding between the venous component of the right atrium and the right pulmonary veins. The inferior rim is directly continuous with the so-called sinus septum that separates the orifices of the inferior caval vein and the coronary sinus (Fig. 2-12).

The region around the coronary sinus is where the right atrial wall overlies the atrioventricular muscular septum. Removing the floor of the coronary sinus reveals the anterior extension of the atrioventricular groove in this region. Only a small part of the anterior rim of the oval fossa is a septal structure. The majority is made up of the anterior atrial wall overlying the aortic root. Thus dissection outside the limited margins of the oval fossa will penetrate the heart to the outside rather than provide access to the left atrium via the septum.

Atrioventricular Septum and Node: Triangle of Koch

In addition to the sinus node, another major area of surgical significance is occupied by the atrioventricular node. This structure lies within the triangle of Koch, which is

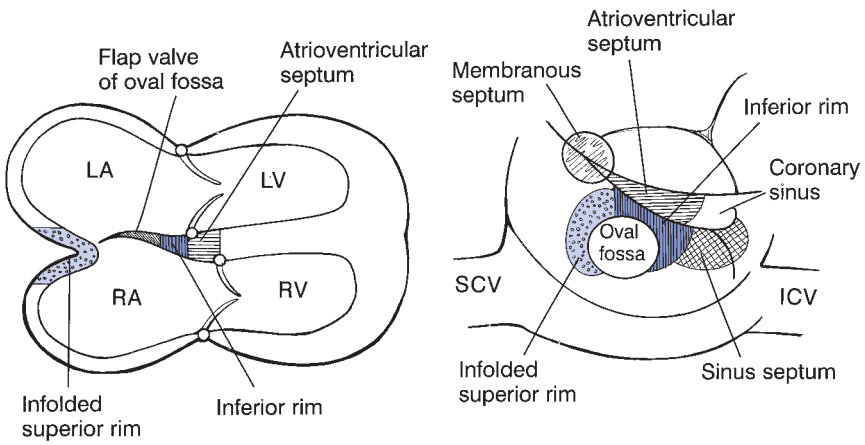

Figure 2-12. This diagram demonstrates the components of the atrial septum. The only true septum between the two atria is confined to the area of the oval fossa. SCV = superior vena cava; ICV = inferior vena cava.

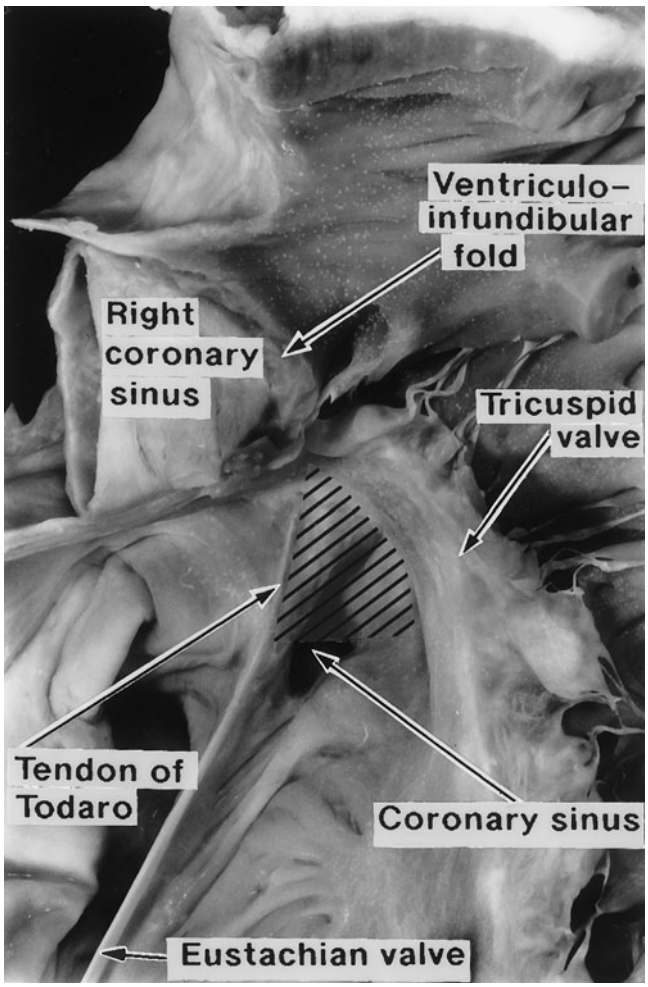

Figure 2-13. This dissection, made by removing part of the subpulmonary infundibulum, shows the location of the triangle of Koch (*shaded area*).

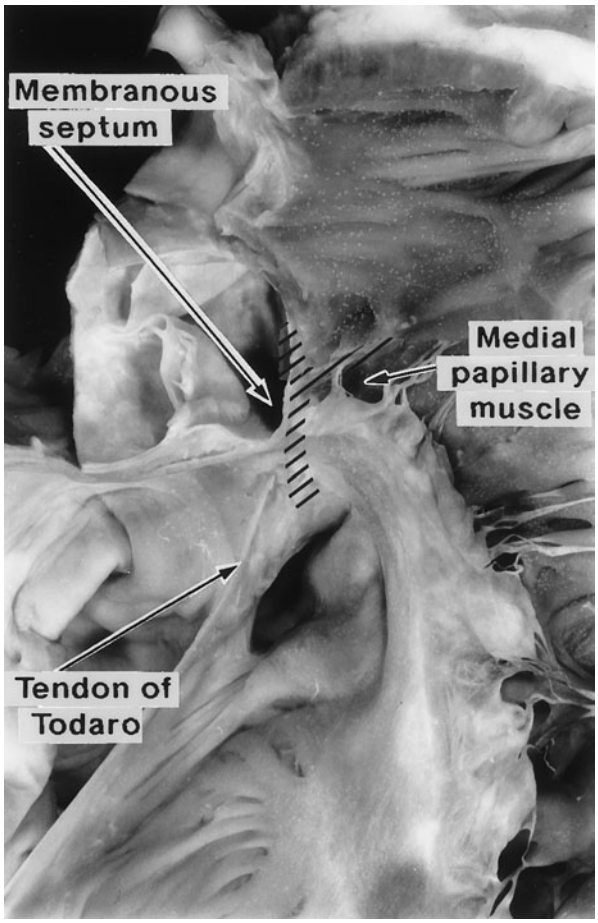

Figure 2-14. Further dissection of the heart shown in Fig. 2-13 reveals that a line joining the apex of the triangle of Koch to the medial papillary muscle marks the location of the atrioventricular conduction axis.

demarcated by the tendon of Todaro, the septal leaflet of the tricuspid valve, and the orifice of the coronary sinus (Fig. 2-13). The tendon of Todaro is a fibrous structure formed by the junction of the eustachian valve and the thebesian valve (the valves of the inferior vena cava and the coronary sinus, respectively). The entire atrial component of the atrioventricular conduction tissues is contained within the triangle of Koch, which must be avoided to prevent surgical damage to atrioventricular conduction. The atrioventricular bundle (of His) penetrates directly at the apex of the triangle of Koch before it continues to branch on the crest of the ventricular septum (Fig. 2-14). The key to avoiding atrial arrhythmias is careful preservation of the sinus and atrioventricular nodes and their blood supply. No advantage is gained in attempting to preserve nonexistent tracts of specialized atrial conduction tissue, although it makes sense to avoid prominent muscle bundles where parallel orientation of atrial myocardial fibers favors preferential conduction (Fig. 2-15).

Tricuspid Valve

The vestibule of the right atrium converges into the tricuspid valve. The three leaflets reflect their anatomic location, being septal, anterosuperior, and inferior (or mural). The leaflets join together over three prominent zones of apposition; the peripheral ends of these zones usually are described as *commissures*. The leaflets are tethered at the commissures by fan-shaped cords arising from prominent papillary muscles. The anteroseptal commissure is supported by the medial papillary muscle. The major leaflets of the valve extend from this position in anterosuperior and septal directions. The third leaflet is less well defined. The anteroinferior commissure is usually supported by the prominent anterior papillary muscle. Often, however, it is not possible to identify a specific inferior papillary muscle supporting the inferoseptal commissure. Thus the inferior leaflet may seem duplicated. There is no well-formed collagenous annulus for the tricuspid valve. Instead, the atrioventricular groove more or less folds directly into the tricuspid valvar leaflets at the vestibule, and

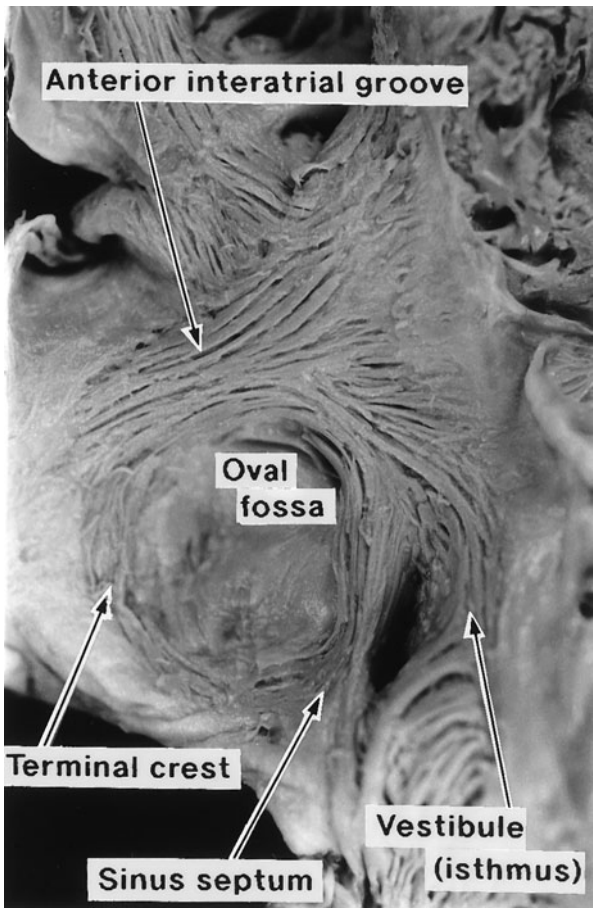

Figure 2-15. This dissection, made by careful removal of the right atrial endocardium, shows the ordered arrangement of myocardial fibers in the prominent muscle bundles that underscore preferential conduction. There are *no* insulated tracts running within the internodal atrial myocardium. (*Dissection made by Prof. Damian Sanchez-Quintana.*)

the atrial and ventricular myocardial masses are separated almost exclusively by the fibrofatty tissue of the groove. The entire parietal attachment of the tricuspid valve usually is encircled by the right coronary artery running within the atrioventricular groove.

THE LEFT ATRIUM AND MITRAL VALVE

Appendage, Vestibule, and Venous Component

Like the right atrium, the left atrium has three basic components: the appendage, the vestibule, and the venous component (Fig. 2-16). Unlike the right atrium, the venous component is considerably larger than the appendage and has a narrow junction with it that is not marked by a terminal groove or crest. There also is an important difference between the relationship of the appendage and vestibule between the left and right atria. As shown, the pectinate muscles within the right atrial appendage extend all around the parietal margin of the vestibule. In contrast, the left atrial appendage has a limited junction with the vestibule, and the pectinate muscles are located almost exclusively within the appendage (see Fig. 2-8). The larger part of the vestibule that supports and inserts directly into the mural leaflet of the mitral valve is directly continuous with the smooth atrial wall of the pulmonary venous component.

Because the left atrium is posterior to and tethered by the four pulmonary veins, the chamber is relatively inaccessible. Surgeons use several approaches to gain access. The most common is an incision just to the right of and parallel to the interatrial groove, anterior to the right pulmonary veins. This incision can be carried beneath both the superior and inferior venae cavae parallel to the interatrial groove to provide wide access to the left atrium. A second approach is

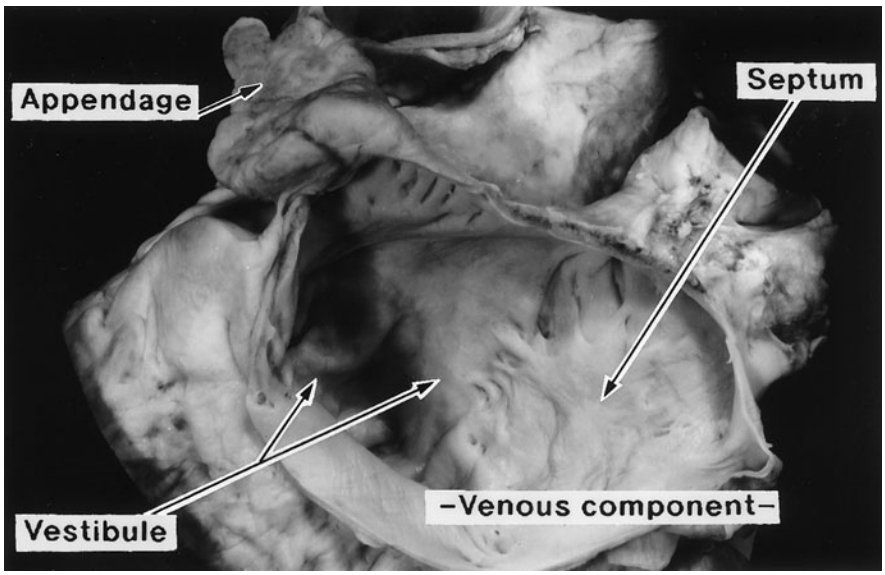

Figure 2-16. Like the right atrium, the left atrium (seen here in anatomic orientation) has an appendage, a venous component, and a vestibule. It is separated from the right atrium by the septum.

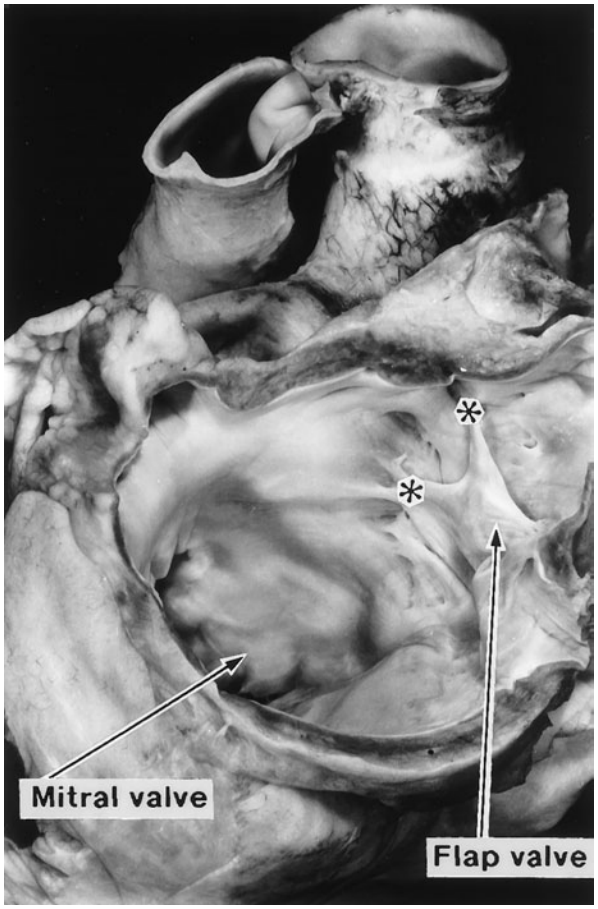

Figure 2-17. This view of the opened left atrium shows how the septal aspect is dominated by the flap valve, which is attached by its horns (*asterisks*) to the infolded atrial groove.

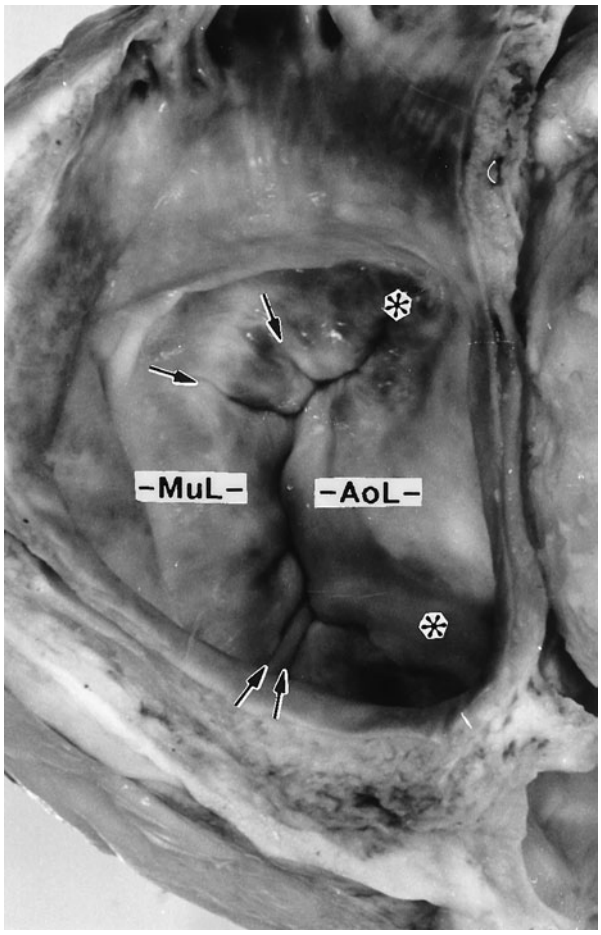

Figure 2-18. This view of the opened left atrium shows the leaflets of the mitral valve in closed position. There is a concave zone of apposition between them (*between asterisks*) with several slits seen in the mural leaflet (MuL). Note the limited extent of the aortic leaflet (AoL) in terms of its circumferential attachments.

through the dome of the left atrium. If the aorta is pulled anteriorly and to the left, an extensive trough may be seen between the right and left atrial appendages. An incision through this trough, between the pulmonary veins of the upper lobes, provides direct access to the left atrium. When this incision is made, it is important to remember the location of the sinus node artery, which may course along the roof of the left atrium if it arises from the circumflex artery. The left atrium also can be reached via a right atrial incision and an opening in the atrial septum.

When the interior of the left atrium is visualized, the small size of the mouth of the left atrial appendage is apparent. It lies to the left of the mitral orifice as viewed by the surgeon. The majority of the pulmonary venous atrium usually is located inferiorly away from the operative field. The vestibule of the mitral orifice dominates the operative view. The septal surface is located anteriorly, with the true septum relatively inferior (Fig. 2-17).

Mitral Valve

The mitral valve is supported by two prominent papillary muscles located in anterolateral and posteromedial positions. The two leaflets of the mitral valve have markedly different appearances (Fig. 2-18). The aortic (or anterior) leaflet is short, relatively square, and guards approximately one-third of the circumference of the valvar orifice. This leaflet is in fibrous continuity with the aortic valve and, because of this, is best referred to as the *aortic leaflet* because it is neither strictly anterior nor superior in position. The other leaflet is much shallower but guards approximately two-thirds of the circumference of the mitral orifice. Since it is connected to the parietal part of the atrioventricular junction, it is most accurately termed the *mural leaflet* but often is termed the *posterior leaflet.* It is divided into a number of subunits that fold against the aortic leaflet when the valve is closed. Although generally there are three, there may be as many as five or six scallops in the mural leaflet.

Unlike the tricuspid valve, the mitral valve leaflets are supported by a rather dense collagenous annulus, although it may take the form of a sheet rather than a cord. This annulus usually extends parietally from the fibrous trigones, the greatly thickened areas at either end of the area of

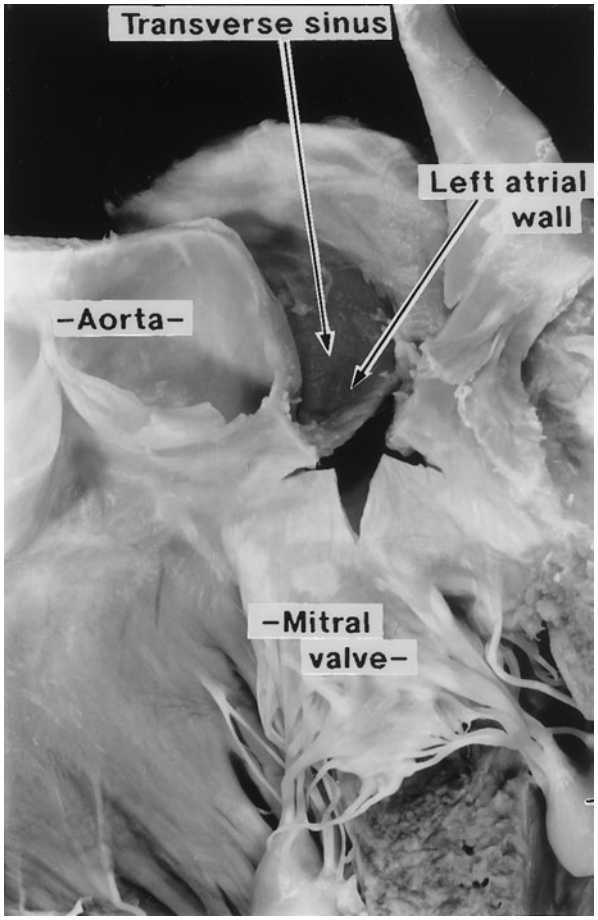

Figure 2-19. This dissection simulates the incision made through the aortic-mitral fibrous curtain to enlarge the orificial diameter of the subaortic outflow tract in a normal heart. (*Dissection made by Dr. Manisha Lal Trapasia.*)

fibrous continuity between the leaflets of the aortic and mitral valves (see Fig. 2-6). The area of the valvar orifice related to the right fibrous trigone and central fibrous body is most vulnerable with respect to the atrioventricular node and penetrating bundle (see Fig. 2-7). The midportion of the aortic leaflet of the mitral valve is related to the commissure between the noncoronary and left coronary cusps of the aortic valve. An incision through the atrial wall in this area may be extended into the subaortic outflow tract and may be useful for enlarging the aortic annulus during replacement of the aortic valve (Fig. 2-19). The circumflex coronary artery is adjacent to the left half of the mural leaflet, whereas the coronary sinus is adjacent to the right half of the mural leaflet (Fig. 2-20). These structures can be damaged during excessive dissection or by excessively deep placement of sutures during replacement or repair of the mitral valve. When the circumflex artery is dominant, the entire attachment of the mural leaflet may be intimately related to this artery (Fig. 2-21).

THE RIGHT VENTRICLE AND PULMONARY VALVE

Inlet and Apical Trabecular Portions

The morphology of both the right and left ventricles can be understood best by subdividing the ventricles into three anatomically distinct components: the inlet, apical trabecular, and outlet portions.[2] This classification is more helpful than the traditional division of the right ventricle into the sinus and conus parts. The inlet portion of the right ventricle surrounds the tricuspid valve and its tension apparatus. A distinguishing feature of the tricuspid valve is the direct attachment of its septal leaflet. The apical trabecular portion of the right ventricle extends out to the apex. Here, the wall of the ventricle is quite thin and vulnerable to perforation by cardiac catheters and pacemaker electrodes.

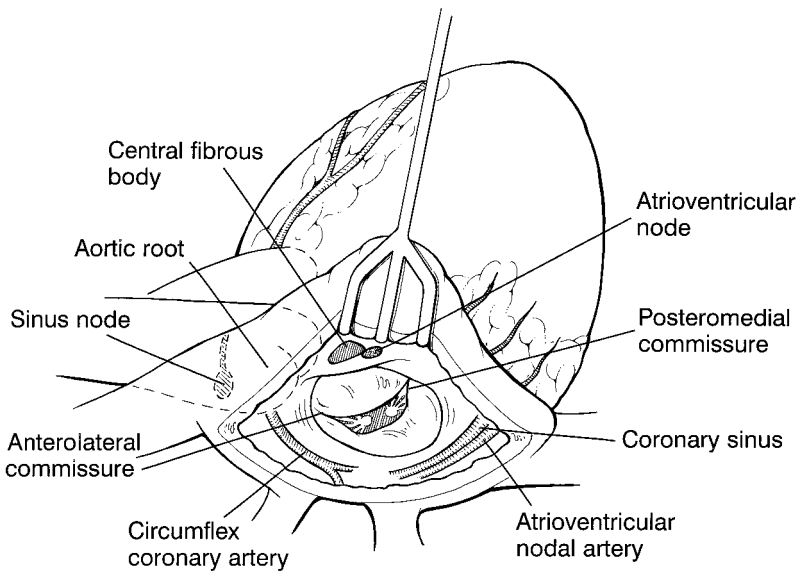

Figure 2-20. This diagram depicts the mitral valve in relationship to its surrounding structures as viewed through a left atriotomy.

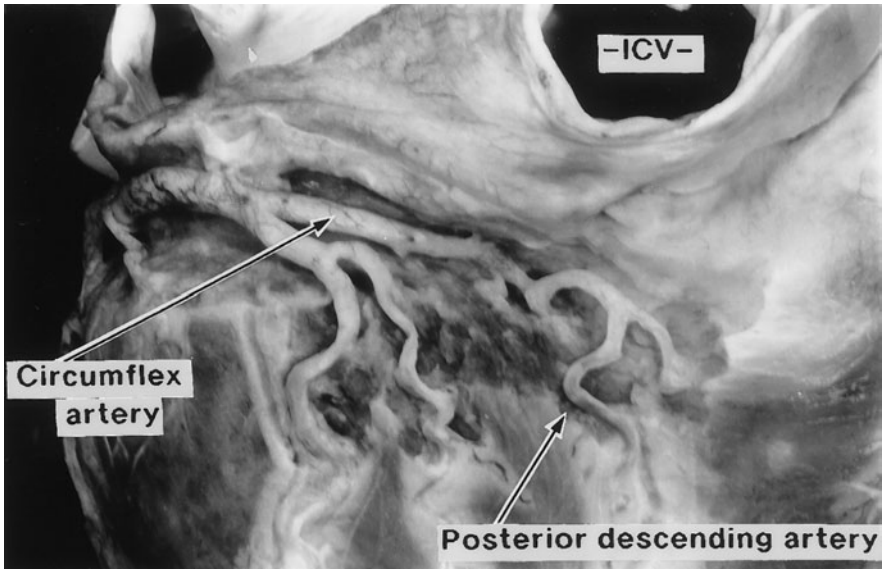

Figure 2-21. The extensive course of a dominant circumflex artery within the left atrioventricular groove shown in anatomic orientation. ICV = inferior vena cava.

Outlet Portion and Pulmonary Valve

The outlet portion of the right ventricle consists of the infundibulum, a circumferential muscular structure that supports the leaflets of the pulmonary valve. Because of the semilunar shape of the pulmonary valvar leaflets, this valve does not have an annulus in the traditional sense of a ringlike attachment. The leaflets have semilunar attachments that cross the musculoarterial junction in a corresponding semilunar fashion (Fig. 2-22). Therefore, instead of a single annulus, three rings can be distinguished anatomically in relation to the pulmonary valve. Superiorly, the sinotubular ridge of the pulmonary trunk marks the level of peripheral apposition of the leaflets (the commissures). A second ring exists at the ventriculoarterial junction. A third ring can be constructed by joining together the basal attachments of the three leaflets to the infundibular muscle. None of these rings, however, corresponds to the attachments of the leaflets, which must be semilunar to permit the valve to open and close competently. In fact, these semilunar attachments, which mark the hemodynamic ventriculoarterial junction, extend from the first ring, across the second, down to the third, and back in each cusp (Fig. 2-23).

Supraventricular Crest and Pulmonary Infundibulum

A distinguishing feature of the right ventricle is a prominent muscular shelf, the supraventricular crest, that separates the tricuspid and pulmonary valves (Fig. 2-24). In reality, this muscular ridge is the posterior part of the subpulmonary muscular infundibulum that supports the leaflets of the pulmonary valve. In other words, it is part of the inner curve of the heart. Incisions through the supraventricular crest run into the transverse septum and may jeopardize the right coronary artery. Although this area is often considered the outlet component of the interventricular septum, in fact, the entire subpulmonary infundibulum, including the ventriculoinfundibular fold, can be removed without entering the left ventricular cavity. This is possible because the leaflets of the pulmonary and aortic valves are supported on separate sleeves of right and left ventricular outlet muscle. There is an extensive external tissue plane between the walls of the aorta and the pulmonary trunk (Fig. 2-25), and the leaflets of the pulmonary and aortic valves have markedly different levels of attachments within their respective ventricles. This feature

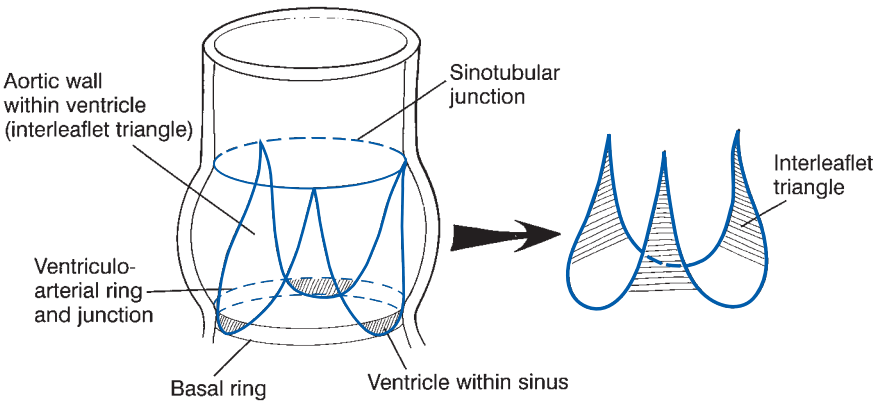

Figure 2-22. The semilunar valves do not have an annulus in the traditional sense. Rather, three rings can be identified anatomically: (1) at the sinotubular junction, (2) at the musculoarterial junction, and (3) at the base of the sinuses within the ventricle.

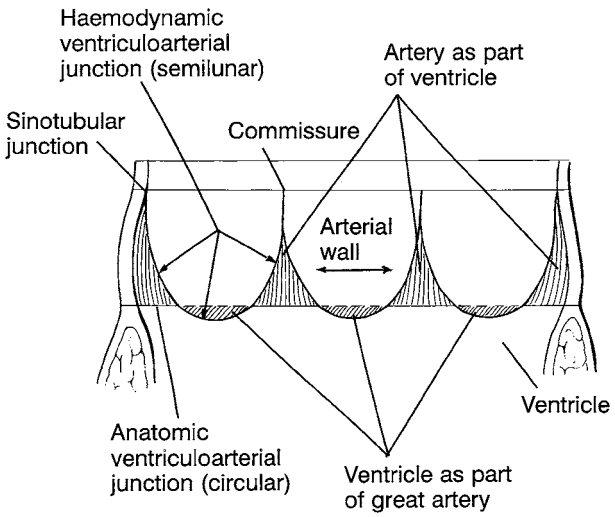

Figure 2-23. The hemodynamic ventriculoarterial junction of the semilunar valves extends from the sinotubular junction across the anatomic ventriculoarterial junction to the basal ring and back in each leaflet (see Fig. 2-22). This creates a portion of ventricle as part of the great artery in each sinus and a triangle of artery as part of the ventricle between each leaflet.

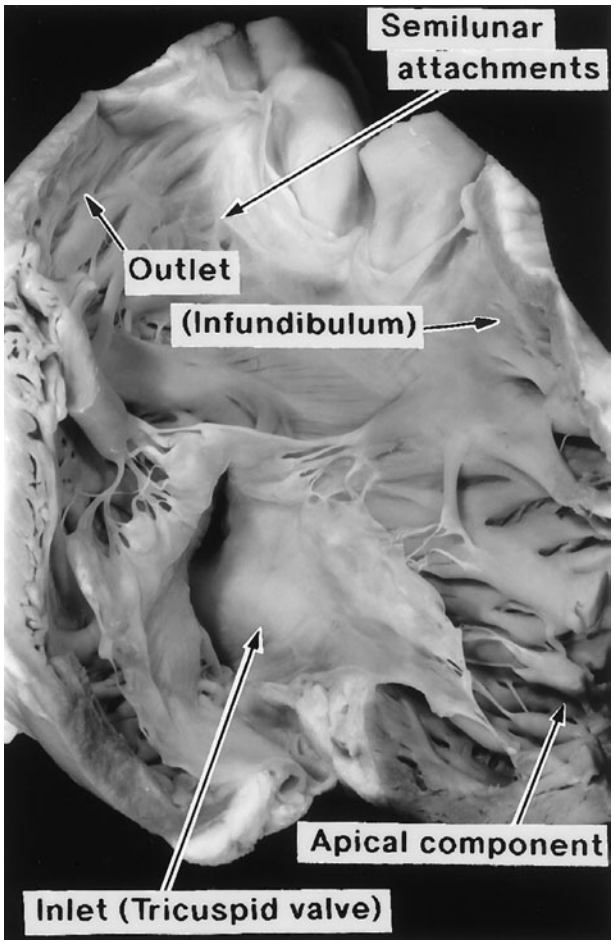

Figure 2-24. View of the opened right ventricle, in anatomic orientation, showing its three component parts and the semilunar attachments of the pulmonary valve. These are supported by the supraventricular crest.

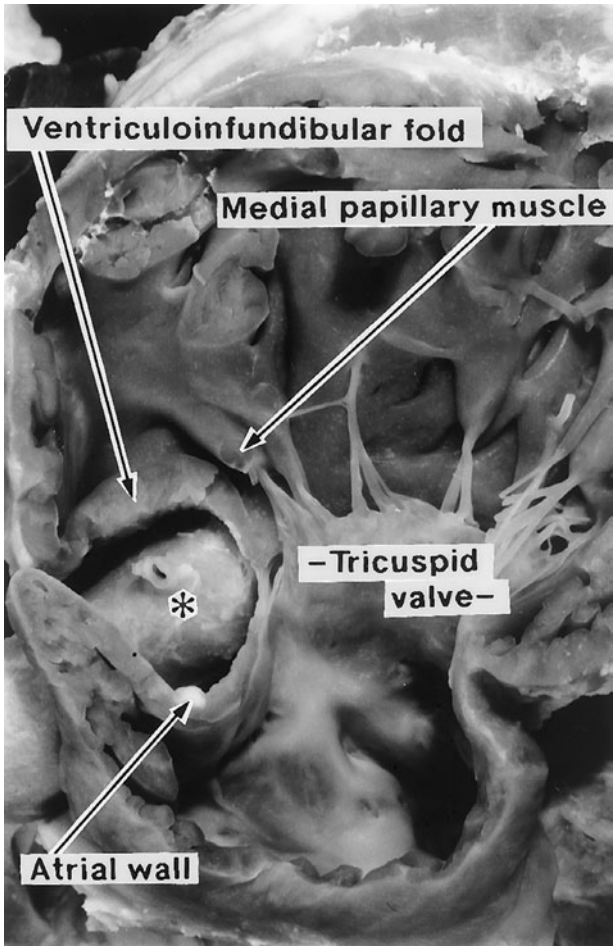

Figure 2-25. This dissection, viewed in surgical orientation, shows how the greater part of the supraventricular crest is formed by the freestanding subpulmonary infundibulum in relation to the right coronary aortic sinus (*asterisk*).

enables enucleation of the pulmonary valve, including its basal attachments within the infundibulum, during the Ross procedure without creating a ventricular septal defect. When the infundibulum is removed from the right ventricle, the insertion of the supraventricular crest between the limbs of the septomarginal trabeculation is visible (Fig. 2-26). This trabeculation is a prominent muscle column that divides superiorly into anterior and posterior limbs. The anterior limb runs superiorly into the infundibulum and supports the leaflets of the pulmonary valve. The posterior limb extends backwards beneath the ventricular septum and runs into the inlet portion of the ventricle. The medial papillary muscle arises from this posterior limb. The body of the septomarginal trabeculation runs to the apex of the ventricle, where it divides into smaller trabeculations. Two of these trabeculations may be particularly prominent. One becomes the anterior papillary muscle, and the other crosses the ventricular cavity as the moderator band (Fig. 2-27).

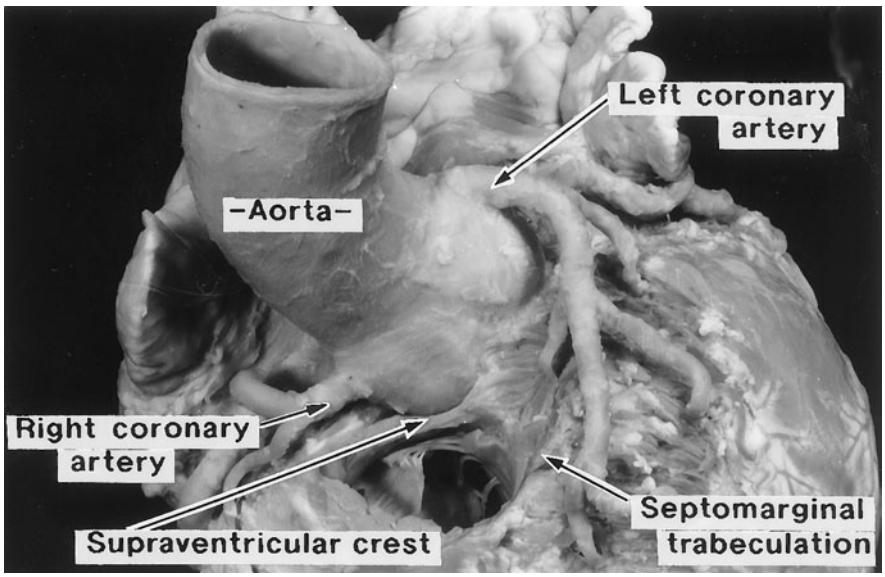

Figure 2-26. Removal of the freestanding subpulmonary infundibulum reveals the insertion of the supraventricular crest between the limbs of the septomarginal trabeculation and shows the aortic origin of the coronary arteries (anatomic orientation).

THE LEFT VENTRICLE AND AORTIC VALVE

Inlet and Apical Trabecular Portions

The left ventricle can be subdivided into three components, similar to the right ventricle. The inlet component surrounds and is limited by the mitral valve and its tension apparatus. The two papillary muscles occupy anterolateral and posteromedial positions and are positioned rather close to each other. The leaflets of the mitral valve have no direct septal attachments because the deep posterior diverticulum of the left ventricular outflow tract displaces the aortic leaflet away from the inlet septum. The apical trabecular component of the left ventricle extends to the apex, where the myocardium is surprisingly thin. The trabeculations of the left ventricle are quite fine compared with those of the right ventricle (Fig. 2-28). This characteristic is useful for defining ventricular morphology on diagnostic ventriculograms.

Outlet Portion

The outlet component supports the aortic valve and consists of both muscular and fibrous portions. This is in contrast to the infundibulum of the right ventricle, which consists entirely of muscle. The septal portion of the left ventricular outflow tract, although primarily muscular, also includes the membranous portion of the ventricular septum. The posterior quadrant of the outflow tract consists of an extensive fibrous curtain that extends from the fibrous skeleton of the heart across the aortic leaflet of the mitral valve and supports the leaflets of the aortic valve in the area of aortomitral continuity (see Fig. 2-5). The lateral quadrant of the outflow tract again is

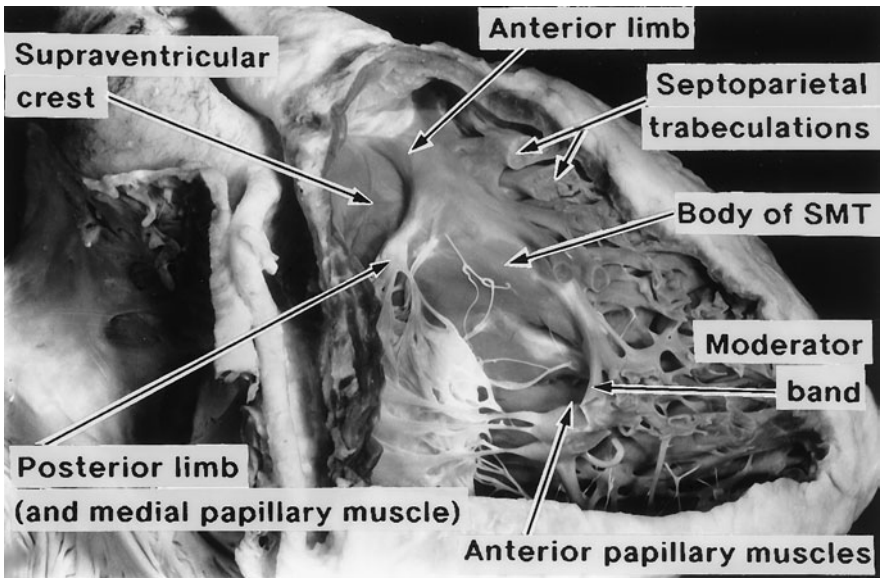

Figure 2-27. This dissection of the right ventricle, in anatomic orientation, shows the relations of supraventricular crest and septomarginal (SMT) and septoparietal trabeculations.

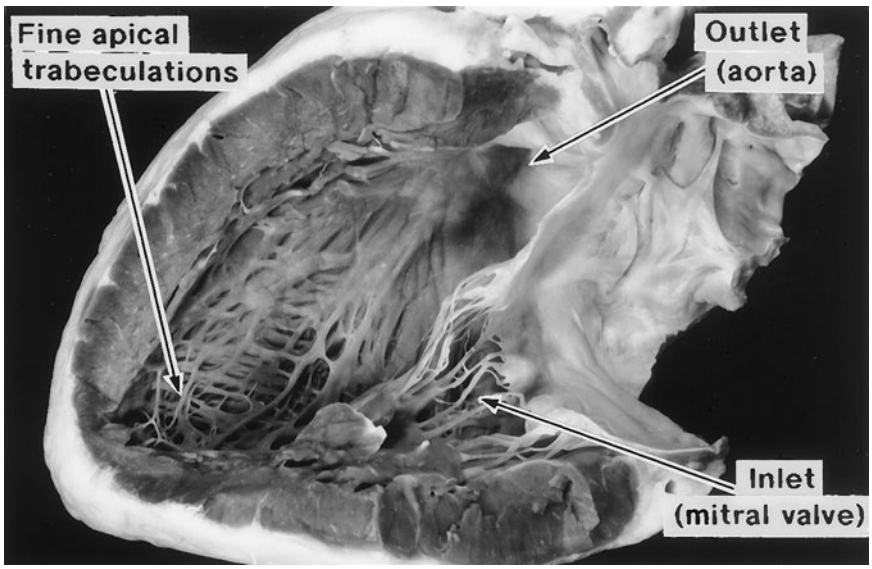

Figure 2-28. This dissection of the left ventricle shows its component parts and characteristically fine apical trabeculations (anatomic orientation).

muscular and consists of the lateral margin of the inner curvature of the heart, delineated externally by the transverse sinus. The left bundle of the cardiac conduction system enters the left ventricular outflow tract posterior to the membranous septum and immediately beneath the commissure between the right and noncoronary leaflets of the aortic valve. After traveling a short distance down the septum, the left bundle divides into anterior, septal, and posterior divisions.

Aortic Valve

The aortic valve is a semilunar valve that is quite similar morphologically to the pulmonary valve. Likewise, it does not have a discrete annulus. Because of its central location, the aortic valve is related to each of the cardiac chambers and valves (see Fig. 2-4). A thorough knowledge of these relationships is essential to understanding aortic valve pathology and many congenital cardiac malformations.

The aortic valve consists primarily of three semilunar leaflets. As with the pulmonary valve, attachments of the leaflets extend across the ventriculoarterial junction in a curvilinear fashion. Each leaflet therefore has attachments to the aorta and within the left ventricle (Fig. 2-29). Behind each leaflet, the aortic wall bulges outward to form the sinuses of Valsalva. The leaflets themselves meet centrally along a line of coaptation, at the center of which is a thickened nodule called the *nodule of Arantius.* Peripherally, adjacent to the commissures, the line of coaptation is thinner and normally may contain small perforations. During systole, the leaflets are thrust upward and away from the center of the aortic lumen, whereas during diastole, they fall passively into the center of the aorta. With normal valvar morphology, all three leaflets meet along lines of coaptation and support the column of blood within the aorta to prevent regurgitation into the ventricle. Two of the three aortic sinuses give rise to coronary arteries, from which arise their designations as *right, left,* and *noncoronary sinuses.*

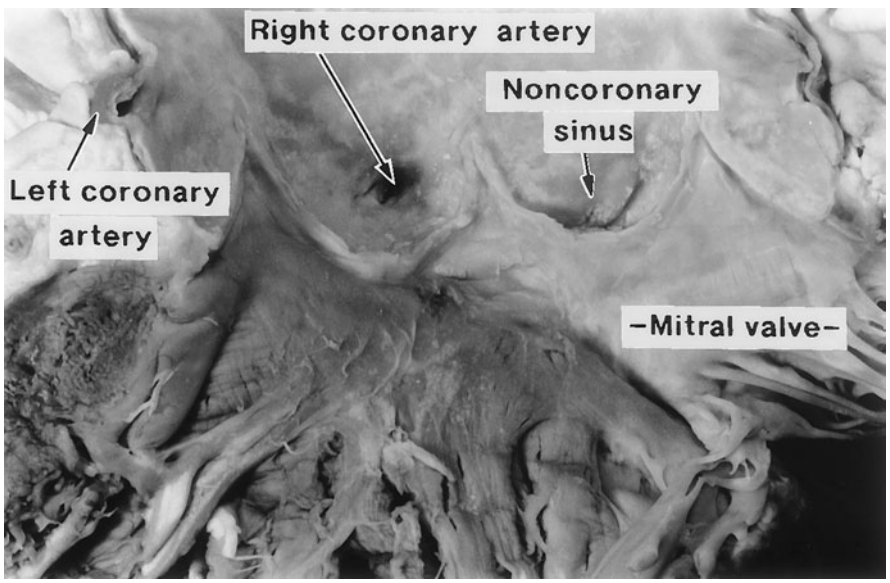

Figure 2-29. This dissection in anatomic orientation, made by removing the aortic valvar leaflets, emphasizes the semilunar nature of the hinge points (see Figs. 2-22 and 2-23). Note the relationship to the mitral valve (see Fig. 2-5).

By sequentially following the line of attachment of each leaflet, the relationship of the aortic valve to its surrounding structures can be clearly understood. Beginning posteriorly, the commissure between the noncoronary and left coronary leaflets is positioned along the area of aortomitral valvar continuity. The fibrous subaortic curtain is beneath this commissure (see Fig. 2-29). To the right of this commissure, the noncoronary leaflet is attached above the posterior diverticulum of the left ventricular outflow tract. Here, the valve is related to the right atrial wall. As the attachment of the noncoronary leaflet ascends from its nadir toward the commissure between the noncoronary and right coronary leaflets, the line of attachment is directly above the portion of the atrial septum containing the atrioventricular node. The commissure between the noncoronary and right coronary leaflets is located directly above the penetrating atrioventricular bundle and the membranous ventricular septum (Fig. 2-30). The attachment of the right coronary leaflet then descends across the central fibrous body before ascending to the commissure between the right and left coronary leaflets. Immediately beneath this commissure, the wall of the aorta forms the uppermost part of the subaortic outflow. An incision through this area passes into the space between the facing surfaces of the aorta and pulmonary trunk (see Fig. 2-30). As the facing left and right leaflets descend from this commissure, they are attached to the outlet muscular component of the left ventricle. Only a small part of this area in the normal heart is a true outlet septum because both pulmonary and aortic valves are supported on their own sleeves of myocardium. Thus, although the outlet components of the right and left ventricle face each other, an incision below the aortic valve enters low into the infundibulum of the right ventricle. As the lateral part of the left coronary leaflet descends from the facing commissure to the base of the sinus, it becomes the only part of the aortic valve that is not intimately related to another cardiac chamber.

Knowledge of the anatomy of the aortic valve and its relationship to surrounding structures is important to successful replacement of the aortic valve, particularly when enlargement of the aortic root is required. The Konno-Rastan aortoventriculoplasty involves opening and enlarging the anterior portion of the subaortic region.[4,5] The incisions for this procedure begin with an anterior longitudinal aortotomy that extends through the commissure between the right and left coronary leaflets. Anteriorly, the incision is extended across the base of the infundibulum. The differential level of attachment of the aortic and pulmonary valve leaflets permits this incision without damage to the pulmonary valve (Fig. 2-31). Posteriorly, the incision extends through the most medial portion of the supraventricular crest into the left ventricular outflow tract. By closing the resulting ventricular septal defect with a patch, the aortic outflow tract is widened to allow implantation of a larger valve prosthesis. A second patch is used to close the defect in the right ventricular outflow tract.

Alternative methods to enlarge the aortic outflow tract involve incisions in the region of aortomitral continuity. In the Manouguian procedure (see Fig. 2-19), a curvilinear aortotomy is extended posteriorly through the commissure between the left and noncoronary leaflets down to and occasionally into the aortic leaflet of the mitral valve.[6] A patch is used to augment the incision posteriorly. When the posterior diverticulum of the outflow tract is fully developed, this incision can be made without entering other cardiac chambers, although not uncommonly the roof of the left atrium is opened. The Nicks procedure for enlargement of the aortic root involves an aortotomy that passes through the middle of the noncoronary leaflet into the fibrous subaortic curtain and may be extended into the aortic leaflet of the mitral valve.[7] This incision also may open the roof of the left atrium. When these techniques are used, any resulting defect in the left atrium must be closed carefully.

As discussed previously, the differential level of attachment of aortic and pulmonary valves, as well as the muscular nature of their support, allows the pulmonary valve to be harvested and used as a replacement for the aortic valve in the Ross procedure.[8,9] This procedure can be combined with the incisions of the Konno-Rastan aortoventriculoplasty to

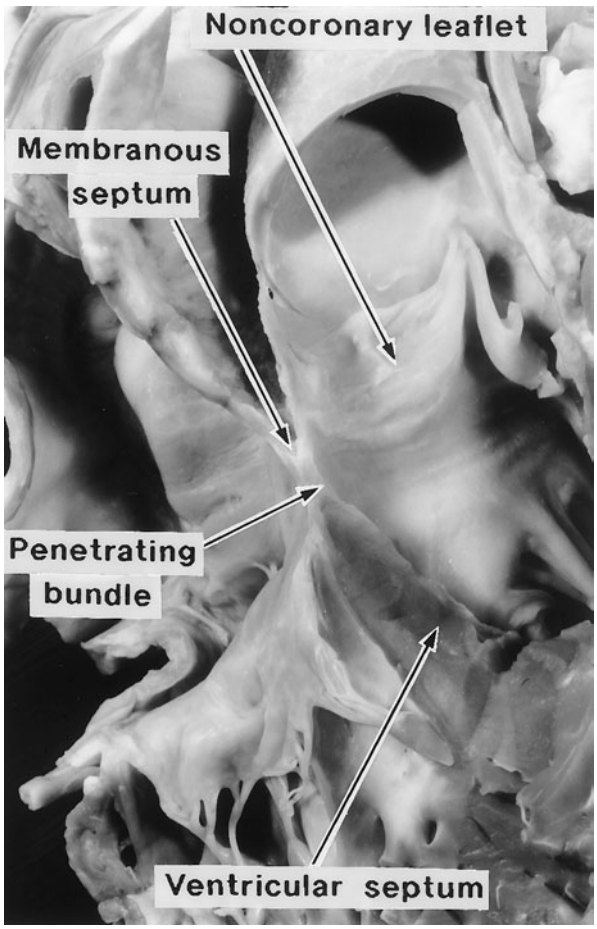

Figure 2-30. Dissection made by removing the right and part of the left aortic sinuses to show the relations of the fibrous triangle between the right and noncoronary aortic leaflets (anatomic orientation).

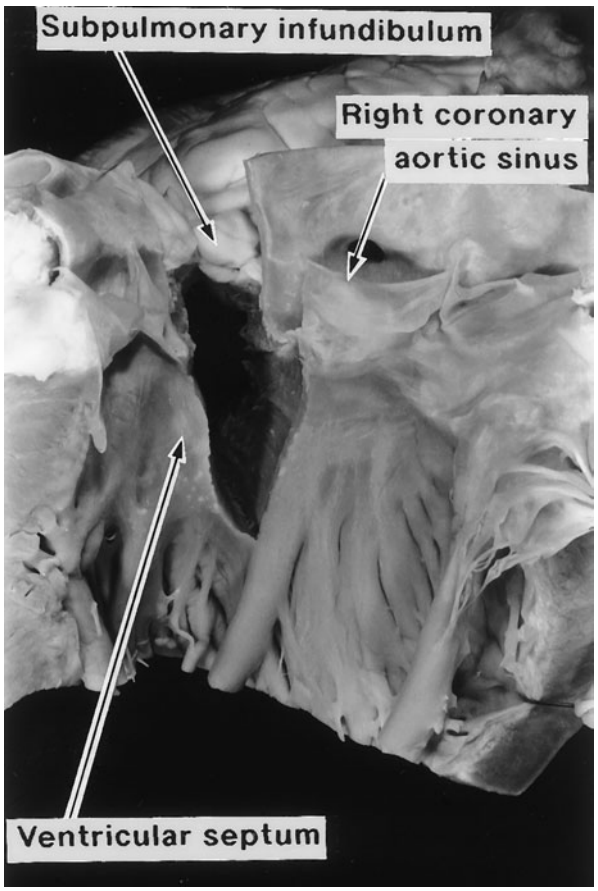

Figure 2-31. This incision, made in a normal heart, simulates the Konno-Rastan procedure for enlargement of the aortic root.

repair left ventricular outflow tract obstructions in young children with a viable autograft that has potential for growth and avoids the need for anticoagulation.

Accurate understanding of left ventricular outflow tract anatomy is also important in the treatment of aortic valvar endocarditis.[10,11] Because of the central position of the aortic valve relative to the other valves and cardiac chambers (see Fig. 2-4), abscess formation can produce fistulas between the aorta and any of the four chambers of the heart. Patients therefore may present with findings of left-sided heart failure, left-to-right shunting, and/or complete heart block in addition to the usual signs of sepsis and systemic embolization.

THE CORONARY ARTERIES[12–14]

The right and left coronary arteries originate behind their respective aortic valvar leaflets (see Fig. 2-26). The orifices usually are located in the upper third of the sinuses of Valsalva, although individual hearts may vary markedly. Because of the oblique plane of the aortic valve, the orifice of the left coronary artery is superior and posterior to that of the right coronary artery. The coronary arterial tree is divided into three segments; two (the left anterior descending artery and the circumflex artery) arise from a common stem. The third segment is the right coronary artery. The dominance of the coronary circulation (right versus left) usually refers to the artery from which the posterior descending artery originates, not the absolute mass of myocardium perfused by the left or right coronary artery. Right dominance occurs in 85 to 90% of normal individuals. Left dominance occurs slightly more frequently in males than in females.

Main Stem of the Left Coronary Artery

The main stem of the left coronary artery courses from the left sinus of Valsalva anteriorly, inferiorly and to the left between the pulmonary trunk and the left atrial appendage (Fig. 2-32). Typically, it is 10 to 20 mm in length but can extend to a length of 40 mm. The left main stem can be absent, with separate orifices in the sinus of Valsalva for its two primary branches (1% of patients). The main stem

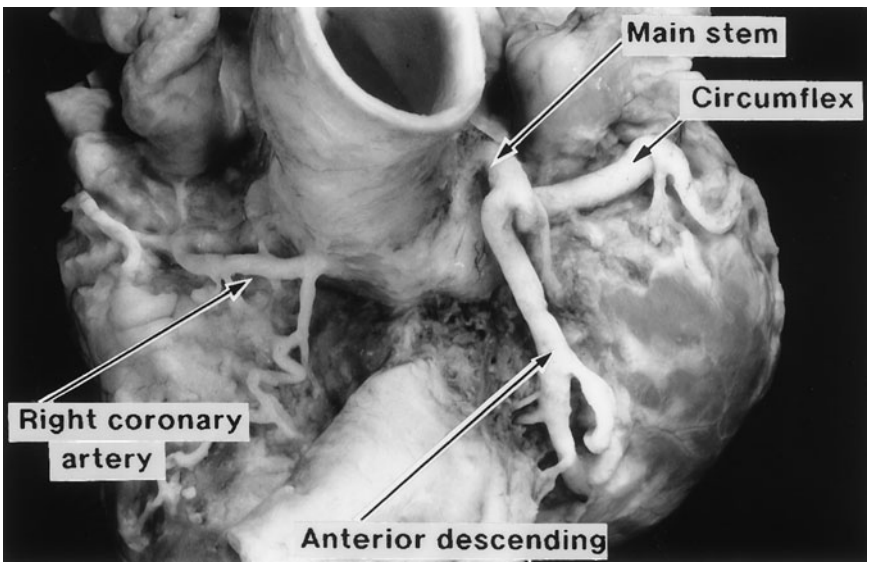

Figure 2-32. The short extent of the main stem of the left coronary artery is seen before it branches into the circumflex and anterior descending arteries. Note the small right coronary artery in this heart, in which the circumflex artery was dominant (see Fig. 2-21).

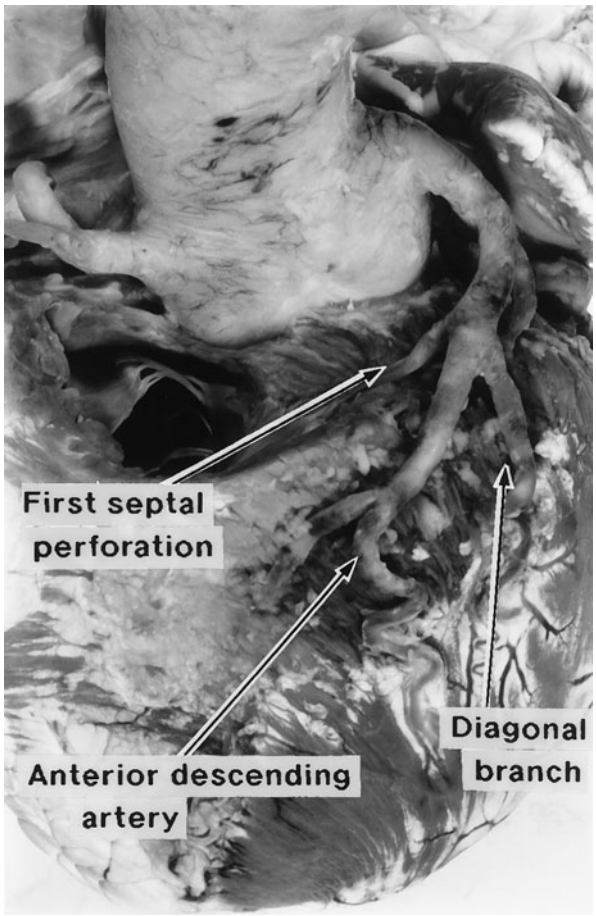

Figure 2-33. The important branches of the anterior descending artery are the first septal perforating and diagonal arteries.

divides into two major arteries of nearly equal diameter: the left anterior descending artery and the circumflex artery.

Left Anterior Descending Artery

The left anterior descending (or interventricular) coronary artery continues directly from the bifurcation of the left main stem, coursing anteriorly and inferiorly in the anterior interventricular groove to the apex of the heart (Fig. 2-33). Its branches include the diagonals, the septal perforators, and the right ventricular branches. The diagonals, which may be two to six in number, course along the anterolateral wall of the left ventricle and supply this portion of the myocardium. The first diagonal generally is the largest and may arise from the bifurcation of the left main stem (formerly known as the *intermediate artery*). The septal perforators branch perpendicularly into the ventricular septum. Typically, there are three to five septal perforators; the initial one is the largest and commonly originates just beyond the takeoff of the first diagonal. This perpendicular orientation is a useful marker for identification of the left anterior descending artery on coronary angiograms. The septal perforators supply blood to the anterior two-thirds of the ventricular septum. Right ventricular branches, which may not always be present, supply blood to the anterior surface of the right ventricle. In approximately 4% of hearts, the left anterior descending artery bifurcates proximally and continues as two parallel vessels of approximately equal size down the anterior interventricular groove. Occasionally, the artery wraps around the apex of the left ventricle to feed the distal portion of the posterior interventricular groove. Rarely, it extends along the entire length of the posterior groove to replace the posterior descending artery.

Circumflex Artery

The left circumflex coronary artery arises from the left main coronary artery roughly at a right angle to the anterior interventricular branch. It courses along the left atrioventricular groove and in 85 to 95% of patients terminates near the obtuse margin of the left ventricle (Fig. 2-34). In 10 to 15% of patients, it continues around the atrioventricular groove to the crux of the heart to give rise to the posterior descending artery (left dominance; see Fig. 2-21). The primary branches of the left circumflex coronary artery are the obtuse marginals. They supply blood to the lateral aspect of the left ventricular myocardium,

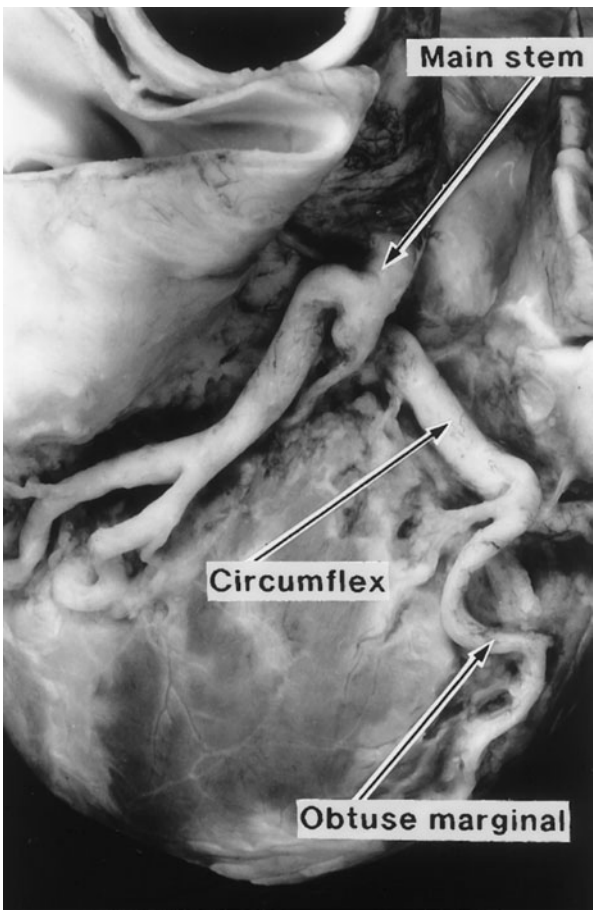

Figure 2-34. The important branches of the circumflex artery, seen in anatomic orientation.

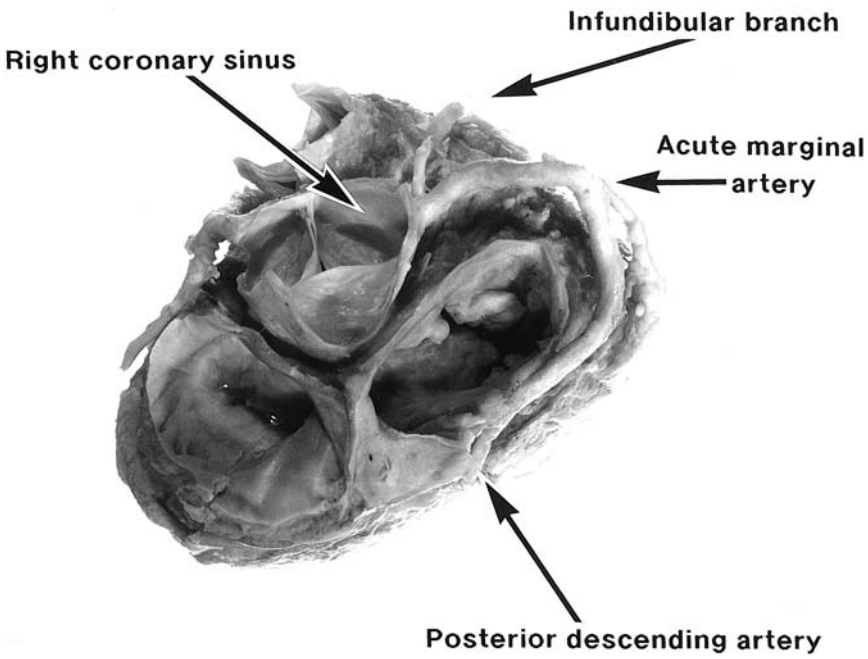

Figure 2-35. This dissection shows the relationships and branches of the right coronary artery.

including the posteromedial papillary muscle. Additional branches supply blood to the left atrium and, in 40 to 50% of hearts, the sinus node. When the circumflex coronary artery supplies the posterior descending artery, it also supplies the atrioventricular node.

Right Coronary Artery

The right coronary artery courses from the aorta anteriorly and laterally before descending in the right atrioventricular groove and curving posteriorly at the acute margin of the right ventricle (Fig. 2-35). In 85 to 90% of hearts, the right coronary artery crosses the crux, where it makes a characteristic U-turn before bifurcating into the posterior descending artery and the right posterolateral artery. In 50 to 60% of hearts, the artery to the sinus node arises from the proximal portion of the right coronary artery. The blood supply to the atrioventricular node (in patients with right-dominant circulation) arises from the midportion of the U-shaped segment. The posterior descending artery runs along the posterior interventricular groove, extending for a variable distance toward the apex of the heart. It gives off perpendicular branches, the posterior septal perforators, that course anteriorly in the ventricular septum. Typically, these perforators supply the posterior one-third of the ventricular septal myocardium.

The right posterolateral artery gives rise to a variable number of branches that supply the posterior surface of the left ventricle. The circulation of the posteroinferior portion of the left ventricular myocardium is quite variable. It may consist of branches of the right coronary artery, the circumflex artery, or both. The acute marginal arteries branch from the right coronary artery along the acute margin of the heart, before its bifurcation at the crux. These marginals supply the anterior free wall of the right ventricle. In 10 to 20% of hearts, one of these acute marginal arteries courses across the diaphragmatic surface of the right ventricle to reach the distal ventricular septum. The right coronary artery supplies important collaterals to the left anterior descending artery through its septal perforators. In addition, its infundibular (or conus) branch, which arises from the proximal portion of the right coronary artery, courses anteriorly over the base of the ventricular infundibulum and may serve as a collateral to the anterior descending artery. Kugel's artery is an anastomotic vessel between the proximal right coronary and the circumflex coronary artery that also can provide a branch that runs through the base of the atrial septum to the crux of the heart, where it supplies collateral circulation to the atrioventricular node.[15]

THE CORONARY VEINS[14]

A complex network of veins drains the coronary circulation. An extensive degree of collateralization among these veins and the coronary arteries and the paucity of valves within coronary veins enable the use of retrograde coronary sinus cardioplegia for intraoperative myocardial protection. The venous circulation can be divided into three systems: the coronary sinus and its tributaries, the anterior right ventricular veins, and the thebesian veins.

Coronary Sinus and Its Tributaries

The coronary sinus predominantly drains the left ventricle and receives approximately 85% of coronary venous blood. It lies within the posterior atrioventricular groove and empties into the right atrium at the lateral border of

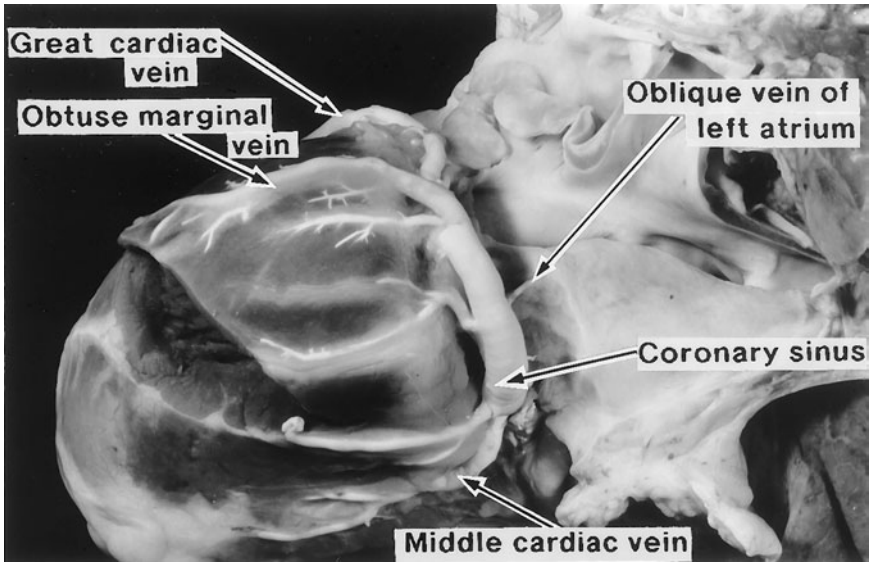

Figure 2-36. The coronary veins on the diaphragmatic surface of the heart, seen in anatomic orientation, have been emphasized by filling them with sealant. The tributaries of the coronary sinus are well demonstrated. Note that, strictly speaking, the sinus does not begin until the oblique vein enters the great cardiac vein.

the triangle of Koch (Fig. 2-36). The orifice of the coronary sinus is guarded by the crescent-shaped thebesian valve. The named tributaries of the coronary sinus include the anterior interventricular vein, which courses parallel to the left anterior descending coronary artery. Adjacent to the bifurcation of the left main stem, the anterior interventricular vein courses leftward in the atrioventricular groove, where it is referred to as the *great cardiac vein*. It receives blood from the marginal and posterior left ventricular branches before becoming the coronary sinus at the origin of the oblique vein (of Marshall) at the posterior margin of the left atrium. The posterior interventricular vein, or *middle cardiac vein,* arises at the apex, courses parallel to the posterior descending coronary artery and extends proximally to the crux. Here, this vein drains either directly into the right atrium or into the coronary sinus just prior to its orifice. The *small cardiac vein* runs posteriorly through the right atrioventricular groove.

Anterior Right Ventricular Veins

The anterior right ventricular veins travel across the right ventricular surface to the right atrioventricular groove, where they either enter directly into the right atrium or coalesce to form the small cardiac vein. As indicated, this vein travels down the right atrioventricular groove, around the acute margin, and enters into the right atrium directly or joins the coronary sinus just proximal to its orifice.

Thebesian Veins

The thebesian veins are small venous tributaries that drain directly into the cardiac chambers. They exist primarily in the right atrium and right ventricle.

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CHAPTER 3

Cardiac Surgical Physiology

Edward B. Savage • R. Saeid Farivar • Eric J. Okum

An open cardiac surgical procedure is the most acute application of basic dynamic physiology (principles learned as a medical student) that exists in medical care. Basic physiologic concepts of electromechanical activation and association, loading conditions, inotropy, etc. all have an impact on achievement of a successful outcome. Working knowledge of these fundamental concepts is imperative to maintain and return a patient to normal function. The purpose of this chapter is to present a manageable, working outline of cardiac physiology that can be used in daily practice as a framework against which pathologic processes can be measured, assessed, and treated.

CELLULAR COMPONENTS AND CELLULAR ACTIVATION

The heart beats continuously based on the unique features of its component cells. A cardiac cycle begins when spontaneous depolarization of a pacemaker cell initiates an action potential; this electrical activity is transmitted to atrial muscle cells, which contract, and to the conduction system, which transmits the electrical activity to the ventricle. Activation depends on components of the cell membrane and cell that induce and maintain the ion currents that maintain and promote electrical activation.

Similar to most excitable cells in the body, the activity of cells in the heart is triggered by an *action potential.* An action potential is a cyclic activation of a cell consisting of a rapid change in the membrane potential (the electrical gradient across the cell membrane) and subsequent return to a resting membrane potential. This process depends on a selectively permeable cell membrane and proteins that actively and passively direct ion passage across the cell membrane. The specific components of the myocyte action potential are detailed in Fig. 3-3. The myocyte action potential is characterized by a rapid initial depolarization mediated by *fast channels* (sodium channels) and then a plateau phase mediated by *slow channels* (calcium channels). Further details of this process are introduced as their components are described.

The Sarcolemma

The cardiac cell is surrounded by a membrane (*plasmalemma,* or more specific to a muscle cell, *sarcolemma*). The structural components of the sarcolemma allow for the origination and then conduction of an electrical signal through the heart with subsequent initiation of the *excitation-contraction coupling process.* This leads to depolarization of atrial myocytes and, with an appropriate delay, depolarization of ventricular myocytes. The sarcolemma also participates in the regulation of excitation, contraction, and intracellular metabolism in response to neuronal and chemical stimulation. Each of these functions will be considered, with emphasis on the features of the cardiac sarcolemma that differ from the plasmalemma of other cells.

The Phospholipid Bilayer

A *phospholipid bilayer* provides a barrier between the extracellular compartment and the intracellular compartment, or *cytosol.* It is only two molecules thick, consists of phospholipids and cholesterol aligned so that the lipid, or hydrophobic, portion of the molecule is on the inside of the membrane, and the hydrophilic portion of the molecule is on the outside (Fig. 3-1). The sarcolemma which is a phospholipid bilayer, provides a fluid barrier that is particularly *impermeable to diffusion of ions.* Small lipid-soluble molecules such as oxygen and carbon dioxide diffuse easily through the membrane. The water molecule, although insoluble in the membrane, is small enough that it diffuses easily through the membrane (or through pores in the membrane). Other, slightly larger molecules (e.g., sodium, chloride, potassium, and calcium) cannot diffuse easily through the lipid bilayer and require specialized channels for transport.[1–3]

The specialized ion-transport systems within the sarcolemma consist of *membrane-spanning proteins* that

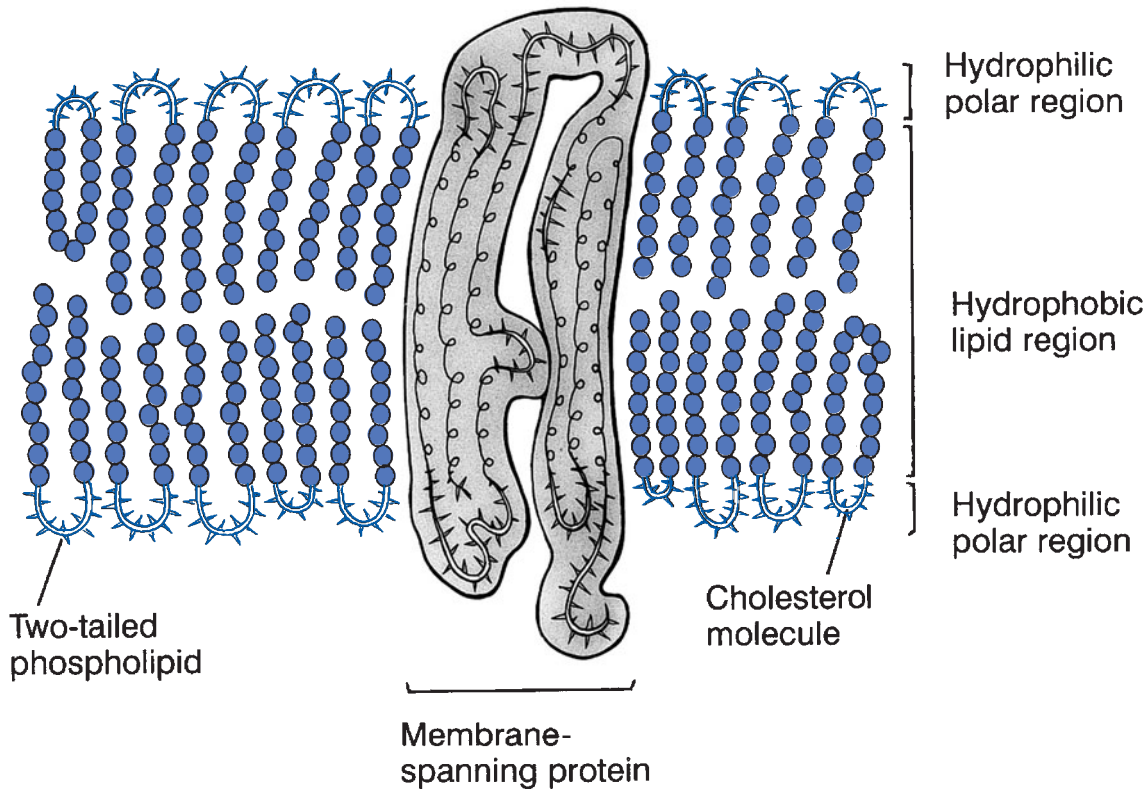

Figure 3-1. The sarcolemma is a bilayer in which phospholipid and cholesterol molecules are arranged with hydrophobic domains within the membrane and hydrophilic domains facing outward. The membrane-spanning protein shown here is similar to many ion channels, with six hydrophobic alpha-helices spanning the membrane and surrounding a central channel.

float in and penetrate through the lipid bilayer. These proteins are associated with three different types of ion transport: (1) *diffusion* through transmembrane channels that can be opened or closed (gated) in response to electrical (*voltage-gated*) or chemical (*ligand-gated*) stimuli, (2) *exchange* of one ion for another with binding of these ions to portions of the transmembrane protein for exchange in response to an electrochemical gradient, and (3) *active (energy-dependent) transport* of ions against an electrochemical gradient.

Other proteins located in the sarcolemma serve as *receptors* for neuronal or chemical control of cellular processes (e.g., beta-adrenergic receptors and muscarinic acetylcholine receptors).

Sarcolemmal channels

Most of the voltage-gated channels consist of tetramers of four subunits that surround the water-filled pore through which ions cross the membrane. A schematic diagram of an ion channel is shown in Fig. 3-2. Each channel contains a *selectivity filter* that selectively allows the passage of particular ions based on pore size and electric charge and an *activation gate* that is regulated by conformational changes induced by either a voltage-sensitive or a ligand-binding region of the protein. Many channels also have an *inactivation gate* that is also controlled either by voltage or by ligands.[1,2,4]

Voltage-gated sodium channels

The voltage-gated sodium channel is prominent in most electrically excitable muscle and nerve cells. Energy-dependent pumps and other ions create a large concentration gradient of sodium (142 mEq/L outside the cell, 10 mEq/L inside the cell) and a large electrical gradient (–70 to –90 mV outside to inside) across the cell membrane. Both the concentration gradient and the electrical force favor the influx of sodium. This influx of positive ions is termed an *inward current.* The inward current of positive sodium ions begins to depolarize (reduce the electrical gradient across) the sarcolemmal membrane. When the membrane potential is raised to between −70 and −50 mV, the activation gate of the sodium channel opens. Once open, sodium ions rapidly rush into the cell, depolarizing the sarcolemmal membrane. The inactivation gate of the sodium channel begins to close at about the same voltage, but with a built-in time delay such that the sodium channel is open for only a few milliseconds. Because these channels open and close so quickly, they have been called *fast channels.* The inactivation gate of the sodium channel remains closed until the cell is repolarized; the resting negative membrane potential of −70 to −90 mV is restored.[5–7]

Voltage-gated calcium channels

There are two important populations of calcium channels. The *type T (transient) calcium channels* open as the membrane potential rises to –60 to –50 mV and then close quickly

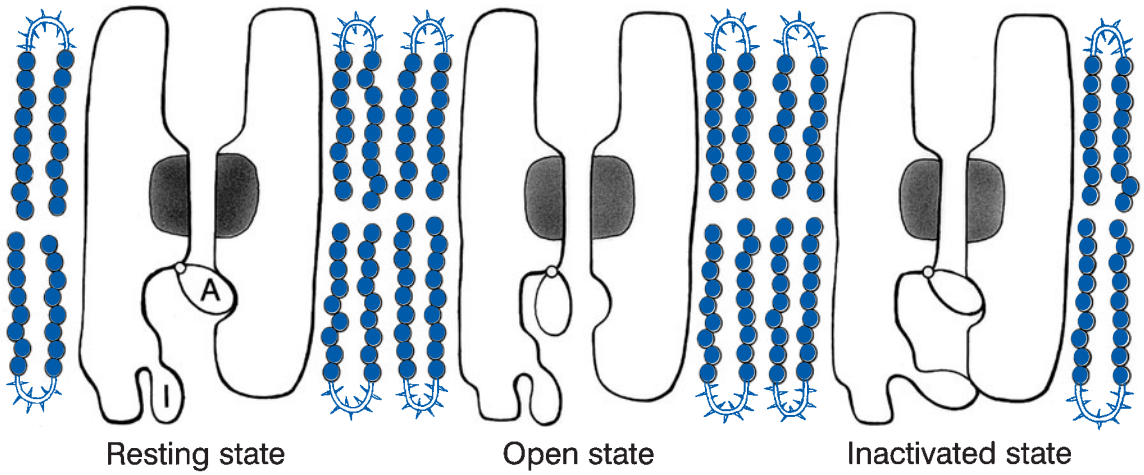

Figure 3-2. A voltage-gated sodium channel is depicted schematically. The shaded region is the selectivity filter. *A* represents the activation gate, and *I* represents the inactivation gate. At rest, the inactivation gate is open, and the activation gate is closed. As the transmembrane potential rises from –80 to –60 mV, the activation gate opens, and sodium ions pass through the channel. Within a few milliseconds, the inactivation gate closes. Once the cell repolarizes, the resting ion channel returns to the resting state.

by action of an inactivation gate. These type T calcium channels are important in early depolarization, especially in atrial pacemaker cells, but they contribute little to the sustained depolarization of the plateau of the action potential and have much less activity in the ventricles.

The second major calcium channel, the *type L (long-lasting) channel,* a *slow channel,* leads to an inward (depolarizing) current that is slowly inactivated and therefore prolonged. These channels open at a less negative potential (–30 to –20 mV). Once open, the slow inactivation allows an inward calcium current (Fig. 3-3) that sustains the action potential. In addition, this increase in cytosolic calcium begins the excitation-contraction sequence. Activity of this channel is altered by catecholamine stimulation. Beta-receptor stimulation induces conformational changes resulting in an increased influx of calcium ions and an associated increase in the strength of sarcomere contraction. This effect is attenuated by stimulation of acetylcholine and adenosine receptors.[8,9]

Potassium channels

A number of potassium channels, both voltage- and ligand-gated, are present in cardiac cells. Three voltage-gated potassium channels moderate the *delayed rectifier current* that repolarizes the cell membrane[10,11] (Fig. 3-3).

Several ligand-gated potassium channels have been identified. *Acetylcholine-* and *adenosine-activated* potassium channels are time-independent and lead to hyperpolarization in pacemaker and nodal cells, thereby delaying spontaneous depolarization. A *calcium-activated* potassium channel opens in the presence of high levels of cytosolic calcium and probably enhances the delayed rectifier current, leading to early termination of the action potential. An *ATP-sensitive* potassium channel is closed in the metabolically normal myocyte but is opened in the metabolically starved myocyte in which ATP stores have been depleted, leading to hyperpolarization of the cell and thereby retarding depolarization and contraction.

Energy-Dependent Ion Pumps and Ion Exchangers

Sodium-potassium-ATP-dependent pump

The sodium-potassium pump uses the energy obtained from the hydrolysis of ATP to move three Na^+ ions out of the cell and two K^+ ions into the cell, each against its respective concentration gradient. Since there is a net outward current (three Na^+ ions for two K^+ ions), the pump contributes about 10 mV to the resting membrane potential. The activity of the pump is strongly stimulated by attachment of sodium to the sodium-binding site on the inside of the membrane. The Na,K-ATPase pump has a very high affinity for ATP, so the pump continues to function even if ATP levels are moderately reduced.

ATP-dependent calcium pump

The ATP-dependent calcium pump transports calcium out of the cell against a strong concentration gradient. This action represents a net outward current, but the magnitude of this current is quite small because the bulk of calcium transferred out of the cell occurs with sodium-calcium exchange (described below). The cytosolic protein *calmodulin* can complex with calcium and facilitate action of the pump; thus increased intracellular calcium levels stimulate the pump.[2,12–14]

Ion exchangers

Multiple proteins that traverse the membrane allow ion exchanges using the potential energy of the electrochemical gradient—the gradient favoring the influx of sodium. The *sodium-calcium exchange pump* exchanges three extracellular sodium ions for one intracellular calcium ion, leading to a net single positive charge transported into the cell with each exchange. The exchange system is sensitive to the concentration of sodium and calcium on both sides of the membrane and to the membrane potential. If external sodium concentrations decrease, the driving force for removal of calcium

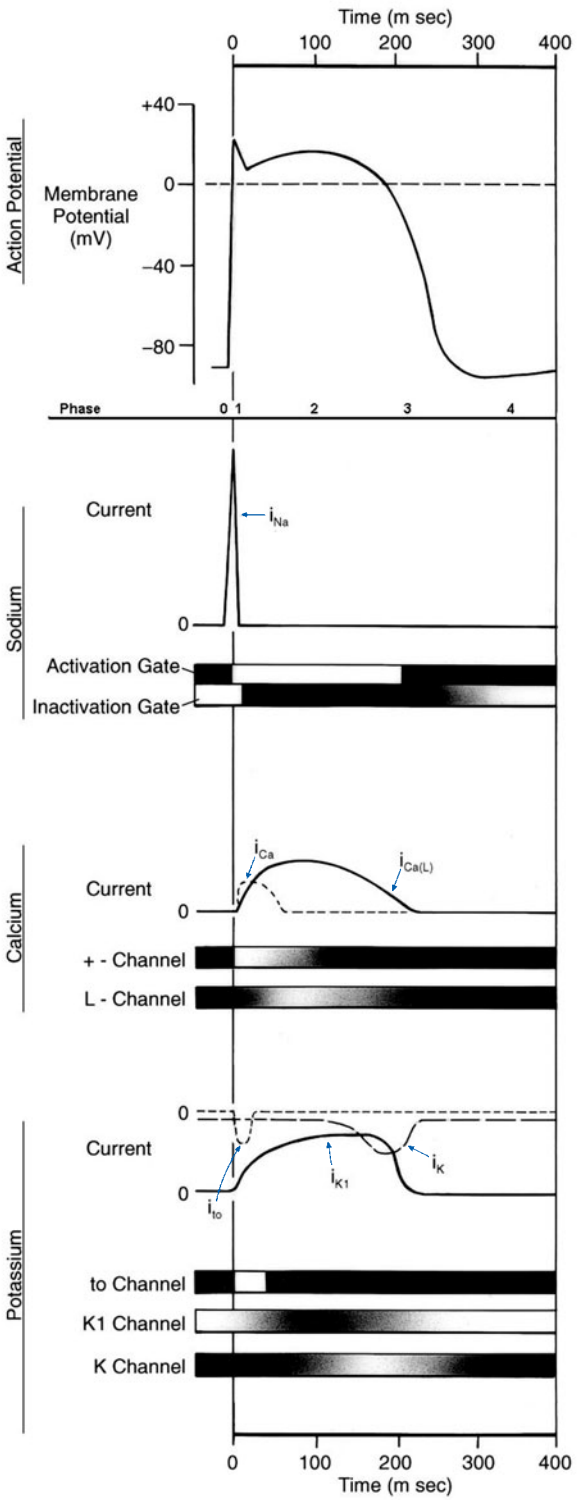

Figure 3-3. A typical ventricular myocyte action potential and the ion currents contributing to it are represented schematically. Inward (depolarizing) currents are depicted as positive, and outward (repolarizing) currents are depicted as negative. The horizontal filled bars show the state of the gate of the ion channel (white = open; black = closed; shaded = partially open). In the case of the sodium channel, both the activation and inactivation gates are shown (*i*, current; Na, sodium; Ca, calcium; K, potassium).

from the cell is decreased, leading to an *increase* in cytosolic calcium (and a consequent increase in contractility). This explains an observation made some years ago that hyponatremia can lead to an *increase* in cardiac contractility. If the intracellular sodium concentration increases, as occurs with ischemia, the gradient for sodium influx is reduced, and the pump slows down or actually reverses, extruding sodium in exchange for an influx (and accumulation) of calcium. This mechanism has been suggested to be central to the accumulation of calcium during ischemia. The sodium-calcium exchange mechanism has a maximum exchange rate that is some 30 times higher than the sarcolemmal ATP-dependent calcium pump described earlier and is likely the primary mechanism for removal of excess cytosolic calcium.[9]

The *sodium-hydrogen exchange pump* extrudes one intracellular hydrogen ion in exchange for one extracellular sodium ion and therefore is electrically neutral. This pump prevents intracellular acidification. Acidification (e.g., during ischemia) increases the affinity of the pump for H^+, promoting the removal of H^+ and preserving intracellular pH at the expense of sodium accumulation. The accumulation of sodium ions then may trigger reversal of the sodium-calcium exchange pump to favor the accumulation of calcium within the cell. This is a purported mechanism underlying injury or cell death during ischemia-reperfusion.

Intracellular Communication Pathways

To allow concurrent activation of all the myofibrils in the muscle cell, the electrical activation signal must be spread rapidly and evenly through all portions of the cell. This is accomplished through the transverse tubules (t-tubules) and the subsarcolemmal cistern and sarcotubular network of the sarcoplasmic reticulum.

T-tubules

The basic contractile unit in a muscle cell is the sarcomere. Sarcomeres are joined together in the myofibril at the z-lines. A system of *transverse tubules* (t-tubules) extends the sarcolemma into the interior of the cardiac cell (Fig. 3-4). These tubules generally are perpendicular to the sarcomere near the z-lines, thus extending the extracellular space into the cell close to the contractile proteins. The t-tubules contain the calcium channels described earlier, which are in close relationship to the *foot proteins* of the *subsarcolemmal cisternae.*

Sarcoplasmic reticulum

The *sarcoplasmic reticulum* is a membrane network within the cytoplasm of the cell surrounding the myofibrils. The primary function of the sarcoplasmic reticulum is *excitation-contraction coupling* by sudden release of calcium to stimulate the contraction proteins and then rapid removal of this calcium to allow relaxation of the contractile elements. The *subsarcolemmal cisternae* and the *sarcotubular network* are the two portions of the sarcoplasmic reticulum that mediate this process.

The *subsarcolemmal cisternae* are beneath the sarcolemma and surround the t-tubules. Specialized bulky proteins are found in the membrane of the sarcoplasmic reticulum

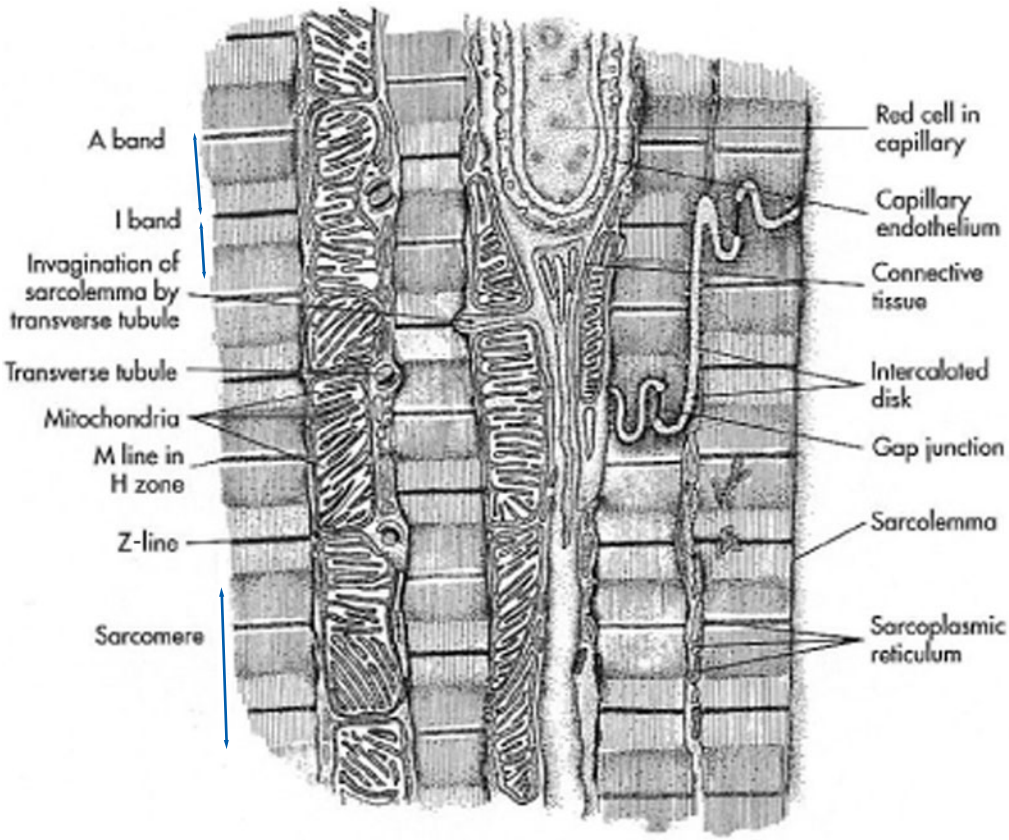

Figure 3-4. Myocyte anatomy. *(From Levy MN: The cardiac pump, in Berne RM, Levy MN, Koeppen BM, Stanton BA, eds: Physiology. St Louis, Mosby, 2004; p 307.)*

with a large protein component extending into the gap between the subsarcolemmal cisternae and the sarcolemma of the t-tubule. These *foot proteins* respond to the release of calcium by the sarcolemma (or t-tubule) by rapid opening of a calcium channel (actually a part of the foot protein), which allows release of a much larger quantity of calcium from the subsarcolemmal cisternae. This is *calcium-triggered calcium release,* with calcium transported across the sarcolemma leading to calcium release from the subsarcolemmal cisternae. The magnitude of calcium release from the subsarcolemmal cisternae appears to be related to the magnitude of the trigger. The calcium channels then close, and the calcium is returned to the sarcoplasmic reticulum by an ATP-dependent calcium pump located primarily in the *sarcotubular network.*[1,2,14] The *sarcotubular network* is the portion of the sarcoplasmic reticulum that surrounds the contractile elements of the sarcomere.

Regulation of calcium transport by the cardiac sarcoplasmic reticulum occurs primarily at the site of the calcium pump. *Phospholamban,* a cytosolic protein, inhibits the basal rate of calcium transport by this calcium pump. This inhibition can be reversed when phospholamban is phosphorylated by a cyclic AMP–dependent or a calcium-calmodulin-dependent protein kinase. This effect appears to be a very important mechanism by which beta-adrenergic stimulation regulates the heart; increased levels of cytosolic cyclic AMP are a consequence of activation of the beta-catecholamine receptor. As phospholamban is phosphorylated, there is accelerated calcium turnover and increased sensitivity of the calcium pump, which facilitates uptake of calcium from the cytosol and relaxation of the heart when the heart comes under the influence of beta-adrenergic agonists. Phosphorylation of phospholamban does not affect the sarcolemmal calcium pump, thereby tending to favor retention of calcium within the cell (increasing the calcium content of the sarcoplasmic reticulum at the expense of calcium removed from the cell through the sarcolemma). This might lead to an increased pulse of calcium within the cell, thereby favoring increased contractility.[9,14]

In this ionic milieu, the importance of maintenance of intracellular pH should be stressed. Regulation of intracellular pH is complex and beyond the scope of this text, but a few simple principles are important to review. Reduced intracellular pH diminishes the amount of calcium released from the sarcoplasmic reticulum and reduces the responsiveness of myofilaments to calcium. Elevation of the pH will have the opposite effect. The clinical relevance of this observation cannot be overstressed.

ELECTRICAL ACTIVATION OF THE HEART

Normal Cardiac Rhythm

The resting membrane potential

The resting state of the cardiac cell is determined by a balance of forces: electrical (based on polarity differences) and chemical (based on gradients across the sarcolemma). At rest

(during diastole), the cardiac cell is polarized. An electrical transmembrane potential across the sarcolemma exists determined primarily by the concentration gradient of potassium across the membrane. This gradient is established by the sodium-potassium pump. However, once this pump shuts off, the steady state is determined by the balance of electrical and chemical forces. As described earlier, the sarcolemma is impermeable to some ions, permeable to others, and selectively permeable to others. Steady-state properties of a mixture of ions of variable permeablities across a membrane are described by the *Gibbs-Donnan equilibrium.*[15] The sarcolemma prevents the diffusion of large anions (e.g., proteins and organic phosphates). At rest, the sarcolemma is relatively permeable to potassium ions owing to the open state of most potassium channels but less permeable to sodium. The concentration gradient established by the sodium-potassium pump promotes the efflux of potassium ions across the sarcolemma. The outward flow of positive ions is counterbalanced by the increasing electronegativity of the interior of the cell owing to the impermeant anions. A Gibbs-Donnan equilibrium is established such that the electronegativity of the cell interior retards potassium ion efflux to the same degree that the concentration gradient favors K^+ efflux. At equilibrium, the forces balance with an intracellular potassium concentration of 135 mM and an extracellular concentration of 4 mM and a predicted resting membrane potential of –94 mV. The actual resting membrane potential is measured at about –90 mV owing to smaller contributions from the current of other less permeable ions (e.g., sodium and calcium). However, the potassium current is the main determinant of the resting membrane potential.[16]

The action potential

The action potential represents the triggered response to a stimulus derived either internally (slow depolarizing ionic currents) or externally (depolarization of adjacent cells). A typical *fast-response* action potential that occurs in atrial and ventricular myocytes and special conduction fibers is depicted in Fig. 3-3. As the transmembrane potential decreases to approximately –65 mV, the "fast" sodium channels open. These channels remain open for a few milliseconds until the inactivation gate of the fast sodium channel closes. The large gradient of sodium ions (extracellular 145 mM, intracellular 10 mM) promotes rapid influx, depolarizing the cell to a slightly positive transmembrane potential. This is *phase 0* of the action potential. A transient potassium current (i_{to}) causes a very early repolarization (*phase 1*) of the action potential, but this fast channel closes quickly. The plateau of the action potential (*phase 2*) is sustained at a neutral or slightly positive level by an inward-flowing calcium current, first from the transient calcium channel and second through the long-lasting calcium channel. The plateau also is sustained by a decrease in the outward potassium current (i_{k1}). With time, the long-lasting calcium channel begins to close, and the repolarizing potassium current (i_k, the delayed rectifier current) leads to the initiation of *phase 3* of the action potential. As repolarization progresses, the stronger first potassium current (i_{k1}) dominates, leading to full repolarization of the membrane to the resting negative potential. During the bulk of the depolarized interval (*phase 4*), the first potassium current predominates in myocytes. Because the sodium channels cannot respond to a second wave of depolarization until the inactivation gates are reopened (by repolarization during phase 3), the membrane is *refractory* to the propagation of a second impulse during this time interval, referred to as the *absolute refractory period.* As the membrane is repolarized during early phase 3 of the action potential, and some of the sodium channels have been reactivated, a short interval exists during which only very strong impulses can activate the cell, which is termed the *relative refractory period.* A drug that acts to speed up the kinetics of the inactivation gate will shorten both the absolute and the relative refractory periods.[1,2,17–19]

Spontaneous depolarization

The action potential of the *slow-response* cells of the nodal tissue [*sinoatrial node* (SA node) and *atrioventricular node* (AV node)] differs from that in the fast-response cells, as shown in Fig. 3-5. The rapid upstroke of *phase 0* is less prominent owing to the absence of fast Na^+ channels. *Phase 1* is absent because there is no rapid inward potassium current. In addition, the plateau phase (*phase 2*) is abbreviated because of the lack of a sustained active Na^+ inward current and the lack of a sustained calcium current. The repolarization phase (*phase 3*) leads to a resting phase (*phase 4*) that begins to depolarize again, as opposed to the relatively stable resting membrane potential of myocytes. The slowly depolarizing phase 4 resting potential is called the *diastolic depolarization current* or the *pacemaker potential.* Continued depolarization of the membrane potential ultimately reduces it to the threshold potential that stimulates another action potential. This diastolic depolarization potential is the mechanism of *automaticity* in cardiac pacemaker cells. Diastolic depolarization is due to the concerted and net actions of (1) a decrease in the outward K^+ current during early diastole (phase 4), (2) persistence of the slow inward Ca^{2+} current, and (3) an increasing inward Na^+ current during diastole. The inward Na^+ current most likely predominates in nodal and conduction tissue. The slope of the diastolic depolarization determines the rate of action potential generation in the pacemaker cells and is the primary mechanism determining heart rate. Of all the cardiac cells, the slope of the diastolic potential is greatest (faster rate of depolarization) in the SA node, and action potentials are generated at a rate of 70 to 80 per minute. The AV node has a slower rate of depolarization, with a frequency of action potential generation of 40 to 60 times per minute. The ventricular myocytes have the slowest rate of depolarization, with a frequency of 30 to 40 times per minute. Once a depolarization is initiated in a pacemaker cell and propagated, it will depolarize the remainder of the heart in a synchronized and sequential manner. If a pacemaker site drops out owing to pathology or drug-induced slowing of the diastolic potential, the next pacemaker site

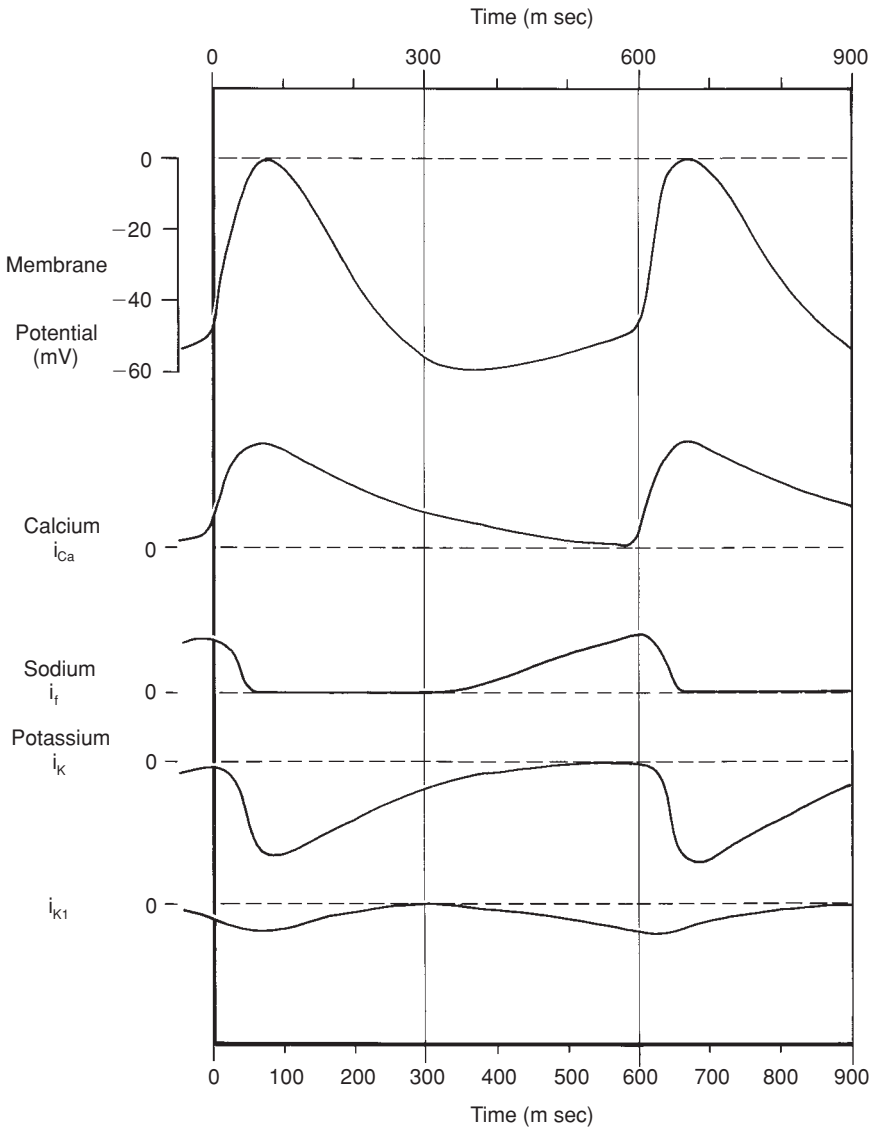

Figure 3-5. The membrane potential of a spontaneously depolarizing cell of the sinoatrial node and the ion currents contributing to it. Inward (depolarizing) currents are depicted as positive, and outward (repolarizing) currents are depicted as negative (*i,* current; Na, sodium; Ca, calcium; K, potassium).

in line will take over, with a heart rate typical for that site. The heart rate can be altered by changing slope of the diastolic depolarization (e.g., acetylcholine decreases the slope and heart rate; beta-adrenergic agonists increase the slope and heart rate). If the slope is unchanged, hyperpolarization (more negative resting potential) or raising the threshold potential will increase the time to reach threshold, resulting in a decrease in heart rate.

Propagation of the action potential

Each myocyte is electrically connected to the next myocyte by an *intercalated disk* at the end of the cell. These disks contain *gap junctions* that facilitate the flow of charged molecules from one cell to the next. These pores in the intercalated disks are composed of a protein, *connexin.* Permeability through the cardiac gap junction is increased by both ATP- and cyclic AMP–dependent kinases. This allows the gap junctions to close if ATP levels fall, thereby reducing electrical and presumably mechanical activity, which is essential in limiting cell death when one region of the heart is damaged. It also allows conduction to increase when cyclic AMP increases in response to adrenergic stimulation.

After spontaneous depolarization occurs in the pacemaker cells of the SA node, the action potential is conducted throughout the heart. Special electrical pathways facilitate this conduction. Three internodal paths exist through the atrium between the SA node and the AV node. After traversing the AV node, the action potential is propagated rapidly through the *bundle of His* and into the *Purkinje fibers* located on the endocardium of the left and right ventricles. Rapid conduction through the atrium causes contraction of most of the atrial muscle synchronously (within 60 to 90 ms). Similarly, the rapid conduction of the signal throughout the ventricle leads to synchronous contraction of the bulk of the ventricular myocardium (within 60 ms). The delay of the propagation of the action potential through the AV node by 120 to 140 ms allows the atria to complete contraction before the ventricles contract. Slow conduction in the AV node is related to a relatively higher internal resistance because of a small number of gap junctions between cells and to slowly

rising action potentials. The nodal delay allows the atrium to pump an aliquot of blood (up to 10% of left ventricular volume) into the ventricle just prior to ventricular contraction, thereby optimizing preload of the ventricle.

Abnormal Cardiac Rhythm

Aberrant pacemaker foci

Many cardiac cells manifest an intrinsic rhythm from spontaneous depolarization. Normally, the SA node spontaneously depolarizes first such that the cardiac beat originates from this primary acemaker site. If the SA node is damaged or slowed by vagal timulation or drugs (e.g., acetylcholine), pacemakers in the AV node or the His-Purkinje system can take over. Occasionally, aberrant foci in the heart depolarize spontaneously, thereby leading to insertion of aberrant beats from either the atrium or the ventricle (noted as premature atrial or ventricular contractions). These beats ordinarily do not interfere with normal depolarization of the heart and have very little tendency to degenerate into disorganized electrical activity.

Reentry arrhythmias

Reentry arrhythmias are perhaps the most common dangerous cardiac rhythm. Under ordinary circumstances, the action potential depolarizes the entire atrium or the entire ventricle in a short enough time interval so that all the muscle is *refractory* to further stimulation at the same time. A reentry arrhythmia is caused by propagation of an action potential through the heart in a "circus" movement. For reentry to occur, there must be a unidirectional block (transient or permanent) to action potential propagation. Additionally, the effective refractory period of the reentered region must be shorter than the propagation time around the loop.[16] For example, if a portion of the previously depolarized myocardium has repolarized before propagation of the action potential is completed throughout the atrium or ventricle, then that action potential can continue its propagation into this repolarized muscle. Such an event generally requires either dramatic slowing of conduction of the action potential, a long conduction pathway, or a shortened refractory period (Fig. 3-6). All these situations occur clinically. Ischemia leads to slowing of the sodium-potassium pump, which leads to a decreased resting membrane potential and *slowing* of propagation of the action potential. Hyperkalemia leads to an increase in the extracellular potassium level, a decrease in the resting membrane potential, and a *slowing* of propagation of the action potential. Progressive atrial dilation creates a *long conduction pathway* around the atrium that can allow a reentry arrhythmia. Adrenergic stimulation leads to a shortened refractory period, which increases the likelihood of a reentry arrhythmia.

A special type of reentry arrhythmia occurs in the Wolff-Parkinson-White (WPW) syndrome in which an *accessory pathway* connects the atrium and the ventricle electrically. This accessory pathway can complete a circular electrical pathway between the atrium and the ventricle: Conduction is unidirectional across the AV node, and the accessory pathway creates a loop that has a propagation time that is greater than the AV node refractory period, resulting in a supraventricular tachycardia. The accessory pathway of the WPW syndrome is dangerous in another way. Because it does not have the inherent delay and refractory period of the AV node, rapid atrial tachycardias can be conducted in a 1:1 manner across the accessory pathway, leading to ventricular rates as fast as 300 beats per minute.

Afterpotentials or parasystole

Most ventricular tachyarrhythmias are reentry arrhythmias. The primary exception to this rule is *parasystole* or

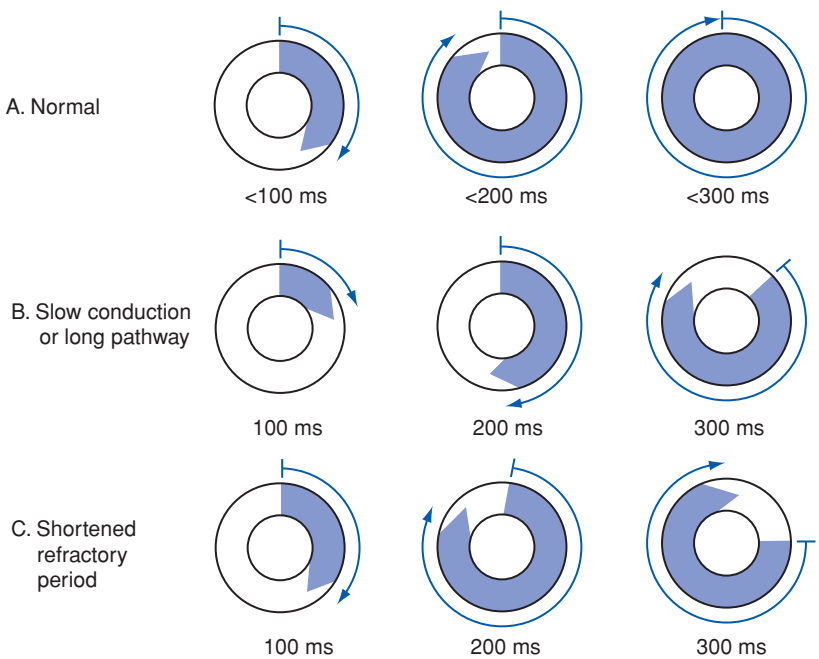

Figure 3-6. Three conditions predisposing to reentry or "circus" pathways for action potential propagation are shown. Muscle that is refractory to action potential propagation is shown as black. Normally, as the action potential travels through the atrium or ventricle, all the muscle is depolarized sufficiently that the action potential encounters no more nonrefractory muscle and stops (*A*). If there is slowed conduction speed or a long pathway (*B*), the action potential may find repolarized (nonrefractory) muscle and continue in a circular path. Similarly, a shortened refractory period (*C*) may lead to rapid repolarization and predispose to a reentry and continuation of the action potential.

afterpotentials. Normally, ventricular action potentials have a flat phase 4 during diastole without spontaneous depolarization. If, however, they have elevated levels of cytosolic calcium, there may be a transient diastolic inward (depolarizing) current, probably related to activity of the sodium-calcium exchange pump. Afterpotentials are thought to underlie the development of ventricular automaticity during digitalis toxicity. The afterdepolarizations associated with digitalis toxicity appear to be *delayed* afterdepolarizations. Another type of afterdepolarization is an *early* afterdepolarization, which occurs *before* the end of complete repolarization. This early afterdepolarization appears to be the mechanism for the ventricular tachycardia called *torsades de pointes,* in which varying QRS complexes appear. A prolongation of the QT interval and the varying QRS complexes in torsades de pointes indicate heterogeneity of the action potential duration within the ventricle, thereby predisposing to ventricular fibrillation.[18]

REGULATION OF CELLULAR FUNCTION BY SARCOLEMMAL RECEPTORS

Parasympathetic Regulation

The parasympathetic nervous system is particularly important in control of the pacemaker cells of the SA node. Acetylcholine released by the nerve endings of the parasympathetic system stimulates *muscarinic receptors* in the heart. These activated receptors, in turn, produce an intracellular stimulatory G-protein that opens *acetylcholine-gated potassium channels.* An increased outward (repolarizing) flow of potassium leads to *hyperpolarization* of the SA node cells. Stimulation of the muscarinic receptors also inhibits the formation of cyclic AMP; decreased cyclic AMP levels inhibit the opening of calcium channels. A decreased inward flow of calcium, combined with an increased outward flow of potassium, leads to a sometimes dramatic slowing of spontaneous diastolic depolarization of the sinoatrial nodal cell (Fig. 3-5). A similar effect in the AV node leads to slowing of conduction through the AV node.[1]

Adrenergic Stimulation and Blockade

Adrenergic receptors affect heart rate, contractility, conduction velocity, and automaticity in cardiac cells and smooth muscle contraction and relaxation in the vasculature. Alpha-adrenergic receptors cause vasoconstriction. There are two types of beta-adrenergic receptors: the $beta_1$-adrenergic receptors, which predominate in the heart, and the $beta_2$-adrenergic receptors, which are present in blood vessels and promote relaxation. The number of beta receptors per unit area (*receptor density*) of the sarcolemma can increase (*upregulation*) or decrease (*downregulation*) in response to various stimuli. Receptor sensitivity also can change depending on ambient conditions and variable stimuli.[20] Cardiopulmonary bypass and ischemia cause downregulation of cardiac beta receptors. Acidemia causes desensitization of beta receptors. This is particularly important in the perioperative period, when acidemia can reduce cardiac contractility, systemic vascular tone, and the response to inotropic agents significantly.

The beta-adrenergic receptor couples with *adenyl cyclase* (Fig. 3-7). When the receptor site is occupied by a catecholamine, a *stimulatory G-protein* is formed that combines with GTP. This activated G-protein–GTP complex then promotes the activity of adenyl cyclase, leading to the formation of *cyclic AMP* from ATP. The G-protein–GTP complex and the cyclic AMP actively promote calcium channel opening. The increased tendency for calcium channels to open during beta-receptor stimulation increases cytosolic calcium and leads to a number of electrophysiologic effects: (1) a positive *chronotropic* (heart rate) effect whereby the heart rate, conduction, and contraction velocity increase and the action potential is shortened leading to a shortening of systole, (2) a positive *dromotropic* (conduction velocity) effect of *accelerated conduction* through the AV node, (3) a positive *inotropic*

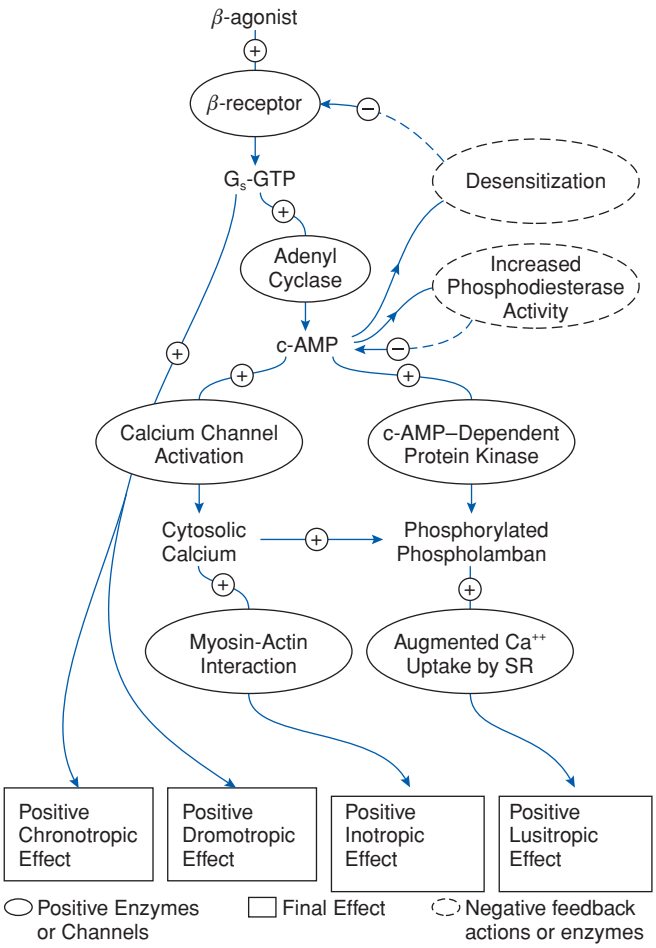

Figure 3-7. Adrenergic stimulation via the action of beta agonists on beta receptors leads to a cascade of events in the myocyte, some of which are shown here. Note that an increase in cAMP causes the activation of two inhibitory pathways, retarding excessively sustained adrenergic stimulation (Gs, stimulatory G-protein; GTP, guanosine triphosphate; SR, sarcoplasmic reticulum; cAMP, cyclic adenosine monophosphate).

(contractility) effect, and (4) increased activity of the sarcoplasmic reticulum calcium pump (more rapid calcium uptake) leading to more rapid relaxation, which facilitates ventricular filling, a positive *lusitropic* (relaxation) effect.[21,22]

Two negative-feedback systems diminish the response to beta agonists when stimulation is repetitive or persistent (tachyphylaxis): Increased cyclic AMP leads to (1) increased phosphorylation of beta receptors, resulting in downregulation, and to (2) increased activity of *phosphodiesterase,* the enzyme that degrades cyclic AMP.

The activity spectrum of adrenergic receptors forms the basis of many therapeutic interventions: perioperatively to support cardiac function and chronically to reduce mortality from myocardial infarction and to treat congestive heart failure. The selectivity of the agonists allows adaptation for various clinical scenarios. $Beta_1$-selective agonists and antagonists are considered *cardioselective.* Some examples are detailed in Table 3-1.

The reduction in inotropy, lusitropy, chronotropy, and dromotropy by beta blockade will reduce myocardial oxygen consumption, contributing to many of its beneficial effects. Since beta blockade will lead to upregulation of sarcolemmal receptors, sudden cessation of beta blockade may cause a temporarily enhanced (and potentially dangerous) sensitivity to adrenergic stimulation.

Phosphodiesterase Inhibition

As discussed previously, cyclic AMP plays a central role in regulation of the cardiac cell. Cytosolic levels of cyclic AMP are increased by activation of receptors other than beta receptors (i.e., for histamine, dopamine, and glucagon) and are decreased by inhibitory G-proteins produced by stimulation of muscarinic receptors by acetylcholine and by stimulation of adenosine receptors. Referring again to Fig. 3-7, one negative-feedback response to the increase in cyclic AMP is an increase in phosphodiesterase, which breaks down cyclic AMP. *Phosphodiesterase inhibitors* (e.g., amrinone and milrinone) inhibit the breakdown of cyclic AMP and thereby increase its level in the cytosol. Their effect is synergistic to that of beta agonists. Since they do not stimulate the production of G-protein–GTP complex, they have a lesser effect on calcium channel activation and therefore fewer of the troublesome positive chronotropic and dromotropic effects of beta-adrenergic stimulation.[22,23]

Adenosine Receptors

There are four types of adenosine receptors. Adenosine receptors are linked to inhibitory and stimulatory G-proteins and various kinases. Activation of adenosine A_1 receptors leads to inhibition of the slow calcium channel and opening of an adenosine-activated ATP-sensitive potassium (K_{ATP}) channel. This leads to hyperpolarization, which delays conduction through the AV node and slows the ventricular response to atrial tachycardia.[1,24] Pretreatment with adenosine (also via A_1-receptor activation) confers a cardioprotective effect during ischemia and can inhibit the inflammatory responses initiated by ischemia and reperfusion.[24]

Table 3–1.

Adrenergic Agonists and Antagonists Correlating Selective Activity with Clinical Usage

	Drug	Alpha	$Beta_1$	$Beta_2$	Clinical usage
Agonists	Epinephrine	Y	Y	Y	Low cardiac output, hypotension
	Norepinephrine	Y	Y		Hypotension
	Phenylephrine	Y			Hypotension
	Dobutamine		Y		Low cardiac output
	Dopamine	Y	Y		Low cardiac output, hypotension
	Isoproterenol		Y	Y	Bradycardia, low cardiac output, pulmonary hypertension
Antagonists (beta blockers)	Metoprolol		Y		Tachycardia, hypertension, MI, angina
	Atenolol		Y		Tachycardia, hypertension, MI, angina
	Esmolol		Y		Tachycardia, hypertension, MI, angina
	Carvedilol	Y ($alpha_1$)	Y	Y	Congestive heart failure

CONTRACTION OF CARDIAC MUSCLE

Molecular Level (The Sarcomere)

The primary contractile unit of all muscle cells is the *sarcomere* (Fig. 3-4). Sarcomeres are connected end to end at the *z-line* to form *myofibrils.* The myocyte contains numerous myofibrils arranged in parallel. A portion of a sarcomere is depicted schematically in Fig. 3-8. *Actin* polymerizes to form the *thin filaments* that are anchored at the z-line. *Myosin* polymerizes to form the *thick filaments* of the sarcomere. Myosin consists of a tail of two "heavy" chains intertwined to form a helix, constituting the rigid backbone of the thick filament. The globular head of myosin is attached to the heavy-chain backbone by a mobile hinge and projects outward. The globular myosin head is an ATPase with a binding sight for actin. Actin monomers polymerize into a double-helical filament with a groove running the length of the filament. Actin binds to the myosin globular head, activating the myosin ATPase to hydrolyze ATP. This leads to a conformational change in the myosin that pulls the filament (Fig. 3-8*B*).

Two proteins modulate the interaction of actin and myosin: *troponin* and *tropomyosin.* Troponin ("T" in Fig. 3-8*A*) is a heterotrimer composed of three units: *Tn-C,* a calcium-binding unit; *Tn-T,* which binds tropomyosin; and *Tn-I,* which facilitates interruption of actin-myosin interaction by tropomyosin. Associated with each troponin complex is tropomyosin, a filamentous protein composed of two tightly coiled helical peptide chains that lies in the groove formed by the two intertwined filaments of actin. The binding of calcium to troponin C removes the troponin I–induced masking of the myosin-binding site on actin, thereby allowing cross-bridge formation between actin and myosin.

During diastole, Ca^{2+} is unavailable to bind troponin C, and the myosin-binding site on actin is blocked. Depolarization of the sarcolemmal membrane and t-tubules leads to an influx of calcium ions. The influx of Ca^{2+} and the subsequent "calcium-triggered, calcium release" from the sarcoplasmic reticulum increase the intracellular Ca^{2+} calcium levels by approximately two orders of magnitude (from 10^{-7} M in diastole to 10^{-5} M in systole). This provides sufficient calcium to bind to troponin C, which causes a conformational change in the troponin molecule, removing the inhibitory effect of troponin I and allowing actin-myosin cross-bridge formation (Fig. 3-8*A*). Cross-bridge formation activates the myosin ATPase and initiates the conformational change in the myosin

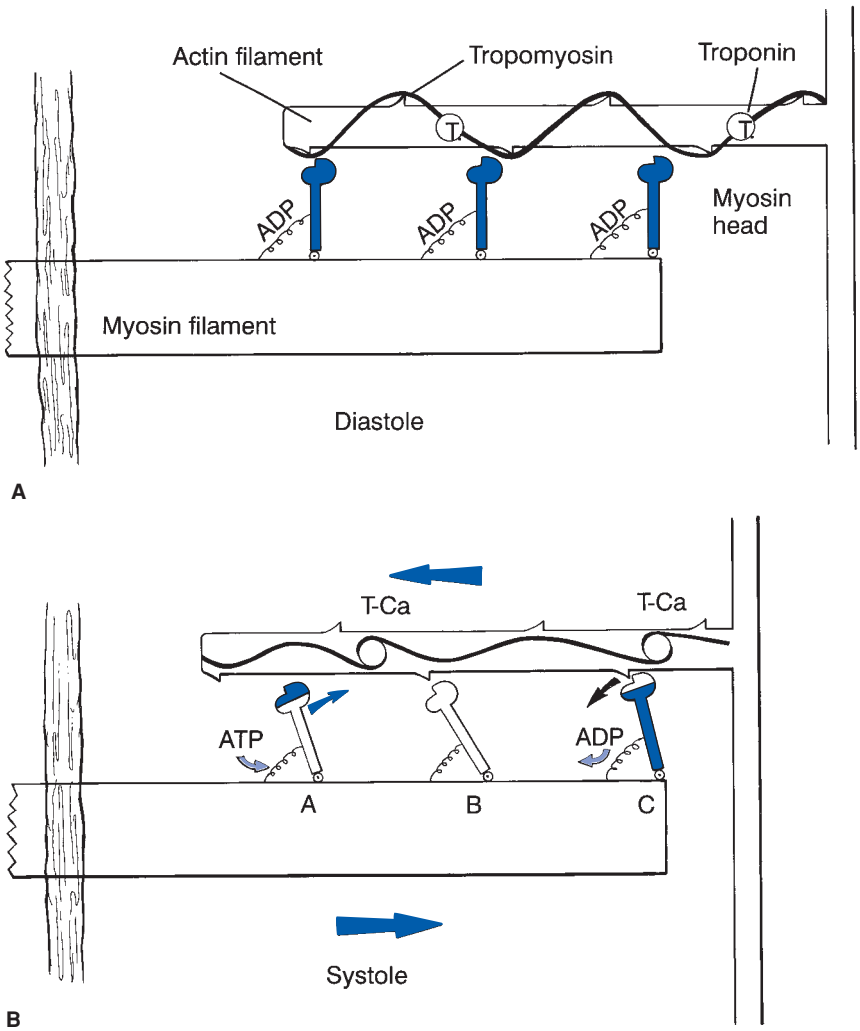

Figure 3-8. The interaction of actin and myosin filaments converts chemical energy into mechanical movement. In diastole, the active sites on the actin filament are covered by tropomyosin. When calcium combines with troponin, the tropomyosin is pulled away from the actin active sites, allowing the energized myosin heads (depicted in solid black and cocked at right angles to the filament) to engage and sweep the actin filament along. The myosin heads are deenergized in this process. Myosin ATPase recocks (reenergizes) the head by using the energy derived from the hydrolysis of ATP. In systole, a deenergizing head (*C*), a deenergized head (*B*), and a reenergizing head (*A*) are shown.

"hinge," drawing the z-lines closer together (Fig. 3-8*B*). ADP and P_i are released, and the myosin head dissociates from the actin. ATP associates with the myosin head, realigning the myosin globular head, preparing it to repeat the process. This process cycles until the end of muscular contraction is signaled by the reduction in intracellular calcium levels by sequestration into the sarcoplasmic reticulum. This is accomplished by sarcoplasmic endoplasmic reticulum calcium ATPase (SERCA) and other energy-dependent pump systems.

The strength of the myocardial contraction is mediated primarily by the degree to which actin-binding sites are exposed. This depends on the affinity of troponin for calcium and the availability of calcium ions. The initial calcium ion influx is altered by cyclic AMP, stimulatory and inhibitory G-proteins, and acetylcholine. The magnitude of the calcium trigger determines the magnitude of the cytosolic calcium release from the sarcoplasmic reticulum. The rate of uptake of calcium from the cytosol is altered by cyclic AMP (Fig. 3-7). Cyclic AMP can phosphorylate a portion of the troponin molecule, facilitating the rapid release of calcium and increasing the rate of relaxation of the actin-myosin complex.[9,25]

Regulation of the Strength of Contraction by Initial Sarcomere Length

In cardiac muscle, the strength of contraction is related to resting sarcomere length (see also "The Frank-Starling Relationship" below). Maximal contraction force occurs when the resting sarcomere length is between 2 and 2.4 μm.[26] At this length, there is optimal overlap of the actin and myosin, maximizing the number of actin-myosin cross-bridges. Force declines at a greater sarcomere length, with decreased overlap of actin and myosin. In the heart, a decrease in contractility related to decreased overlap of the filaments does not seem to occur clinically because the resting length of the cardiac sarcomere rarely exceeds 2.2 to 2.4 μm. Once this length is reached, a stiff parallel elastic element prevents further dilation. If chamber dilation does occur, it appears to be primarily through *slippage* of fibers or myofibers rather than stretching of sarcomeres.[1] Stretching the myocardium increases contractility by increasing the sensitivity of troponin C to calcium. This length-dependent sensitivity to calcium is an important part of the ascending limb of the Starling curve observed in the intact ventricle.

THE PUMP

Mechanics

Clinically observable physiologic parameters

Cardiac surgeons can assess the function of the heart in a number of ways. Most simply, systemic, pulmonary artery, pulmonary capillary wedge, and central venous pressures can be measured directly. Cardiac output can be estimated using thermodilution or based on oxygen saturation measurements. From these direct measurements, other parameters can be derived—though less accurately because of the cumulative error of the measured parameters inherent in the calculation—such as pulmonary and systemic vascular resistance, ventricular stroke work, etc. Ejection fraction—defined as stroke volume/end-diastolic volume—can be estimated by echocardiography and ventriculography but is subject to change based on loading conditions, heart rate, and degree of contractility. Although useful clinically, these parameters do not measure contractility directly.

The Frank-Starling relationship

Almost a century ago, two physiologists (Frank and Starling) simultaneously developed the concept that, within physiologic limits, the heart will function as a sump pump; the more the heart is filled during diastole, the greater the quantity of blood that will be pumped out of the heart during systole. (This relationship was introduced earlier in the section entitled, "Regulation of the Strength of Contraction by Initial Sarcomere Length.")

Under normal circumstances, the heart pumps all the blood that comes back to it without excessive elevation of venous pressures. In the normal heart, as ventricular filling is increased, the strength of ventricular contraction increases as sarcomeres are stretched. The influence of sarcomere length on the force of contraction is called the *Frank-Starling relationship*. This relationship for the left ventricle is depicted in Fig. 3-9. Also depicted in the figure are two other states, a condition of normal adrenergic stimulation and a condition of maximal adrenergic stimulation. Force is increased for the same diastolic left atrial pressure by adrenergic stimulation; this is a positive inotropic effect.

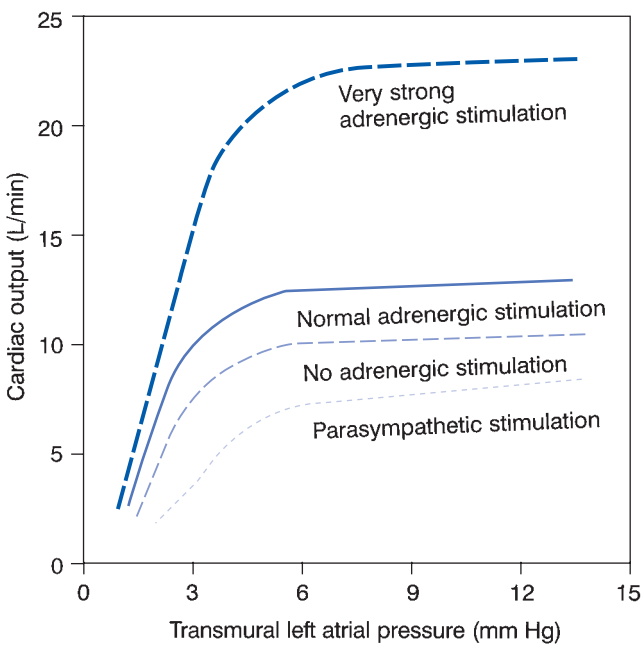

Figure 3-9. Starling curves for the left ventricle. The influence of four different states of neurohumoral stimulation on global ventricular performance is shown.

Preload, diastolic distensibility, and compliance

Preload is the load placed on a resting muscle that stretches it to its functional length. In the heart, preload references the volume of blood in the cavity immediately prior to contraction (at end diastole) because volume determines the degree of stretch imposed on the resting sarcomere. Since volume cannot be assessed easily clinically, pressure is used as a surrogate; thus the concept of preload is represented as the filling pressure of a chamber. The relationship between the end-diastolic pressure and the end-diastolic volume is complex. Several different diastolic pressure-volume relationships are shown in Fig. 3-11 (bold line). As end-diastolic volume increases and the heart stretches, the end-diastolic pressure also increases. The *compliance*, or distensibility, of the ventricle is defined as the change in volume divided by the change in pressure. Conversely, the *stiffness* of the ventricle is the reciprocal of compliance, or the change in pressure divided by the change in volume.

A number of factors affect the diastolic pressure-volume relationship. A fibrotic heart, a hypertrophied heart, or an aging heart becomes increasingly stiff (Fig. 3-11*C* and *E*). In the case of fibrosis, this increasing stiffness is related to the development of a greater collagen network. In the case of hypertrophy, this increased stiffness is related to both stiffening of the noncontractile components of the heart and impaired relaxation of the heart. Relaxation is an active, energy-requiring process. This process is accelerated by catecholamine stimulation but is impaired by ischemia, hypothyroidism, and chronic congestive heart failure. Examination of the diastolic pressure-volume curves in Fig. 3-11 reveals the importance of changes in diastolic distensibility in pathologic cardiac conditions.[27,28]

Afterload: vascular impedance

The *afterload* of an isolated muscle is the tension against which it contracts. In simplest terms, for the heart, the afterload is determined by the pressure against which the ventricle must eject. The greater the afterload, the more mechanical energy must be imparted to the blood mass (potential energy) to begin ejection. In addition to the potential energy imparted to the ejected blood by a change in pressure, the contracting left ventricle generates kinetic energy that overcomes the compliance of the distensible aorta and systemic arterial tree to move the blood into the arterial system. The energy necessary for this flow to occur is relatively small (potential energy >> kinetic energy). *Resistance*, which equals the change in pressure divided by cardiac output, reflects the potential energy imparted to blood. To describe the forces overcome to eject blood from the ventricle accurately, the compliance of the vascular system and kinetic energy imparted also must be considered: the *impedance* of the vascular system (commonly but less accurately referred to as *aortic impedance*). Compliance reflects the capacity of the vascular system to accept the volume of ejected blood. When the vascular system is very compliant, resistance ≈ impedance. As compliance decreases (e.g., with arteriosclerosis), resistance is less than impedance.[29] The interaction of resistance and compliance defines the dicrotic notch marking end systole (ES), closure of the aortic valve, on the aortic pressure tracing (Fig. 3-10).

The cardiac cycle

Multiple parameters of the cardiac cycle are represented in Fig. 3-10. By convention, the cardiac cycle begins at end diastole (ED), just prior to electrical activation of the ventricle. As the heart contracts, intracavitary pressure closes the mitral valve and then increases rapidly until the systemic diastolic pressure is reached (isovolumic contraction) and

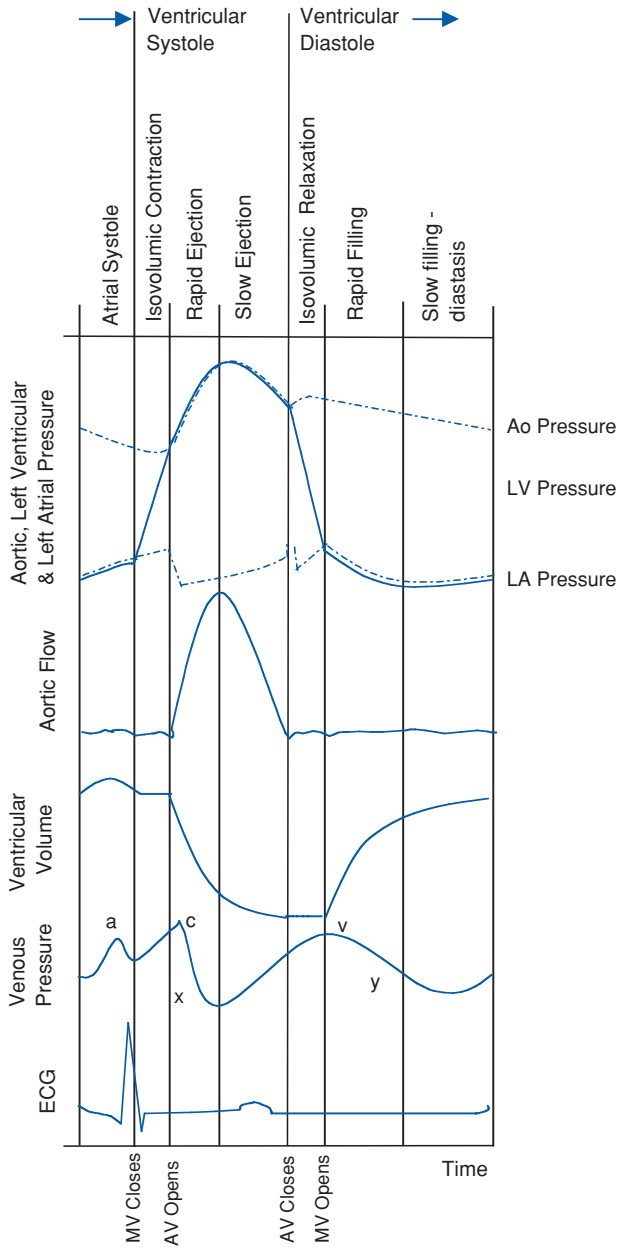

Figure 3-10. Temporal correlation of left atrial and ventricular, aortic, and systemic venous pressures, aortic flow, left ventricular volume, and surface electrocardiogram.

the aortic valve opens. Ejection begins and the intracavitary pressure continues to rise and then fall as the ventricular volume decreases (ejection). When ejection ceases and the aortic valve closes, intracavitary pressure decreases rapidly until the mitral valve opens (isovolumic relaxation). Once the mitral valve opens, the ventricle fills rapidly and then more slowly as the intracavitary pressure slightly increases from distension prior to atrial systole (diastolic filling phase). The completion of atrial systole is the end of ventricular diastole.

A conceptual understanding of the venous pressure changes is important in diagnosing certain pathologic processes. The right atrial pressure is measured easily, and pulmonary capillary wedge pressure is reflective of left atrial pressure. The *a* wave corresponds to atrial systole as pressure increases at ED to complete ventricular filling. The *c* wave reflects pressure pushing the atrioventricular (AV) valve back into the atrium as the ventricular pressure rises and then falls during systole. The *x* descent results from atrial relaxation and downward displacement of the AV valve with ventricular emptying. The *v* wave reflects the increasing atrial pressure from filling before the AV valve opens. The *y* descent is due to rapid emptying of the atrium after the AV valve opens. Characteristic changes in these waveforms are used to diagnose and differentiate constrictive and restrictive processes, as discussed elsewhere in this text. A prominent left atrial *v* wave suggests mitral regurgitation.

Ventricular pressure-volume relationships

The function of the heart can be described and quantified based on the relative intraventricular pressure and volume during the cardiac cycle (Fig. 3-11). Based on this relationship, various measures can be derived to assess cardiac performance (discussed below). The ventricular pressure-volume relationship derives from the Frank-Starling relationship of sarcomere length and peak developed force: The force and extent of contraction (*stroke volume*) is a function of end-diastolic length (*volume*).

ED is represented at the lower right corner of the loop in Fig. 3-11*A*. The pressure-volume loop then successively tracks changes through isovolumic contraction (up to the upper right corner), ejection [left to the upper left corner—which represents ES], isovolumic relaxation (down to the bottom left corner), and then filling (right to the lower right corner). Descriptive data to assess ventricular function are derived from the *end-systolic pressure-volume point* located in the upper left corner of the loop and the *end-diastolic pressure-volume point* located in the lower right corner of the loop. The area within the pressure-volume loop represents the *internal work* of the chamber.

Contractility

The term *contractility* (inotropic state) refers to the intrinsic performance of the ventricle for a given preload, afterload, and heart rate. Although the inotropic state affects cardiac output, it is difficult to quantify in clinically useful terms. For research purposes, the pressure-volume relationship can be used to quantify contractility by deriving the *end-systolic pressure-volume relationship* (ESPVR): Contractility is reflected in the slope (E_{ES}) and volume axis intercept (V_0) of the ESPVR (Fig. 3-12). Holding afterload and heart rate constant, a series of pressure-volume loops is inscribed during transient preload reduction induced by temporary vena caval occlusion; the area of the loops decreases, and the loops are shifted to the left. The progressive pressure-volume points at ES then are linearized to derive the ESPVR. Within a clinical range of systolic pressures (80 to 120 mm Hg), the end-systolic pressure-volume line is largely linear. An increase in inotropic state of the left ventricle is expressed as an increase in E_{ES} and sometimes a decrease in V_0. Conversely, a decrease in inotropic state is expressed as a decrease in E_{ES} and sometimes an increase in V_0 (Fig. 3-12). As the ESPVR describes systolic function, the *end-diastolic pressure volume relationship* (EDPVR; Fig. 3-12) describes ventricular diastolic compliance (specifically, the inverse of the slope of the EDPVR is compliance).

Pressure-volume loops can be used to analyze various physiologic situations. Increased afterload (Fig. 3-11*B*) moves the end-systolic pressure-volume point slightly upward and to the right. If stroke volume is maintained, end-diastolic volume must increase. Thus, although contractility is unchanged, ejection fraction is slightly decreased. Figure 3-11*C* shows the effect of a decrease in ventricular compliance (increased EDPVR) such as may result from hypertrophy, fibrosis, or cardiac tamponade. Systolic function is maintained (E_{ES} and V_0 are unchanged), and stroke volume and ejection fraction can be maintained but require an increased end-diastolic pressure. The positive inotropic (increased E_{ES}) and lusitropic (decreased EDPVR) effects of adrenergic stimulation (Fig. 3-11*D*), at constant stroke volume, shift the pressure-volume loop to the left and increase the ejection fraction. In the hypertrophied heart (Fig. 3-11*E*), in contrast to Fig. 3-11*C*, diastolic compliance is decreased, and systolic contractility is increased. A constant stroke volume leads to an increase in end-diastolic filling pressure and decreased end-diastolic volume. The pressure-volume loop shifts to the left with an increase in ejection fraction. The ability of the hypertrophied heart to increase stroke volume is limited. Acute ischemia (Fig. 3-11*F*) decreases diastolic compliance (increased EDPVR) and contractility. The pressure-volume loop shifts to the right and up to maintain stroke volume, consistent with the clinical observation of an acute decrease in ejection fraction and increase in left ventricular filling pressure. In the dilated heart of chronic congestive heart failure (Figure 3-11*G*), the pressure-volume loop is shifted to the right. Note that the slope of the end-diastolic pressure-volume curve (EDPVR) changes little; rather, the curve shifts to the right. The end-diastolic pressure is not increased owing to a change in compliance; instead, to maintain stroke volume, the pressure-volume loop has moved upward on the compliance curve. Contrast this with the fibrotic process discussed earlier. The effect of afterload reduction on the chronically failing heart from Fig. 3-11*G* is demonstrated in Fig. 3-11*H*. Note that the ESPVR, EDPVR, and stroke volume are unchanged. The

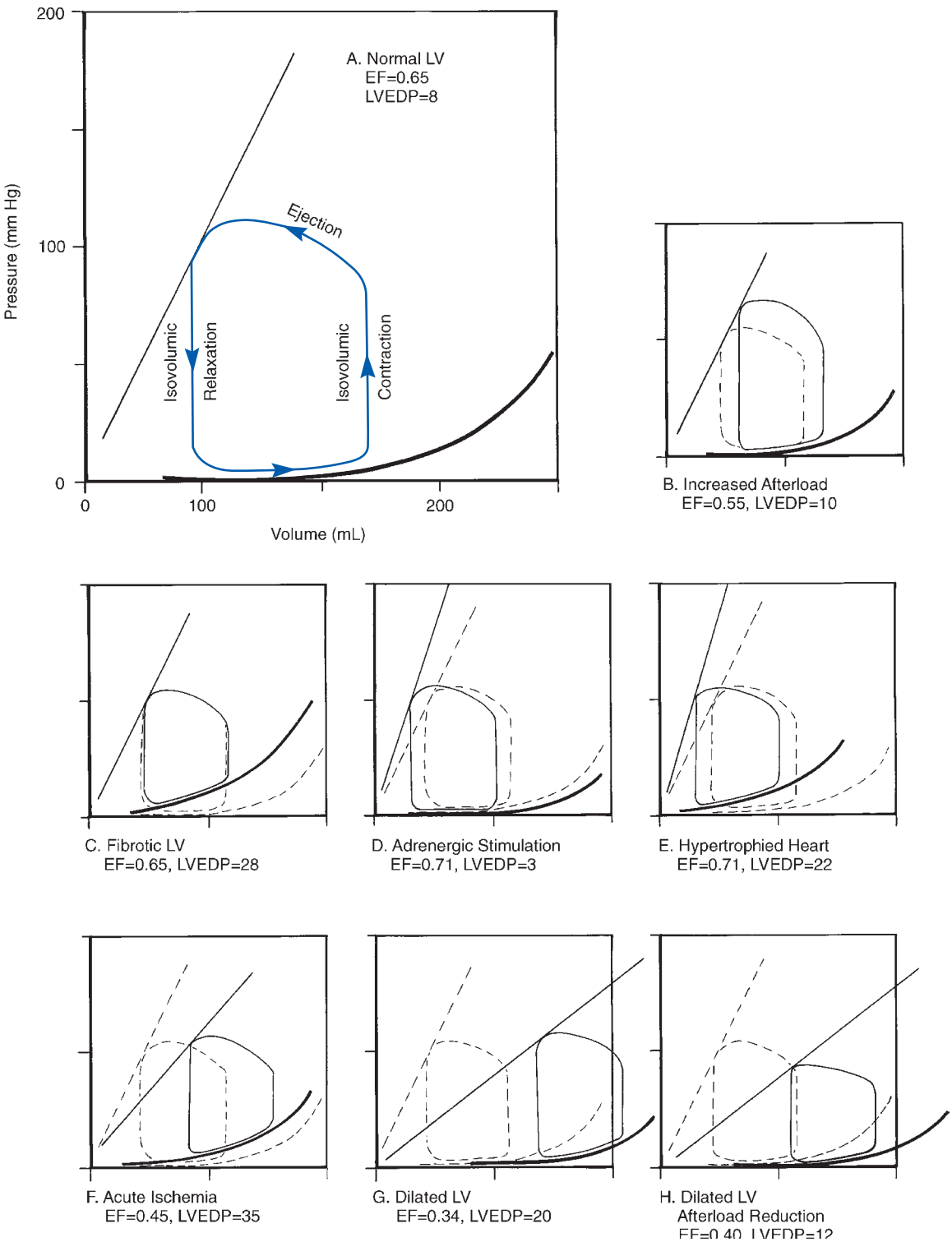

Figure 3-11. Left ventricular pressure-volume curves for various physiologic and pathologic conditions (detailed descriptions are in the text). The bold curved line at the bottom of each loop series represents the diastolic pressure-volume relationship. The straight line located on the upper left side of each loop series is the end-systolic pressure-volume relationship. The stroke volume for each curve has been arbitrarily set at 75 mL. Systolic aortic pressure is 115 mm Hg in all curves except *B* (increased afterload, systolic pressure 140 mm Hg) and *H* (reduced afterload, systolic pressure 90 mm Hg). LV, left ventricle; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure in mm Hg.

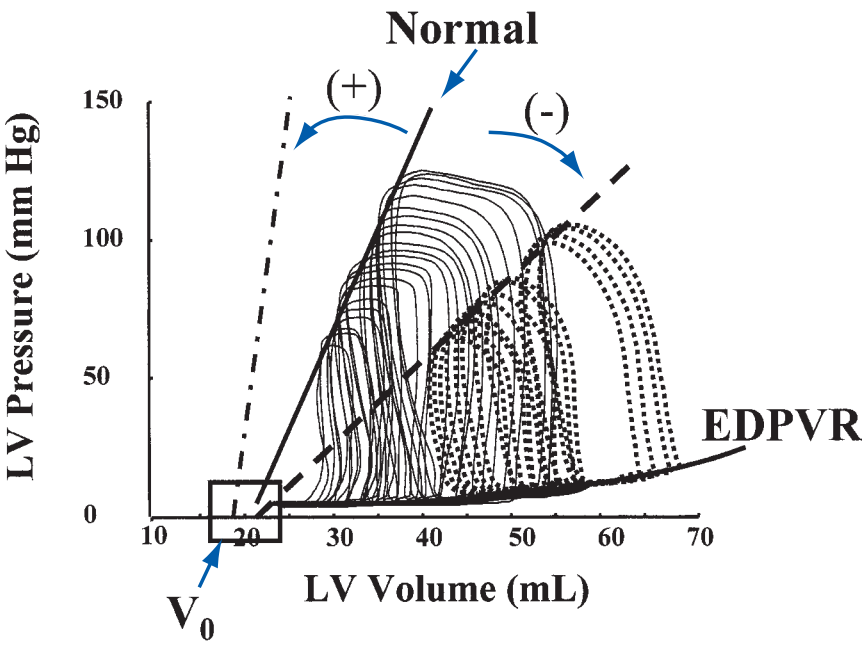

Figure 3-12. Two series of declining left ventricular pressure-volume loops generated during transient bicaval occlusion. Loops were generated in normal left ventricles (Normal) and after 30 minutes of global normothermic ischemia and subsequent reperfusion (*dashed lines*). The end-systolic pressure-volume points from each series are connected by a line generated by linear regression. The end-diastolic pressure-volume relationship indicating chamber stiffness (inverse of compliance) is generated by fitting the end-diastolic point from each loop to an exponential curve. The volume axis intercept (V_0) is shown in the inset. A negative inotropic effect (i.e., ischemia-reperfusion) is characterized by a decrease in the ESPVR slope, whereas a positive inotropic state is characterized by an increase in ESPVR slope. Notice that the V_0 for these conditions are in close proximity (*inset*). In some cases, a negative inotropic state is associated with a decrease in slope and an increase in V_0.

pressure-volume loop has moved back to the left, decreasing the degree of chamber dilatation, the end-diastolic pressure, and the ejection fraction. A positive inotropic agent would shift the ESPVR line to the left (toward the dashed line), the degree of dilatation would be reduced, and both stroke volume and ejection fraction would be increased. It is important to remember that these relationships are idealized and may not reflect true clinical responses. For example, reduced diastolic dilatation from afterload reduction could return the ventricle to a state of improved intrinsic contractility. Despite these interactions, the pure concepts discussed here are very helpful in understanding the response of the heart to clinical interventions.

Another index of contractility, perhaps less influenced by other parameters, is the *preload recruitable stroke work* (PRSW) relationship. *Stroke work* is the area of the pressure-volume loop. For each pressure-volume loop derived by vena caval occlusion, the stroke work is plotted relative to its end-diastolic volume[30] (Fig. 3-13). The slope of the derived linear relationship is a measure of contractility independent (within physiologic ranges) of preload and afterload. The PRSW relationship reflects overall performance of the left ventricle, combining systolic and diastolic components.[31]

Clinical indices of contractility

Clearly, from the preceding discussion, the degree of contractility can be assessed, but unlike blood pressure, an ideal number or range to describe it cannot be derived. Since ESPVR and PRSW are unique for each ventricle, these parameters more accurately measure changes in contractility. The greatest impediment to the clinical application of the ESPVR and PRSW is the difficulty in measuring ventricular volume and inducing preload reduction to derive the pressure-volume loops. More easily measurable indices of contractility have been actively sought.

Ejection fraction is used by many clinicians as a measure of contractility. However, as noted in the discussion of Fig. 3-11, ejection fraction is influenced by preload and afterload alterations without any change in contractility. Depending on loading conditions, hearts with a lower ejection fraction can produce a greater cardiac output. Although roughly indicative of cardiac reserve, ejection fraction is an inconsistent marker for overall cardiac function perioperatively.

Myocardial wall stress

The left ventricle is a pressurized, irregularly shaped chamber. During systole, wall stress develops to overcome afterload and eject the blood. The pressure within the chamber and the geometry of the ventricle determine the tension in the wall. A model of the ventricle as a cylinder can be used to examine the effects of chamber size and wall thickness on

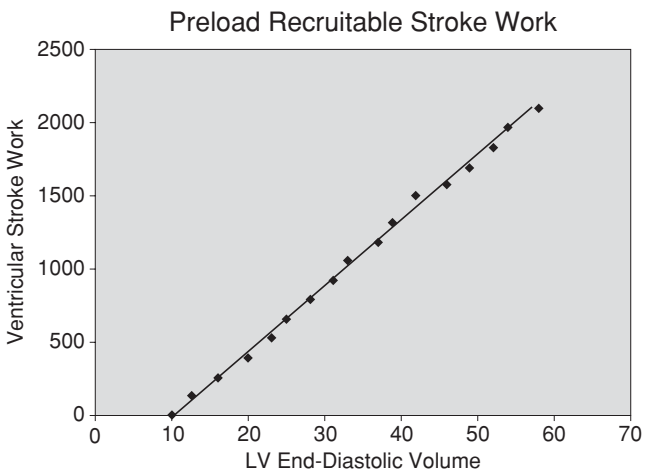

Figure 3-13. Plot of hypothetical measurement of preload recruitable stroke work.

wall stress. In this model, circumferential stress is based on the *law of LaPlace,* that is,

$$\sigma = \frac{Pr}{w}$$

where σ is wall stress, P is transmural pressure, r is radius, and w is wall thickness. This relationship has several important clinical implications. Wall tension must be balanced by the energy available. The only nutrient nearly completely extracted from the blood by the heart is oxygen, and wall tension is the primary determinant of oxygen consumption.

In one scenario, the heart can compensate for changes in wall stress. If systolic pressure within the ventricle is increased chronically (e.g., aortic stenosis or systemic hypertension), then compensatory hypertrophy or thickening of the ventricular wall can return systolic wall stress close to normal. However, as detailed in Fig. 3-11*E,* the price paid is that end-diastolic pressures must be higher.

In another scenario, the function of a heart that has dilated for other reasons is further compromised by the relationship between wall stress and oxygen consumption. As a result of or to compensate for systolic failure, the ventricle will dilate. The increased diastolic diameter proportionally increases wall stress and oxygen consumption. The ability of the heart to increase cardiac output in response to exercise will be limited, leading to symptoms.

Energetics

Chemical fuels

Nearly all chemical energy used by the heart is generated by oxidative phosphorylation. Anaerobic metabolism is very limited because anaerobic enzymes are not present in sufficient concentrations. The major fuels for the myocardium are carbohydrates (i.e., glucose and lactate) and free fatty acids. When sufficient oxygen is present, these fuels are used to generate ATP. Most of the ATP used by the heart (60 to 70%) is expended in the cyclic contraction of the muscle; 10 to 15% is required for maintaining the concentration gradients across the cell membrane; the rest is used in the constant uptake and release of calcium by mitochondria, the breakdown and regeneration of glycogen, and the synthesis of triglycerides.

The heart is quite flexible in the aerobic state in its use of fuels. In the fasting state, lipids may account for 70% of the fuel used by the heart. After a high-carbohydrate meal, blood glucose and insulin levels are high and free fatty acids are low, and glucose accounts for close to 100% of the metabolism. During exercise, elevated lactate levels inhibit the uptake of free fatty acids, and carbohydrates, mostly lactate, can account for up to 70% of the metabolism.[32]

Whatever the fuel source, oxygen is necessary for its efficient utilization. In the absence of oxygen, there are two mechanisms to provide ATP, glycolysis and conversion of phosphate stored in creatine phosphate, because free fatty acids and the by-products of glycolysis cannot be metabolized. Glycolysis is very inefficient—for 1 mol of glucose, 2 mol of ATP is produced by anaerobic glycolysis, compared with 38 mol of ATP with aerobic metabolism. One by-product of glycolysis is lactic acid, which lowers intracellular pH, impairing muscular function. Phosphate stored in creatine phosphate can convert ADP to ATP, but this is not stored in significant amounts.

With ischemia and hypoxia, ATP breaks down to ADP and subsequently to AMP, adenosine, and inosine. The nucleoside building blocks of ATP—adenosine, inosine, and hypoxanthine—are lost from the ischemic myocardium. If oxygen is restored, ATP levels can be restored rapidly in part by salvage pathways with inosine, hypoxanthine, or inosine monophosphate. However, *de novo* synthesis of ATP is also required and can take hours or even days to restore significant ATP levels.

Determinants of oxygen consumption

Since nearly all the energy used by the heart is generated by oxidative metabolism, the rate of oxygen consumption ($M\dot{V}O_2$) is indicative of the metabolic rate of the heart:

$$M\dot{V}O_2 = \frac{(CaO_2 - CvO_2)/CBF}{\text{mass}}$$

where $M\dot{V}O_2$ is myocardial oxygen consumption, CaO_2 is arterial oxygen content in milliliters of O_2 per 100 mL of blood, CvO_2 is coronary venous oxygen content in milliliters of O_2 per 100 mL of blood, and CBF is coronary blood flow in milliliters per minute. Since the bulk of the energy is expended on contraction, changes in the rate of oxygen consumption of the heart are directly related to changes in the contraction cycle and workload. Energy utilization can be increased by an increase in cardiac workload or by a decrease in the efficiency of conversion of chemical to mechanical energy.

Minute work of the heart is the product of heart rate, stroke volume, and developed pressure. A change in each of these factors alters oxygen demand; however, minute work is not the direct determinant of oxygen consumption. As noted earlier, the primary determinant of oxygen demand is the wall tension or stress developed in each cardiac cycle. Indeed, during the period of isovolumic contraction, energy is expended by the heart without the delivery of any kinetic energy to the blood.[33] The energetic cost of ejecting blood from the ventricular chamber is approximately 20 to 30% of that required for isovolumic contraction. To restate this simply, the principal determinant of the cardiac energy requirement is the pressure against which blood is ejected and the volume ejected at that pressure.

Cardiac efficiency relates oxygen consumption to cardiac work. Hence cardiac efficiency = work /$M\dot{V}O_2$. The overall efficiency of the heart ranges from 5 to 40% depending on the type of work (pressure versus volume versus velocity) performed.[34–37] The low efficiency of the heart is due to the expenditure of a predominant portion of the oxygen consumed in generating pressure and stretching internal

elastic components of the myocardium during isovolumic systole (a form of internal work). The velocity of shortening, affected in part by the inotropic state of the myocardium, also is not factored into the work equation but contributes significantly to oxygen consumption.

Following cardiac surgery, cardiac efficiency generally decreases owing to the increase in $M\dot{V}O_2$ relative to the cardiac work performed. The additional oxygen consumed may be due to an increase in basal metabolism and/or an increase in the cost of the excitation-contraction process or inefficiencies of ATP production at the mitochondrial level.

A clear understanding of the role of wall tension and its relation to oxygen demand is essential in cardiac surgery. Excessive systemic pressure may place inordinate energy demands on a compromised ventricle. An intra-aortic balloon pump may shift the energy balance by reducing afterload and improving coronary blood flow. Ventricular distension from an incompetent aortic valve in the absence of left ventricular venting, during the weaning process after removal of the aortic cross-clamp, or with heart failure may create wall stress that outstrips the capacity to deliver oxygen to the myocardium. In the failing heart, where stroke volume is reduced, cardiac output is maintained by increasing heart rate, which increases the percentage of time that the myocardial wall stress is elevated, reduces the time when diastolic blow flow occurs, and creates an imbalance between oxygen demand and delivery.

CORONARY BLOOD FLOW

Normal Coronary Blood Flow

Resting coronary blood flow is slightly less than 1 mL/g of heart muscle per minute. This blood flow is delivered to the heart through large epicardial conductance vessels and then into the myocardium by penetrating arteries leading to a plexus of capillaries. The bulk of the resistance to coronary flow is in the penetrating arterioles (20 to 120 μm in size). Because the heart is metabolically very active, there is a high density of capillaries such that there is approximately one capillary for every myocyte, with an intercapillary distance at rest of approximately 17 μm. Capillary density is greater in subendocardial myocardium than in subepicardial tissue. When there is an increased myocardial oxygen demand (e.g., with exercise), myocardial blood flow can increase to three or four times normal (coronary flow reserve). This increased blood flow is accomplished by vasodilation of the resistance vessels and by recruitment of additional capillaries (many of which are closed in the resting state). This capillary recruitment is important in decreasing the intercapillary distance and thereby decreasing the distance that oxygen and nutrients must diffuse through the myocardium. The blood flow pattern from a coronary artery perfusing the left ventricle, measured by flow probe, is phasic in nature, with greater blood flow occurring in diastole than in systole.[38] The cyclic contraction and relaxation of the left ventricle produce this phasic blood flow pattern by extravascular compression of the arteries and intramyocardial microvessels during systole. There is a gradient in these systolic extravascular compressive forces, being greater or equal to intracavitary pressure in the subendocardial tissue and decreasing toward the subepicardial tissue. Measurement of transmural blood flow distribution during systole shows that subepicardial vessels are perfused preferentially, whereas subendocardial vessels are hypoperfused significantly. Toward the end of systole, blood flow actually reverses in the epicardial surface vessels.[39] Hence the subendocardial myocardium is perfused primarily during diastole, whereas the subepicardial myocardium is perfused during both systole and diastole. A greater capillary density per square millimeter in the subendocardium than in the subepicardial tissue facilitates the distribution of blood flow to the inner layer of myocardium, and myocardial blood flow normally is greater in the subendocardial tissue than in the subepicardial tissue.[40] This places the subendocardium at greater risk of dysfunction, tissue injury, and necrosis during any reduction in perfusion. This is related to (1) the greater systolic compressive forces, (2) the smaller flow reserve owing to a greater degree of vasodilation, and (3) the greater regional oxygen demands owing to wall tension and segmental shortening. If end-diastolic pressure is elevated to 25, 30, or 35 mm Hg, then there is diastolic as well as systolic compression of the subendocardial vasculature. Flow to the subepicardium is effectively autoregulated as long as the pressure in the distal coronary artery is above approximately 40 mm Hg. Flow to the subendocardium, however, is effectively autoregulated only down to a mean distal coronary artery pressure of approximately 60 to 70 mm Hg. Below this level, local coronary flow reserve in the subendocardium is exhausted, and local blood flow decreases linearly with decreases in distal coronary artery pressure. Subendocardial perfusion is further compromised by pathologic processes that increase wall thickness and systolic and diastolic wall tension. Aortic regurgitation in particular threatens the subendocardium because systemic diastolic arterial pressure is reduced and intraventricular systolic and diastolic pressures are elevated.[38,41]

In contrast to the phasic nature of blood flow in the left coronary artery, blood flow in the right coronary artery is relatively constant during the cardiac cycle. The constancy of blood flow is related to the lower intramural pressures and near absence of extravascular compressive forces in the right ventricle compared with the left ventricle.

Control of Coronary Blood Flow

Coronary blood flow is tightly coupled to the metabolic needs of the heart. Under normal conditions, 70% of the oxygen available in coronary arterial blood is extracted, near the physiologic maximum. Any increase in oxygen delivery comes mostly from an increase in blood flow. To maximize efficiency, local coronary blood flow is precisely controlled by a balance of vasodilator and vasoconstrictor mechanisms, including (1) a *metabolic vasodilator system,* (2) a *neurogenic control system,* and (3) the *vascular endothelium.*[42] Blood flow

is controlled by moment-to-moment adjustment of coronary tone of the resistance vessels, i.e., arterioles and precapillary sphincters.

The metabolic vasodilator mechanism responds rapidly when local blood flow is insufficient to meet metabolic demand. The primary mediator is adenosine generated within the myocyte and released into the interstitial compartment. Adenosine relaxes arteriolar smooth muscle cells by activation of A_2 receptors. Adenosine is formed when the oxygen supply cannot sustain the rapid rephosphorylation of ADP to ATP. Once sufficient oxygen is supplied to the myocardium, less adenosine is formed. Adenosine is therefore the coupling agent between oxygen demand and supply. Other local vasodilators that influence coronary blood flow are carbon dioxide, lactic acid, and histamine.

The sympathetic nervous system acts through *alpha receptors* (which cause vasoconstriction) and *beta receptors* (which cause vasodilation). There is direct innervation of the large conductance vessels and lesser direct innervation of the smaller resistance vessels. Sympathetic receptors on the smooth muscle cells of the resistance vessels respond to humoral catecholamines. Alpha receptors predominate over beta receptors such that when norepinephrine is released from the sympathetic nerve endings, vasoconstriction ordinarily occurs.

Endothelium-dependent regulation of coronary artery blood flow is a dynamic balance between vasodilating and vasoconstricting factors. Vasodilators include nitric oxide ($NO^{\bullet}$) synthesized from L-arginine by endothelial nitric oxide synthase and endothelially released adenosine. The principal vasoconstrictor is the endothelially derived constricting peptide endothelin-1. Other vasoconstrictors include angiotensin II and superoxide free radical.[43] $NO^{\bullet}$ is dominant in local regulation of coronary arterial tone by overwhelming the action of endothelium-derived vasoconstrictor substances, which are tonically released by the coronary artery endothelium. $NO^{\bullet}$ is released by the coronary vascular endothelium by both soluble factors (e.g., acetylcholine, adenosine, and ATP) and mechanical signals (e.g., shear stress and pulsatile stress secondary to increased intraluminal blood flow). If the endothelium is intact, acetylcholine from the sympathetic nerves causes vasodilation through generation of $NO^{\bullet}$. If the endothelium is not functionally intact, acetylcholine causes vasoconstriction by direct stimulation of the vascular smooth muscle. $NO^{\bullet}$ is a potent inhibitor of platelet aggregation and neutrophil function (i.e., superoxide generation, adherence, and migration), which has implications in the anti-inflammatory response to ischemia-reperfusion and cardiopulmonary bypass.

Endothelin-1 (ET-1) interacts principally with specific endothelin receptors (ET_A) on vascular smooth muscle and causes smooth muscle vasoconstriction. Endothelin-1 counteracts the vasodilator effects of endogenous adenosine, $NO^{\bullet}$, and prostacyclin (PGI_2). Endothelin-1 is synthesized rapidly in vascular endothelium, particularly during ischemia, hypoxia, and other stress conditions, where it acts in a paracrine fashion. ET-1 has a short half-life (4 to 7 minutes), which exceeds that of adenosine (8 to 12 seconds) and $NO^{\bullet}$ (microseconds). However, the avid binding of ET-1 to ET_A receptors prolongs its effects beyond the half-life. Human coronary arteries demonstrate abundant ET-1 binding sites, suggesting that ET-1 has an important role in the control of coronary blood flow in humans. Changes in coronary blood flow in ischemia-reperfusion, congestive heart failure, hypertension, and atherosclerosis may be, in part, mediated or exacerbated by an overexpression of ET-1, which may overwhelm the vasodilating effects of local autacoids such as adenosine and $NO^{\bullet}$.[44] Increased age may exacerbate the vasoconstrictor responses to ET-1, which are further exaggerated by a concomitant decrease in tonic $NO^{\bullet}$ production. In addition, the levels of ET-1 have been observed to increase with myocardial ischemia-reperfusion and after cardiac surgery.

Under ordinary circumstances, the metabolic vasodilator system is the dominant force acting on the resistance vessels. For example, the increased metabolic activity caused by sympathetic stimulation leads to vasodilation of the coronary arterioles through the metabolic system despite a direct vasoconstriction effect of norepinephrine.[45–47]

Coronary artery blood flow is also determined by perfusion pressure. However, in the coronary vasculature, blood flow can remain constant over a range of perfusion pressures. The control mechanisms described allow *autoregulation* of blood flow, adjusting vascular resistance to match blood flow requirements. The autoregulatory "plateau" occurs between approximately 60 and 120 mm Hg of perfusion pressure. If distal coronary artery perfusion pressure is reduced by a critical stenosis or hypotension, vasodilator capacity will be exhausted, and coronary blood flow will decrease, following a linear relationship with perfusion pressure. Since the subendocardial regional of the left ventricle has a lower coronary vascular reserve, maximal dilation is reached in this region before it occurs in the subepicardial tissue, and a preferential hypoperfusion of the subendocardial tissue results.

Hemodynamic Effect of Coronary Artery Stenosis

Surgically treatable atherosclerotic disease primarily affects the large conductance vessels of the heart. The hemodynamic effect of a stenosis is determined by *Poiseuille's law,* which describes the resistance of a viscous fluid to laminar flow through a cylindrical tube; specifically,

$$Q = \frac{\pi(\Delta P)}{8\eta} \cdot \frac{r^4}{l}$$

where Q is flow, ΔP is the pressure change, η is viscosity, r is radius, and l is the length of the resistance segment. Resistance (pressure change/flow)

$$R = \frac{(\Delta P)}{Q} = \frac{8\eta}{\pi} \cdot \frac{l}{r^4}$$

is inversely proportional to the *fourth* power of the radius and directly proportional to the length of the narrowing. There-

Table 3–2.

Effect of Degree and Length of Stenosis on Resistance to Flow Based on Poisenille's Law

Percent stenosis of a 1-cm–diameter vessel	Radius (cm)	Proportional resistance for various segment lengths (cm)		
		0.25 cm	1 cm	2 cm
0	0.5	1	4	8
50	0.25	16	64	128
60	0.2	39	156	313
70	0.15	123	494	988
80	0.1	625	2500	5000
90	0.25	10,000	40,000	80,000
Proportional increase in resistance 80% vs. 60% stenosis		16		
Proportional increase in resistance 90% vs. 60% stenosis		256		

Note: The value for a reference vessel of length 0.25 cm with 0% stenosis (in the box) is set to 1 for comparison.

fore, a small change in diameter has a magnified effect on vascular resistance (Table 3-2). Conductance vessels are sufficiently large that a 50% reduction in the diameter of the vessel has minimal hemodynamic effect. A 60% reduction in the diameter of the vessel has only a very small hemodynamic effect. As the stenosis progresses beyond 60%, small decreases in diameter have significant effects on blood flow. For a given segment length, an 80% stenosis has a resistance that is 16 times greater than that of a 60% stenosis. For a 90% stenosis, the resistance is 256 times greater than that of a 60% stenosis.[48] Furthermore, for successive stenoses in the same vessel, the resistance is additive. An additional factor in resistance to flow is turbulence. Stenotic lesions can cause conversion from laminar to turbulent flow.[49] With laminar flow, the pressure drop is proportional to flow rate Q; with turbulent flow, pressure drop is proportional to (Q^2). For all these reasons, patients who have had a small progression in the degree of coronary stenosis may experience a rapid acceleration of symptoms.

Atherosclerosis also alters normal vascular regulatory mechanisms. The endothelium is often destroyed or damaged, so vasoconstrictor mechanisms are relatively unopposed by the impaired vasodilator mechanism; constriction is exaggerated, and responses to stimuli that require dilatation are blunted.[50]

As noted earlier, when a stenosis is less than 60%, little change is flow is noted. This is due to compensation by the coronary flow reserve of the resistance vessels distal to the stenotic conductance vessel. Since resistance to flow is additive, a decrease in distal resistance will balance an increase in proximal resistance, and flow will be unchanged. As flow reserve decreases, any stimulus that increases myocardial oxygen demand (such a tachycardia, hypertension, or exercise) cannot be met by dilation of the distal vasculature, and myocardial ischemia results.[42]

In the human, coronary arterial vessels are end vessels with little collateral flow between major branches except in pathologic situations. With sudden coronary occlusion, though, there usually is modest collateral flow through very small vessels (20 to 200 μm in size); this flow generally is insufficient to maintain cellular viability. Collateral flow gradually begins to increase over the next 8 to 24 hours, doubling by about the third day after total occlusion. Collateral blood flow development appears to be nearly complete after 1 month, restoring normal or nearly normal resting flow to the surviving myocardium in the ischemic region. Previous ischemic events or gradually developing stenoses can lead to larger preexisting collaterals in the human heart. The presence of these preexisting collaterals has been shown to be important in the prevention of ischemic damage if coronary occlusion should occur.[51]

Endothelial Dysfunction

As noted previously, NO$^{\bullet}$, adenosine, and endothelin-1 are synthesized and released by the endothelium.[52,53] Ischemia-reperfusion, hypertension, diabetes, and hypercholesterolemia can impair generation of NO$^{\bullet}$, and vasoconstriction may predominate, mediated by the relative overexpression of endothelin-1. Reperfusion after temporary myocardial ischemia is one situation in which NO$^{\bullet}$ production may be impaired, leading to a vicious cycle in which the vasodilator reserve of the resistance vessels is reduced with a consequent and progressive "low flow" or "no flow" phenomenon. The coronary vascular NO$^{\bullet}$ system also may be impaired in some cases after coronary artery bypass surgery.

The endothelium helps to prevent cell-cell interactions between blood-borne inflammatory cells (i.e., leukocytes and platelets) that initiate a local or systemic inflammatory reaction. Inflammatory cascades occur with sepsis, ischemia-reperfusion, and cardiopulmonary bypass. Under normal conditions, the vascular endothelium resists interaction with neutrophils and platelets by tonically releasing adenosine and $NO^{\bullet}$, which have potent antineutrophil and platelet-inhibitory effects. Damage to the endothelium lowers the resistance to neutrophil adhesion. Neutrophils can damage the endothelium by adhesion to its surface and subsequent release of oxygen radicals and proteases. This amplifies the inflammatory response and decreases the tonic generation and release of adenosine and $NO^{\bullet}$, which then permits further interaction with activated inflammatory cells. The products released by activated neutrophils have downstream physiologic consequences on other tissues, notably the heart, including increasing vascular permeability, creating blood flow defects (no-reflow phenomenon), and promoting the pathogenesis of necrosis and apoptosis.[54]

The triggers of these inflammatory reactions in the heart include cytokines [i.e., interleukin 1 (IL-1), IL-6, and IL-8], complement fragments (C3a, C5a, membrane attack complex), oxygen radicals, and thrombin, which upregulate adhesion molecules expressed on both inflammatory cells (CD11a/CD18) and endothelium (e.g., P-selectin, E-selectin, and ICAM-1). The release of cytokines and complement fragments during cardiopulmonary bypass activates the vascular endothelium on a systemic basis, which contributes to the inflammatory response to cardiopulmonary bypass.[55] Both adenosine and $NO^{\bullet}$ have been used therapeutically to reduce the inflammatory responses to cardiopulmonary bypass and to reduce ischemia-reperfusion injury. This treatment has reduced endothelial damage from surgical and nonsurgical ischemia-reperfusion injury and cardiopulmonary bypass.[56–58]

The Sequelae of Myocardial Hypoperfusion: Infarction, Myocardial Stunning, and Myocardial Hibernation

Normally contracting muscle in the left ventricle uses 8 mL of oxygen per 100 g of muscle every minute. Of this, 1.3 mL/100 g of muscle per minute is necessary for cell survival; the rest supports contraction. As oxygen delivery is reduced, contraction strength decreases rapidly (within 8 to 10 heartbeats). This is seen acutely in response to acute ischemia and is reversed rapidly with reperfusion. If the extent of reduction of coronary blood flow is severe, mild to moderate abnormalities in cellular homeostasis occur. Reduced cellular levels of ATP lead to a loss of adenine nucleotides from the cell. If the reduction in coronary blood flow is sustained, progressive loss of adenine nucleotides and elevation of intracellular and intramitochondrial calcium may lead to cellular death and subsequent necrosis. If the myocyte is reperfused before subcellular organelles are irreversibly damaged, the myocyte may recover slowly. A period of days is necessary for full recovery of myocyte ATP levels because adenine nucleotides must be resynthesized. During this time, contractile processes are impaired. This impairment is related to reversible damage to the contractile proteins such that their responsiveness to cytosolic levels of calcium is diminished. The magnitude of the cytosolic pulse of calcium with each heartbeat appears to be nearly normal, but the magnitude of the consequent contraction is greatly reduced. Over a period of 1 to 2 weeks, this myocardium recovers gradually. This viable but dysfunctional myocardium is called *stunned myocardium.*[59,60,65]

Chronic hypoperfusion and oxygen delivery at a reduced level but above the level required for cell viability can cause a chronic hypocontractile state known as *hibernation.* Hibernation appears to be associated with a decrease in the magnitude of the pulse of calcium involved in the excitation-contraction process such that the calcium levels developed within the cytosol during each heartbeat are inadequate for effective contraction to occur. Histologic examination shows islets in the subendocardium where there is a loss of contractile proteins and sarcoplasmic reticulum and alterations in other subcellular structures.[61,62] With reperfusion, hibernating myocardium can resume normal and effective contraction very quickly, although complete recovery may be delayed for several months.[63–66] This is of particular importance for patients with poor ventricular function but viable heart muscle.[67]

Reperfusion of acutely ischemic myocardium may cause further cellular damage and necrosis rather than immediate recovery. The etiology of *reperfusion injury* is multifactorial. Damage to endothelium in the reperfused region fails to prevent adhesion and activation of leukocytes and platelets. Oxygen free radicals are released. Derangement of the ATP-dependent sodium-potassium pump disrupts cell volume regulation with consequent leakage of water into the cell, explosive cell swelling, and rupture of the cell membrane. Techniques attempting to reduce reperfusion injury, minimize adverse sequelae, and preserve myocytes include leukocyte depletion or inactivation, prevention of endothelial activation, free-radical scavenging, reperfusion with solutions low in calcium, and reperfusion with hyperosmolar solutions.[68,69] Both adenosine and low-dose $NO^{\bullet}$ are potent cardioprotective agents that attenuate neutrophil-mediated damage, infarction, and apoptosis.[56,70]

The metabolic changes that occur with ischemia-reperfusion represent a complex system of adaptive mechanisms that allow the myocyte to survive despite a temporary reduction in oxygen delivery. These adaptive mechanisms may be triggered by a very brief coronary occlusion (as short as 5 minutes) such that the negative sequelae of a subsequent prolonged coronary occlusion are greatly minimized. This phenomenon has been called *ischemic preconditioning.* A coronary occlusion that might cause as much as 40% myocyte death in a region subjected to prolonged ischemia may be reduced to only 10% myocyte death if the prolonged period of ischemia is preceded by a 5-minute interval of "preconditioning" coronary occlusion.[68,71,72]

PHYSIOLOGY OF HEART FAILURE

Definition and Classification

Heart failure is the inability of the heart to deliver adequate blood to the tissues to meet metabolic needs at rest or during mild to moderate exercise. Components include low cardiac output, an impaired exercise capacity, neurohormonal activation, enhanced oxidative stress, and premature myocardial cell death. Processes that cause heart failure can impair systolic function (the ability to contract and empty) or diastolic function (the ability to relax and fill) or both. The acute and chronic stages of a myocardial infarction involving a large area of the left ventricle cause systolic heart failure. The acute loss of contractile function compromises the ability of the ventricle to maintain a normal stroke volume (Fig. 3-11*F*). As the infarction heals, the adaptive response of ventricular dilation reduces the heart's systolic functional reserve. Cardiomyopathies affect the myocardium globally, leading to reduced systolic function. In both cases, the left ventricle dilates, which causes the pressure-volume relations of the left ventricle to shift to the right (Fig. 3-11*G*). In this situation, the diastolic portion of the pressure-volume curves is not greatly changed. However, the global systolic performance of the heart (i.e., the ability to pump blood) may be inadequate to meet even resting needs (particularly if there is systolic bulging of a large infarction).[73,74]

Diastolic failure may occur without an impairment of systolic contractility if the myocardium becomes fibrotic or hypertrophied or if there is an external constraint on filling such as with pericardial tamponade.[75] Increased stiffness of the left ventricular myocardium is associated with an excessive upward shift in the diastolic pressure-volume curve (Fig. 3-11*C* and *E*). The most common cause of increased myocardial stiffness is chronic hypertension with consequent left ventricular hypertrophy and diastolic stiffness (related both to myocyte hypertrophy and to increased fibrosis of the ventricle).[76,77]

It should be noted from these examples that although one process may predominate, most patients with heart failure manifest both systolic and diastolic dysfunction.

Early Cardiac and Systemic Sequelae of Heart Failure

The adaptive homeostatic reactions of the body leading to heart failure depend on the duration of the ongoing pathologic process. When cardiac function deteriorates acutely and cardiac output diminishes, neurohumoral reflexes attempt to restore both cardiac output and blood pressure. Activation of the sympathetic adrenergic system in the heart and in the peripheral vasculature causes systemic vasoconstriction (via an alpha-adrenergic effect) and increases heart rate and contractility (via a beta-adrenergic effect). A number of mediators formed during this adaptive stage, including norepinephrine, angiotensin II, vasopressin, brain natriuretic peptide (BNP), and endothelin, not only help in renal retention of salt and water leading to rapid volume expansion but also cause vasoconstriction. Aldosterone output is increased, again helping conserve sodium. The concerted responses of the adrenergic system and the renin-angiotensin system, therefore, recruit changes in the primary determinants of stroke volume and cardiac output—preload, afterload, and contractility. The heart responds to loss of systolic function by dilating progressively. This dilation leads to preservation of stroke volume by Frank-Starling mechanisms, but increased stroke volume is achieved at the expense of ejection fraction, as shown in Fig. 3-11*G* as a right shift in the pressure-volume relationship of the left ventricle with an increase in end-diastolic volume (and pressure). In addition to a global dilatation response, acute alterations in cardiac geometry may occur early after a large myocardial infarction, with thinning of the left ventricular wall in the region of the infarct as well as expansion of overall left ventricular cavity size. This is particularly true if the infarct is apical because of geometric considerations related to the thinness of the left ventricular wall in the region of the apex and to the short radius of curvature of the left ventricular apex. As volume expansion occurs, production of the cardiac atrial natriuretic peptide is increased, which tends to prevent excessive sodium retention and inhibit activation of the renin-angiotensin and aldosterone systems.[78–84]

Cardiac and Systemic Maladaptive Consequences of Chronic Heart Failure

The acute-phase response just described, while acutely beneficial, becomes maladaptive and contributes significantly to long-term problems in patients with heart failure (Figure 3-14). In the latter stages of heart failure, the kidney tends to retain sodium and become hyporesponsive to atrial natriuretic peptide and BNP.[79] Desensitization of beta-adrenergic receptors is a consequence of sustained stimulation with a reduced response to elevated circulating catecholamine levels.[20]

Left ventricular dilation is due to hypertrophy of the myocytes as well as lengthening of the myocytes as sarcomeres are added. However, there is significant slippage of myofibrils, leading to dilation without an increase in the number of myocytes. Progressive dilation of the heart leads to an increase in oxygen consumption during systole. Ventricular remodeling leads to progressive fibrosis.

Angiotensin and aldosterone stimulate collagen formulation and proliferation of fibroblasts in the heart, leading to an increase in the ratio of interstitial tissue to myocardial tissue in the noninfarcted regions of the heart.[85] The impact of aldosterone has been documented by the effectiveness of aldosterone receptor antagonists in improving the morbidity and mortality of patients with heart failure.[86] The progressive fibrosis leads to increased diastolic stiffness, which limits diastolic filling and increases end-diastolic pressure. Fibrosis and increased ventricular size predispose to reentry ventricular arrhythmias that are a common cause of death in the late stages of heart failure. This rapidly deteriorating clinical cycle explains the result in one clinical study in which the 5-year survival rate was only 25% in men and 38% in

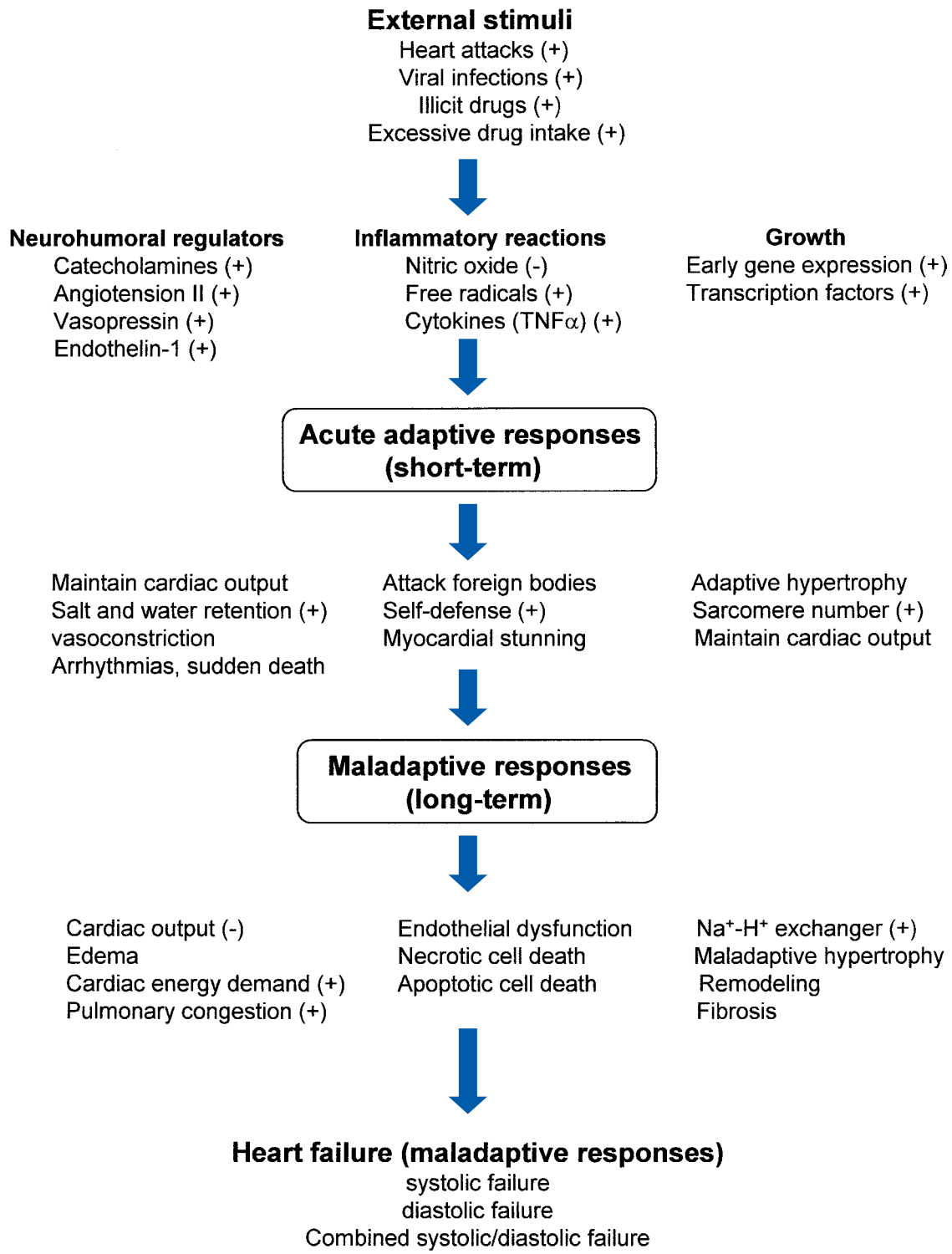

Figure 3-14. Pathophysiology of heart failure from stimulus (etiology) to acute adaptive and chronic maladaptive responses. (+) indicates positive stimulation; (−) indicates negative factors that tend to reduce stimulation of heart failure.

women.[81,83,84,87] Hence heart failure progresses as a result of a vicious cycle of left ventricular dilatation and remodeling, responses that decrease cardiac performance further.

Evidence has accumulated over the past decade that suggests that endothelial dysfunction, release of cytokines, and apoptotic cell death may participate in the development of heart failure as a maladaptive reaction (Fig. 3-14). Reduced availability of nitric oxide and increased production of vasoconstrictor agents such as endothelin and angiotensin II have been reported in failing hearts.[88,89] Heart failure is often accompanied by changes in the endogenous antioxidant defense mechanisms of the heart, as well as evidence of

oxidative injury to the myocardium. Cytokines, released from systemic and local inflammatory responses in the failing heart, directly activate inflammatory cells to release superoxide radicals and cause endothelial dysfunction by augmenting inflammatory cell–endothelial cell interactions. Cytokines also may induce necrotic and apoptotic myocyte cell death directly.[90,91]

Cardiac secretion of B-type natriuretic peptide (BNP) has been shown to be increased with heart failure.[92] BNP is a cardiac neurohormone released as preproBNP that is enzymatically cleaved to N-terminal proBNP and BNP on ventricular myocyte stretch.[93] The physiologic effects of BNP include natriuresis, vasodilation, and neurohumoral changes. Plasma measurement of BNP is emerging as a useful and cost-effective marker for heart failure. A BNP level below 100 pg/mL excludes acutely decompensated heart failure.[94] However, BNP is not specific for heart failure. Other factors rather than stretch may stimulate BNP release, including fibrosis, arrhythmias, ischemia, endothelial dysfunction, and cardiac hypertrophy. BNP levels greater than 20 pg/mL are associated with an increased risk for atrial fibrillation and heart failure. Nesiritide is a synthetic analogue of human BNP. In clinical trials, nesiritide has been shown to decrease cardiac filling pressures, increase cardiac index, and improve the clinical status of patients with acute decompensated heart failure.[95]

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CHAPTER 4

Cardiac Surgical Pharmacology

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Clinical pharmacology associated with cardiac surgery is an important part of patient management. Patients in the perioperative period receive multiple agents that affect cardiovascular and pulmonary function. In this chapter we summarize the pharmacology of the agents commonly used for treating the primary physiologic disturbances associated with cardiac surgery, hemodynamic instability, respiratory insufficiency, and alterations of hemostasis. For cardiovascular drugs, the common theme is that pharmacologic effects are produced by intracellular ion fluxes.

Several basic subcellular/molecular pathways are important in cardiovascular pharmacology, as shown in Fig. 4-1. The action potential in myocardial cells is a reflection of ion fluxes across the cell membrane, especially Na^+, K^+, and Ca^{2+}.[1,2] Numerous drugs used to control heart rate and rhythm act by altering Na^+ (e.g., lidocaine and procainamide), K^+ (e.g., amiodarone, ibutilide, and sotalol), or Ca^{2+} (e.g., diltiazem) currents. Calcium also has a dominant effect on the inotropic state.[3,4] Myocardial contractility is a manifestation of the interaction of actin and myosin, with conversion of chemical energy from ATP hydrolysis into mechanical energy. The interaction of actin and myosin in myocytes is inhibited by the associated protein tropomyosin. This inhibition is "disinhibited" by intracellular calcium. A similar situation occurs in vascular smooth muscle, where the interaction of actin and myosin (leading to vasoconstriction) is modulated by the protein calmodulin, which requires calcium as a cofactor. Thus intracellular calcium has a "tonic" effect in both the myocardium and in vascular smooth muscle.

Numerous drugs used during or around cardiac surgery act by altering intracellular calcium.[3,4] Catecholamines (e.g., norepinephrine, epinephrine, and dobutamine) with beta-agonist activity regulate intramyocyte calcium levels via the nucleotide cyclic adenosine monophosphate (cAMP) (Fig. 4-2). Beta agonists bind to receptors on the cell surface that are coupled to the intracellular enzyme adenylate cyclase via the stimulatory transmembrane GTP-binding protein. This leads to increased cAMP synthesis, and cAMP, in turn, acts as a "second messenger" for a series of intracellular reactions resulting in higher levels of intracellular calcium during systole. Less well known is that drugs with only alpha-adrenergic agonist activity also may increase intracellular Ca^{2+} levels, although by a different mechanism.[5,6] While under investigation, the probable basis for the inotropic effect of alpha-adrenergic drugs is the stimulation of phospholipase C, which catalyzes hydrolysis of phosphatidyl inositol to diacylglycerol and inositol triphosphate (see Fig. 4-2). Both these compounds increase the sensitivity of the myofilament to calcium, whereas inositol triphosphate stimulates the release of calcium from its intracellular storage site, the sarcoplasmic reticulum. There is still some debate about the mechanism for the inotropic effect of alpha-adrenergic agonists and its significance for the acute pharmacologic manipulation of contractility, but there is little debate about the importance of this mechanism in vascular smooth muscle, where the increase in intracellular calcium stimulated by alpha-adrenergic agonists can increase smooth muscle tone significantly. However, intracellular calcium in vascular smooth muscle is also controlled by cyclic nucleotides.[7,8] In contrast to the myocyte, in vascular smooth muscle, cAMP has a primary effect of stimulating the uptake of calcium into intracellular storage sites, decreasing its availability (Fig. 4-3). Thus drugs that stimulate cAMP production (beta agonists) or inhibit its breakdown (phosphodiesterase inhibitors) will cause vasodilation. In addition, cyclic guanosine monophosphate (cGMP) also increases intracellular calcium storage (see Fig. 4-3), decreasing its availability for modulating the interaction of actin and myosin. Several commonly used pharmacologic agents act via cGMP. For example, nitric oxide stimulates the enzyme guanylate cyclase, increasing cGMP levels. Drugs such as nitroglycerin and sodium nitroprusside achieve their effect by producing nitric oxide as a metabolic product. Vasodilation

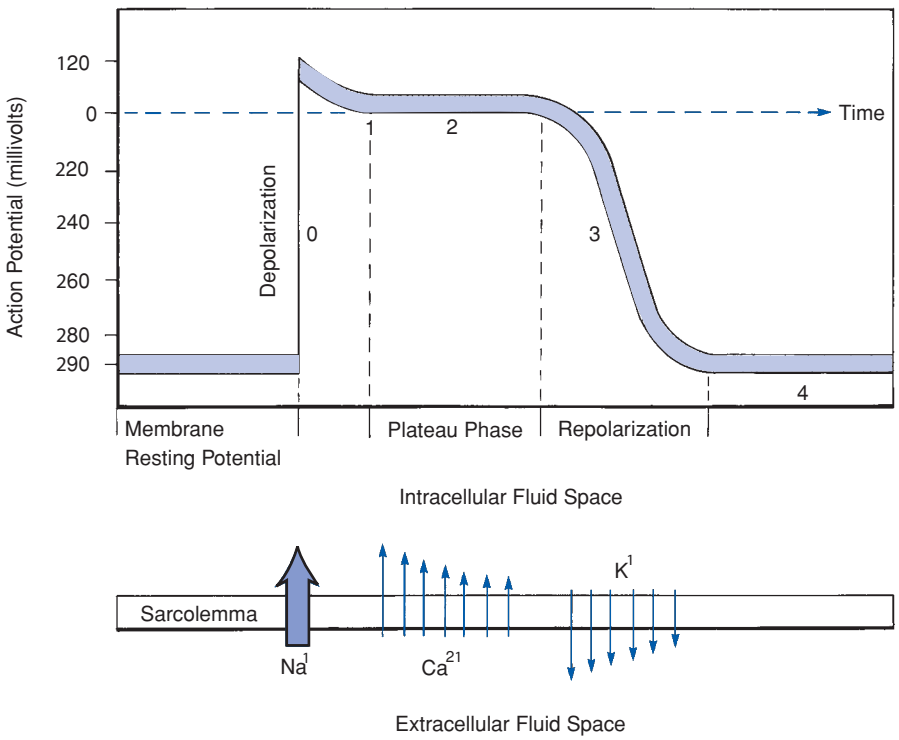

Figure 4-1. Cardiac ion fluxes and the action potential. The resting membrane potential is largely a reflection of the intercellular/intracellular potassium gradient. Depolarization of the membrane during phase 4 triggers an initial fast sodium channel with overshoot (phase 0) followed by recovery (phase 1) to a plateau (phase 2) maintained by an inward calcium flux and then repolarization owing to an outward potassium flux (phase 3).

is also produced by "cross-talk" between K^+ and Ca^{2+} fluxes. Decreased levels of ATP, acidosis, and elevated tissue lactate levels increase the permeability of the ATP-sensitive K^+ channel. This increased permeability results in hyperpolarization of the cell membrane that inhibits the entry of Ca^{2+} into the cell. This results in decreased vascular tone.

The simplistic overview of pathways of cardiac pharmacology as summarized in Figs. 4-1 through 4-3 also suggests the primary cause of difficulty in the clinical use of the drugs discussed in this chapter. The mechanisms of action for control of heart rate and rhythm, contractility, and vascular tone are interrelated. For example, beta-adrenergic agonists not only increase intracellular calcium to increase contractility, but they also alter K^+ currents, leading to tachycardia. Catecholamines not only have beta-adrenergic agonist activity, with inotropic and chronotropic effects, but they also possess alpha-agonist activity, leading to increased intracellular calcium in vascular smooth muscle and vasoconstriction. Phosphodiesterase inhibitors not only may increase contractility by increasing cAMP in the myocyte, but they also may cause excessive vasodilation by increasing cAMP in the vasculature. The interplay of the various mechanisms means the clinical art of cardiac surgical pharmacology lies as much in selecting drugs for their side effects as for their primary therapeutic effects.

ANTIARRHYTHMICS

Arrhythmias are common in the cardiac surgical period. A stable cardiac rhythm requires depolarization and repolarization in a spatially and temporally coordinated manner, and dysrhythmias may occur when this coordination is disturbed. The mechanisms for arrhythmias can be divided into abnormal impulse initiation, abnormal impulse conduction, and combinations of both.[9,10] Abnormal impulse initiation occurs as a result of increased automaticity (spontaneous depolarization of tissue that does not normally have pacemaking activity) or as a result of triggered activity from abnormal conduction after depolarizations during phase 3 or 4 of the action potential. Abnormal conduction often involves reentry phenomena, with recurrent depolarization around a circuit owing to unilateral conduction block in ischemic or damaged myocardium and retrograde activation by an alternate pathway through normal tissue. In this simplistic view, it is logical that dysrhythmias could be suppressed by slowing the conduction velocity of ectopic foci, allowing normal pacemaker cells to control heart rate, or by prolonging the action potential duration (and hence refractory period) to block conduction into a limb of a reentry circuit.

A scheme proposed originally by Vaughan Williams and modified subsequently[11,12] is used often to classify antidysrhythmic agents, and although alternative schemes describing specific channel-blocking characteristics have been proposed and may be more logical,[13] we will organize our discussion using the Vaughan Williams system of four major drug categories. In this scheme, class I agents are those with local anesthetic properties that block Na^+ channels, class II drugs are beta-blocking agents, class III drugs prolong action potential duration, and class IV drugs are calcium entry blockers. Amiodarone will be discussed in detail owing to its expanding role in treating both supraventricular and ventricular arrhythmias and because its use has replaced many of the previously used agents. Because of the efficacy of intravenous amiodarone and its recommendations in Advanced Cardiac Life Support

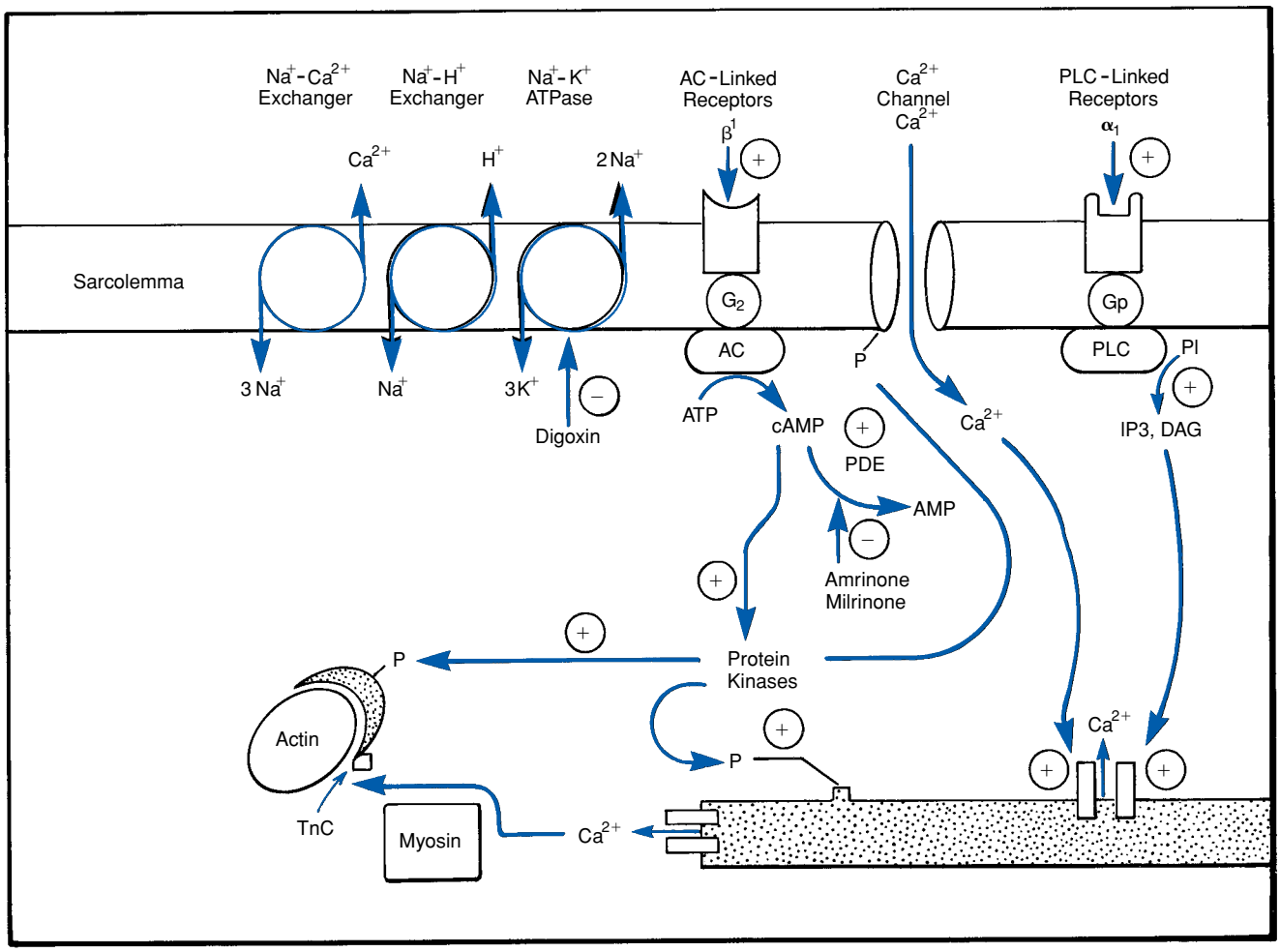

Figure 4-2. Mediators of cardiac contractility. Myocardial contractility is a manifestation of the interaction of actin and myosin, which is facilitated by the binding of calcium to troponin C (TnC). Intercellular calcium levels are controlled by direct flux across the membrane, by cyclic AMP, and by inositol triphosphate (IP_3) and diacylglycerol (DAG) produced by the action of phospholipase C (PLC). The synthesis of cyclic AMP is catalyzed by adenylate cyclase (AC), which is activated by binding of agonist to the beta-adrenergic receptor, and its breakdown is catalyzed by phosphodiesterase (PDE), which is inhibited by amrinone and milrinone. The action of PLC is activated by binding of agonist to the alpha-adrenergic receptor.

(ACLS) guidelines, many of the older drugs used in cardiac surgery have a historical perspective and will be considered briefly.

Class I Agents

While each of the class I agents blocks Na^+ channels, they may be subclassified based on electrophysiologic differences. These differences can be explained, to some extent, by consideration of the kinetics of the interaction of the drug and the Na^+ channel.[14,15] Class I drugs bind most avidly to open (phase 0 of the action potential; see Fig. 4-1) or inactivated (phase 2) Na^+ channels. Dissociation from the channel occurs during the resting (phase 4) state. If the time constant for dissociation is long in comparison with the diastolic interval (corresponding to phase 4), the drug will accumulate in the channel to reach a steady state, slowing conduction in normal tissue. This occurs with class Ia (e.g., procainamide, quinidine, and disopyramide) and class Ic (e.g., encainide, flecainide, and propafenone) drugs. In contrast, for the class Ib drugs (e.g., lidocaine and mexiletine), the time constant for dissociation from the Na^+ channel is short, drug does not accumulate in the channel, and conduction velocity is affected minimally. However, in ischemic tissue, the depolarized state is more persistent, leading to greater accumulation of agent in the Na^+ channel and slowing of conduction in the damaged myocardium.

Procainamide is a class Ia drug that has various electrophysiologic effects.[16] Administration may be limited by the side effects of hypotension and decreased cardiac output.[17,18] The loading dose is 20 to 30 mg/min, up to 17 mg/kg, and should be followed by an intravenous infusion of 20 to 80 mg/kg per minute. Since procainamide prolongs action potential duration, widening of the QRS complex often heralds a potential overdose. The elimination of procainamide involves hepatic metabolism, acetylation to a metabolite with antiarrhythmic and toxic side effects, and

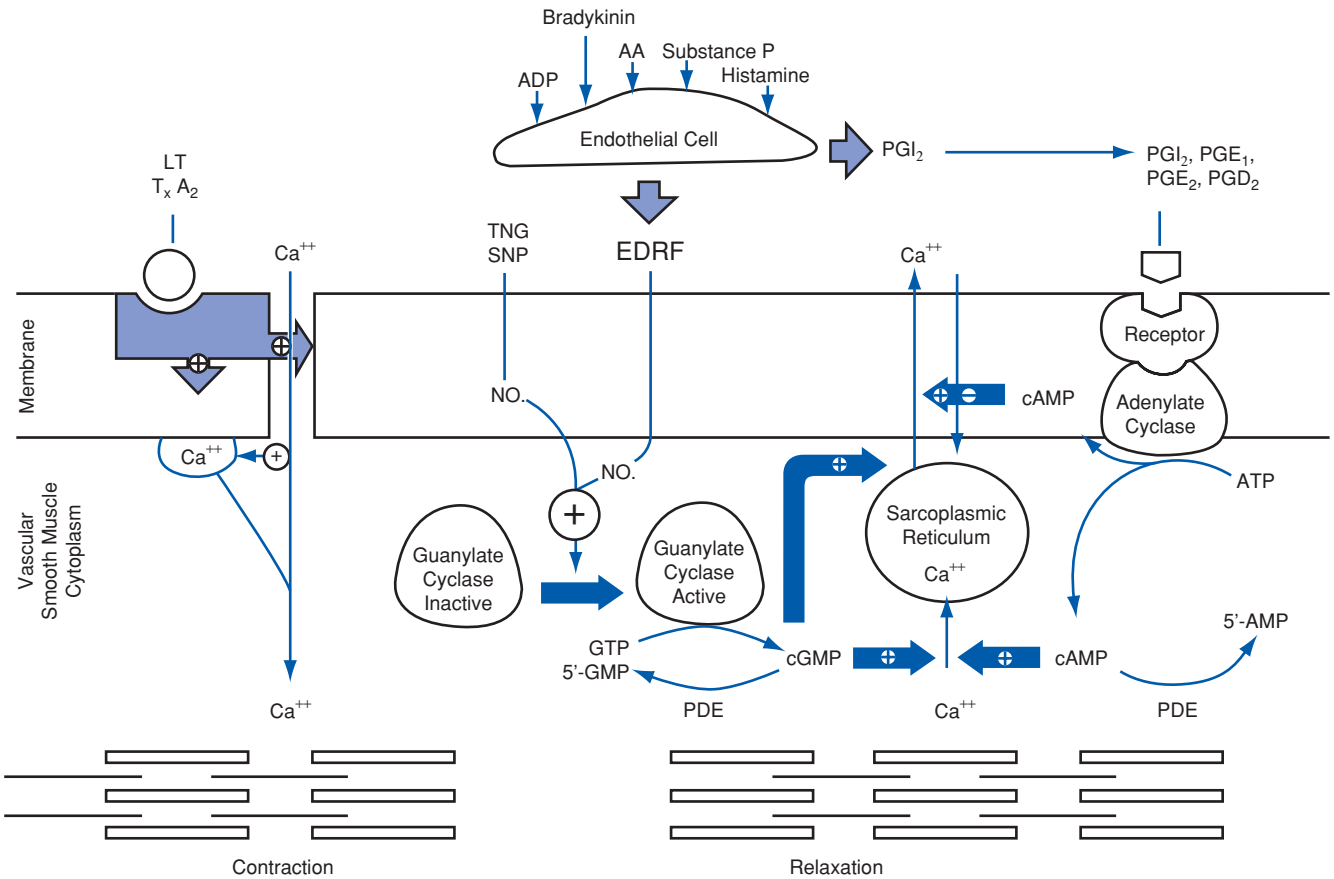

Figure 4-3. Mediators of vascular tone. Cyclic AMP and cyclic GMP increase the uptake of calcium into cellular storage sites in vascular smooth muscle, leading to vasodilation. The synthesis of cyclic GMP is catalyzed by guanylate cyclase, which is activated by nitric oxide (NO), which, in turn, is produced by nitroglycerin (NTG) and sodium nitroprusside (SNP). Excessive vasodilation often is a reflection of other endogenous mediators such as prostaglandins (PGI_2, PGE_1, PGE_2, and PGD_2) and thromboxane A_2 (TxA_2). Several mediators, such as arachidonic acid (AA), bradykinin, histamine, and substance P, stimulate the release of endothelium-derived relaxing factor (EDRF), which is identified with NO. (*Reproduced with permission from Levy.*[103])

renal elimination of this metabolite. Thus the infusion rate for patients with significant hepatic or renal disease should be at the lower end of this range.

Class Ib drugs include what is probably the best-known antiarrhythmic agent, lidocaine. As noted earlier, lidocaine is a Na^+ channel blocker that has little effect on conduction velocity in normal tissue but slows conduction in ischemic myocardium.[14,15] Other electrophysiologic effects include a decrease in action potential duration but a small increase in the ratio of effective refractory period to action potential duration. The exact role of these electrophysiologic effects on arrhythmia suppression is unclear. Lidocaine has no significant effects on atrial tissue, and it is not recommended for therapy in shock-resistant ventricular tachycardia/fibrillation (VT/VF) in the Guidelines 2000 for Emergency Cardiovascular Care.[19] After an initial bolus dose of 1 to 1.5 mg/kg of lidocaine, plasma levels decrease rapidly owing to redistribution to muscle, fat, etc. Effective plasma concentrations are maintained only by following the bolus dose with an infusion of 20 to 50 mg/kg per minute.[20] Elimination occurs via hepatic metabolism to active metabolites that are cleared by the kidney. Consequently, the dose should be reduced by approximately 50% in patients with liver or kidney disease. The primary toxic effects are associated with the central nervous system, and a lidocaine overdose may cause drowsiness, depressed level of consciousness, or seizures in very high doses. Negative inotropic or hypotensive effects are less pronounced than with most other antiarrhythmics. The other class Ib drugs likely to be encountered in the perioperative period are the oral agents tocainide and mexiletine, which have effects similar to lidocaine.[15]

The class Ic agents, including flecainide, encainide, and propafenone, markedly decrease conduction velocity.[20,21] The Cardiac Arrhythmia Suppression Trial (CAST) study[20,21] of moricizine found that while ventricular arrhythmias were suppressed, the incidence of sudden death was greater than with placebo with encainide and flecainide, and these drugs are not in wide use. Propafenone is available for oral use. The usual adult dose is 150 to 300 mg every 8 hours. It has beta-blocking (with resulting negative inotropic effects) as well as NA^+ channel-blocking activity; lengthens the PR, QRS, and QT duration; and may be used to treat both atrial and ventricular dysrhythmias.[15]

Class II Agents

Beta-receptor blocking agents are another important group of antiarrhythmic (denoted class II in the Vaughan Williams scheme). However, because of their use as antihypertensive as well as antiarrhythmic agents, they are discussed elsewhere in this chapter, and we will move on to consider bretylium, amiodarone, and sotalol, the class III agents in the Vaughan Williams scheme. These drugs have a number of complex ion channel-blocking effects, but possibly the most important activity is K^+ channel blockade.[22] Since the flux of K^+ out of the myocyte is responsible for repolarization, an important electrophysiologic effect of class III drugs is prolongation of the action potential.[23]

Class III Agents

Ibutilide, dofetilide, sotalol, and bretylium are class III agents. Intravenous ibutilide and oral dofetilide are approved for the treatment of atrial fibrillation but carry the risk of torsades de pointes.[24,25] Sotalol is a nonselective beta blocker that also has K^+ channel-blocking activity.[26] In the United States, it is available only for oral administration and has an approved indication for treating life-threatening ventricular arrhythmias, although it is effective against atrial arrhythmias as well. Bretylium is not used widely in 2006 and is not recommended in the Guidelines 2000 for Emergency Cardiovascular Care.[19]

Class IV Agents

Calcium entry blockers (class IV in the Vaughan Williams scheme), including verapamil and diltiazem, are antiarrhythmics. In sinoatrial and atrioventricular nodal tissue, Ca^{2+} channels contribute significantly to phase 0 depolarization, and the atrioventricular (AV) nodal refractory period is prolonged by Ca^{2+} entry blockade.[27,28] This explains the effectiveness of verapamil and diltiazem in treating supraventricular arrhythmias. It is also clear why these drugs are negative inotropes. Both verapamil and diltiazem are effective in slowing the ventricular response to atrial fibrillation, flutter, and paroxysmal supraventricular tachycardia and in converting to sinus rhythm.[29–31] Verapamil has greater negative inotrope effects than diltiazem, and therefore, it is used rarely for supraventricular arrhythmias. The intravenous dose of diltiazem is 0.25 mg/kg, with a second dose of 0.35 mg/kg if the response is inadequate after 15 minutes. The loading dose should be followed by an infusion of 5 to 15 mg/h. Intravenous diltiazem, although useful for rate control, has been replaced by intravenous amiodarone in clinical therapy of supraventricular tachycardia (SVT) and prophylaxis (see "Amiodarone" below).

Other Drugs

One of the difficulties of classifying antiarrhythmics by the Vaughan Williams classification is that not all drugs can be incorporated into this scheme. Three examples are digoxin, adenosine, and magnesium, each of which has important uses in the perioperative period.

Digoxin inhibits the Na^+,K^+-ATPase pump, leading to decreased intracellular K^+, a less negative resting membrane potential, increased slope of phase 4 depolarization, and decreased conduction velocity. These direct effects, however, usually are dominated by indirect effects, including inhibition of reflex responses to congestive heart failure and a vagotonic effect.[10,32] The net effect is greatest at the AV node, where conduction is slowed and the refractory period is increased, explaining the effectiveness of digoxin in slowing the ventricular response to atrial fibrillation. The major disadvantages of digoxin are the relatively slow onset of action and many side effects, including proarrhythmia effects, and it is now used rarely for rate control in acute atrial fibrillation because of the advent of IV amiodarone and diltiazem.

Adenosine is an endogenous nucleoside that has an electrophysiologic effect similar to that of acetylcholine. Adenosine decreases AV node conductivity, and its primary antiarrhythmic effect is to break AV nodal reentrant tachycardia.[33] An intravenous dose of 100 to 200 μg/kg is the treatment of choice for paroxysmal supraventricular tachycardia. Adverse effects, such as bronchospasm, are short-lived because its plasma half-life is so short (1 to 2 seconds). This short half-life makes it ideal for treating reentry dysrhythmia, in which transient interruption can fully suppress the dysrhythmia.

Appropriate acid-base status and electrolyte balance are important because electrolyte imbalance can perturb the membrane potential, leading to arrhythmia generation, as can altered acid-base status, by effects on K^+ concentrations and sympathetic tone. Therapy for dysrhythmia should include correction of acid-base and electrolyte imbalances. Magnesium supplementation should be considered.[34] Magnesium deficiency is common in the perioperative period, and magnesium administration has been shown to decrease the incidence of postoperative dysrhythmia.[35]

AMIODARONE

Intravenous amiodarone has become one of the most administered intravenous antiarrhythmics used in cardiac surgery because of its broad spectrum of efficacy. Amiodarone was developed originally as an antianginal agent because of its vasodilating effects, including coronary vasodilation.[36] It has various ion channel-blocking activities.[10,29,36] The resulting electrophysiologic effects are complex, and there are differences in acute intravenous and chronic oral administration. Acute intravenous administration can produce decreases in heart rate and blood pressure, but there are minimal changes in QRS duration or QT interval. After chronic use, there may be significant bradycardia and increases in action potential duration in AV nodal and ventricular tissue, with increased QRS duration and QT interval.[37–39]

Pharmacokinetics

Amiodarone is a complex drug, markedly lipophilic, that undergoes variable absorption (35 to 65%) after oral administration and is taken up extensively by multiple tissues with interindividual variation and complex pharmacokinetics.[38–40] The short initial context-sensitive half-life after intravenous administration represents drug redistribution. The true elimination half-life for amiodarone is extremely long, up to 40 to 60 days. Because of the huge volume of distribution (~60 L/kg) and a long duration of action, an active metabolite loading period of several months may be required before reaching steady-state tissue concentrations. Further, in life-threatening arrhythmias, intravenous loading often is starting to establish initial plasma levels. Measuring amiodarone plasma concentrations is not useful owing to the complex pharmacokinetics and the metabolites of the parent drug. Plasma concentrations greater than 2.5 mg/L have been associated with an increased risk of toxicity. The optimal dose of amiodarone has not been well characterized and may vary depending on the specific arrhythmias treated. Further, there may be differences in dose requirements for therapy of supraventricular and ventricular arrhythmias.[37–40]

Because of these distinctive pharmacokinetic properties, steady-state plasma levels are achieved slowly. Oral administration for a typical adult consists of a loading regimen of 80 to 1600 mg/d (in two or three doses) for 10 days, 600 to 800 mg/d for 4 to 6 weeks, and then maintenance doses of 200 to 600 mg/d. For intravenous loading, specific studies will be reviewed, but recommended dosing is 150 mg given over 10 minutes for acute therapy in an adult, followed first by a secondary loading infusion of 60 mg/h for 6 hours and then by a maintenance infusion of 30 mg/h to achieve a 1000 mg/d dosing.[37–40]

Electrophysiology

The electrophysiologic actions of amiodarone are complex and incompletely understood. Amiodarone produces all four effects according to the Vaughan Williams classification. It also has been shown to have use-dependent class I activity, inhibition of the inward sodium currents, and class II activity.[10] The antiadrenergic effect of amiodarone, however, is different from that of beta-blocker drugs because it is noncompetitive and additive to the effect of beta blockers. Amiodarone depresses sinoatrial (SA) node automaticity, which slows the heart rate and conduction and increases refractoriness of the AV node, properties useful in managing supraventricular arrhythmia. Its class III activity results in increases in atrial and ventricular refractoriness and in prolongation of the QTc interval. The effects of oral amiodarone on SA and AV nodal function are maximal within 2 weeks, whereas the effects on ventricular tachycardia (VT) and ventricular refractoriness emerge more gradually during oral therapy, becoming maximal after 10 weeks or more.

Indications

The primary indication for amiodarone is ventricular tachycardia or fibrillation refractory to other therapy.[40–48] It is the most efficacious agent for reducing ventricular arrhythmias and suppresses the incidence of post–myocardial infarction sudden death.[37] It is also effective, in doses lower than those used for ventricular dysrhythmia, for the treatment of atrial dysrhythmia and is effective in converting atrial fibrillation to sinus rhythm (see "Atrial Fibrillation" below).

Side Effects

Although there are numerous adverse reactions to amiodarone, they occur with long-term oral administration and have not been associated with acute intravenous administration. The most serious is pulmonary toxicity, which has not been reported with acute administration in a perioperative setting. Some case series have reported an increased risk of marked bradycardia and hypotension immediately after cardiac surgery in patients already on amiodarone at the time of surgery.[49,50] Other case-control studies, however, have not reproduced this finding.[51] None of the placebo-controlled trials of prophylactic amiodarone for perioperative atrial fibrillation prevention found any adverse cardiovascular effects of the drug.[52–56] Thus it is unlikely that amiodarone poses a serious cardiovascular risk to the postoperative patient. Case reports and case series of postoperative acute pulmonary toxicity are similarly lacking in the rigor of randomized, controlled methodology.

PHARMACOLOGIC THERAPY OF SPECIFIC ARRHYTHMIAS

Ventricular Tachyarrhythmias

Intravenous amiodarone is approved for rapid control of recurrent VT or VF. Three randomized, controlled trials of patients with recurrent in-hospital, hemodynamically unstable VT or VF with two or more episodes within the past 24 hours who failed to respond to or were intolerant of lidocaine, procainamide, and (in two of the trials) bretylium have been reported.[42,44,46] Patients were critically ill with ischemic cardiovascular disease, 25% were on a mechanical ventilator or intra-aortic balloon pump before enrollment, and 10% were undergoing cardiopulmonary resuscitation at the time of enrollment. One study compared three doses of IV amiodarone: 525, 1050, and 2100 mg/d.[44] Because of the use of investigator-initiated intermittent open-label amiodarone boluses for recurrent VT, the actual mean amiodarone doses received by the three groups were 742, 1175, and 1921 mg/d. There was no statistically significant difference in the number of patients without VT/VF recurrence during the 1-day study period: 32 of 86 (41%), 36 of 92 (45%), and 42 of 92 (53%) for the low-, medium-, and high-dose groups, respectively. The number of supplemental 150-mg bolus

infusions of amiodarone given by blinded investigators was statistically significantly less in those randomized to higher doses of amiodarone.

A wider range of amiodarone doses (125, 500, and 1000 mg/d) was evaluated by Sheinman and colleagues, including a low dose that was expected to be subtherapeutic.[46] This stronger study design, however, also was confounded by open-label bolus amiodarone injections given by study investigators. There was, however, a trend toward a relationship between intended amiodarone dose and VT/VF recurrence rate ($p = .067$). After adjustment for baseline imbalances, the median 24-hour recurrence rates of VT/VF, from lowest to highest doses, were 1.68, 0.96, and 0.48 events per 24 hours.

The third study compared two intravenous amiodarone doses (125 and 1000 mg/d) with bretylium (2500 mg/d).[42] Once again, the target amiodarone dose ratio of 8:1 was compressed to 1.8:1 because of open-label boluses. There was no significant difference in the primary outcome, which was median VT/VF recurrence rate over 24 hours. For low-dose amiodarone, high-dose amiodarone, and bretylium, these rates were 1.68, 0.48, and 0.96 events per 24 hours, respectively ($p = .237$). There was no difference between high-dose amiodarone and bretylium; however, more than 50% of patients had crossed over from bretylium to amiodarone by 16 hours.

The failure of these studies to provide clear evidence of amiodarone efficacy may be related to the "active-control study design" used, a lack of adequate statistical power, high rates of supplemental amiodarone boluses, and high crossover rates. Nonetheless, these studies provide some evidence that IV amiodarone (1 g/d) is moderately effective during a 24-hour period against VT and VF.

Sustained monomorphic ventricular tachycardia and wide qrs tachycardia

Although the most effective and rapid treatment of any hemodynamically unstable sustained ventricular tachyarrhythmia is electrical cardioversion or defibrillation, intravenous antiarrhythmic drugs can be used for arrhythmia termination if the VT is hemodynamically stable. The Guidelines 2000 for Emergency Cardiovascular Care[19] removed the former recommendation of lidocaine and adenosine use in stable wide QRS tachycardia, now labeled as "acceptable" but not primarily recommended (lidocaine) or not recommended (adenosine). Intravenous procainamide and sotalol are effective, based on randomized but small studies[10]; amiodarone is also considered acceptable.[19]

Shock-resistant ventricular fibrillation

The Guidelines 2000 for Emergency Cardiovascular Care recommend at least three shocks and epinephrine or vasopressin before any antiarrhythmic drug is administered.[10,19] No large-scale controlled, randomized studies have demonstrated efficacy for lidocaine, bretylium, or procainamide in shock-resistant VF,[10,19] and lidocaine and bretylium are no longer recommended in this setting.[19] Two pivotal studies have been reported recently studying the efficacy of agents in acute shock-resistant cardiac arrest.

The Amiodarone in the Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachycardia (ARREST) study was randomized, double- blind, and placebo-controlled. The ARREST study in 504 patients showed that amiodarone 300 mg administered in a single intravenous bolus significantly improves survival to hospital admission in cardiac arrest still in VT or VF after three direct-current shocks (44% versus 34%; $p < .03$).[43] Although the highest survival rate to hospital admission (79%) was achieved when the amiodarone was given within 4 to 16 minutes of dispatch, there was no significant difference in the proportional improvement in the amiodarone group compared with the placebo group when drug administration was delayed (up to 55 minutes). Amiodarone also had the highest efficacy in patients (21% of all study patients) who had a return of spontaneous circulation before drug administration (survival to hospital admission increased to 64% from 41% in the placebo group). Among patients with no return of spontaneous circulation, amiodarone only slightly improved outcome (38% versus 33%).

Dorian performed a randomized trial comparing intravenous lidocaine with intravenous amiodarone as an adjunct to defibrillation in victims of out-of-hospital cardiac arrest.[48] Patients were enrolled if they had out-of-hospital ventricular fibrillation resistant to three shocks, intravenous epinephrine, and a further shock or if they had recurrent ventricular fibrillation after initially successful defibrillation. They were randomly assigned in a double-blind manner to receive intravenous amiodarone plus lidocaine placebo or intravenous lidocaine plus amiodarone placebo. The primary endpoint was the proportion of patients who survived to be admitted to the hospital. In total, 347 patients (mean age 67 $\pm$ 14 years) were enrolled. The mean interval between the time at which paramedics were dispatched to the scene of the cardiac arrest and the time of their arrival was 7 $\pm$ 3 minutes, and the mean interval from dispatch to drug administration was 25 $\pm$ 8 minutes. After treatment with amiodarone, 22.8% of 180 patients survived to hospital admission compared with 12.0% percent of 167 patients treated with lidocaine ($p = .009$). Among patients for whom the time from dispatch to the administration of the drug was equal to or less than the median time (24 minutes), 27.7% of those given amiodarone and 15.3% of those given lidocaine survived to hospital admission ($p = .05$). The authors concluded that compared with lidocaine, amiodarone leads to substantially higher rates of survival to hospital admission in patients with shock-resistant out-of-hospital ventricular fibrillation.

Supraventricular Arrhythmias

A supraventricular arrhythmia is any tachyarrhythmia that requires atrial or atrioventricular junctional tissue for initiation and maintenance. It may arise from reentry caused by

unidirectional conduction block in one region of the heart and slow conduction in another, from enhanced automaticity akin to that seen in normal pacemaker cells of the sinus node and in latent pacemaker cells elsewhere in the heart, or from triggered activity, a novel type of abnormally enhanced impulse initiation caused by membrane currents that can be activated and inactivated by premature stimulation or rapid pacing.[56–58] Pharmacologic approaches to treating supraventricular arrhythmias, including atrial fibrillation, atrial flutter, atrial tachycardia, AV reentrant tachycardia, and AV nodal reentrant tachycardia, continue to evolve.[56–60] Because atrial fibrillation is perhaps the most common arrhythmia after cardiac surgery, this condition will be emphasized in detail.

Atrial Fibrillation

Atrial fibrillation (AF) is a common complication of cardiac surgery that increases the length of stay in the hospital with resulting increases in health care resource utilization.[56–61] Advanced age, previous AF, and valvular heart operations are the most consistently identified risk factors for this arrhythmia. Because efforts to terminate AF after its initiation are problematic, current interests are directed at therapies to prevent postoperative AF. Most studies suggest that prophylaxis with antiarrhythmic compounds can decrease the incidence of AF, length of hospital stay, and cost significantly. Class III antiarrhythmic drugs (e.g., sotalol and ibutilide) also may be effective but potentially pose the risk of drug-induced polymorphic ventricular tachycardia (torsades de pointes). Newer promising intravenous agents (RSD1235) are also being investigated. Defining which subpopulations benefit most from such therapy is important as older and more critically ill patients undergo surgery.

Amiodarone is also an effective approach for prophylactic therapy of AF. Intravenous amiodarone is an important consideration because loading with oral therapy is often not feasible in part owing to time required. There also may be added benefits of prophylactic therapies in high-risk patients, especially those prone to ventricular arrhythmias (i.e., patients with preexisting heart failure).

Two studies deserve mention regarding prophylaxis with amiodarone. To determine if IV amiodarone would prevent atrial fibrillation and decrease hospital stay after cardiac surgery, Daoud assessed preoperative prophylaxis in 124 patients who were given either oral amiodarone (64 patients) or placebo (60 patients) for a minimum of 7 days before elective cardiac surgery.[62] Therapy consisted of 600 mg amiodarone per day for 7 days and then 200 mg/d until the day of discharge from the hospital. The preoperative total dose of amiodarone was 4.8 ± 0.96 g over 13 ± 7 days. Postoperative atrial fibrillation occurred in 16 of the 64 patients in the amiodarone group (25%) and 32 of the 60 patients in the placebo group (53%). Patients in the amiodarone group were hospitalized for significantly fewer days than were patients in the placebo group (6.5 ± 2.6 versus 7.9 ± 4.3 days; $p = .04$). Total hospitalization costs were significantly less for the amiodarone group than for the placebo group ($18,375 ± $13,863 versus $26,491 ± $23,837; $p = .03$). Guarnieri evaluated 300 patients randomized in a double-blind fashion to IV amiodarone (1 g/d for 2 days) versus placebo immediately after open-heart surgery.[54] The primary endpoints of the trial were incidence of atrial fibrillation and length of hospital stay. Atrial fibrillation occurred in 67 of 142 (47%) patients on placebo versus 56 of 158 (35%) on amiodarone ($p = .01$). Length of hospital stay for the placebo group was 8.2 ± 6.2 days, and 7.6 ± 5.9 days for the amiodarone group. Low-dose IV amiodarone was safe and effective in reducing the incidence of atrial fibrillation after heart surgery but did not significantly alter length of hospital stay.

In summary, AF is a frequent complication of cardiac surgery. Many cases can be prevented with appropriate prophylactic therapy. Beta-adrenergic blockers should be administered to most patients without contraindication. Prophylactic amiodarone should be considered in patients at high risk for postoperative AF. The lack of data on cost benefits and cost-efficiency in some studies may reflect the lack of higher-risk patients in the study. Patients who are poor candidates for beta blockade may not tolerate sotalol, whereas amiodarone does not have this limitation. Additional studies also need to be performed to better assess the role of prophylactic therapy in off-pump cardiac surgery.

INOTROPIC AGENTS

Some depression of myocardial function is common after cardiac surgery.[63–65] The etiology is multifactorial—preexisting disease, incomplete repair or revascularization, myocardial edema, postischemic dysfunction, reperfusion injury, etc.—and usually is reversible. Adequate cardiac output usually can be maintained by exploiting the Starling curve with higher preload, but often the cardiac function curve is flattened, and it is necessary to use inotropic agents to maintain adequate organ perfusion.

The molecular basis for the contractile property of the heart is the interaction of the proteins actin and myosin, in which chemical energy (in the form of ATP) is converted into mechanical energy. In the relaxed state (diastole), the interaction of actin and myosin is inhibited by tropomyosin, a protein associated with the actin-myosin complex. With the onset of systole, Ca^{2+} enters the myocyte (during phase 1 of the action potential). This influx of Ca^{2+} triggers the release of much larger amounts of Ca^{2+} from the sarcoplasmic reticulum. The binding of Ca^{2+} to the C subunit of the protein troponin interrupts inhibition of the actin-myosin interaction by tropomyosin, facilitating the hydrolysis of ATP with the generation of a mechanical force. With repolarization of the myocyte and completion of systole, Ca^{2+} is taken back up into the sarcoplasmic reticulum, allowing tropomyosin to again inhibit the interaction of actin and myosin with consequent relaxation of contractile force. Thus inotropic action is mediated by intracellular Ca^{2+}.[66] A novel

drug, levosimendan, currently under clinical development in the United States but approved in several countries, increases the sensitivity of the contractile apparatus to Ca^{2+},[67] whereas the positive inotropic agents available for clinical use achieve their end by increasing intracellular Ca^{2+} levels.

The first drug to be considered is simply Ca^{2+} itself. In general, administration of calcium will increase the inotropic state of the myocardium when measured by load-independent methods, but it also will increase vascular tone (afterload) and impair diastolic function. In addition, the effects of calcium on myocardial performance depend on the plasma Ca^{2+} concentration. Ca^{2+} plays important roles in cellular function, and the intracellular Ca^{2+} concentration is highly regulated by membrane ion channels and intracellular organelles.[68,69] If the extracellular Ca^{2+} concentration is normal, administration of Ca^{2+} will have little effect on the intracellular level and will have less pronounced hemodynamic effects. On the other hand, if the ionized plasma calcium concentration is low, exogenous calcium administration may increase cardiac output and blood pressure.[70] It also should be realized that even with normal plasma Ca^{2+} concentrations, administration of Ca^{2+} may increase vascular tone, leading to increased blood pressure but no change in cardiac output. This increased afterload, as well as the deleterious effects on diastolic function, may be the basis of the observation that Ca^{2+} administration can blunt the response to epinephrine.[71] Routine use of Ca^{2+} at the end of bypass should be tempered by the realization that Ca^{2+} may have little effect on cardiac output while increasing systemic vascular resistance, although this in itself may be of importance. If there is evidence of myocardial ischemia, Ca^{2+} administration may be deleterious because it may exacerbate both coronary spasm and the pathways leading to cellular injury.[72,73]

Digoxin, while not effective as acute therapy for low-cardiac-output syndrome in the perioperative period, nevertheless well illustrates the role of intracellular Ca^{2+}. Digoxin functions by inhibiting Na^+,K^+-ATPase, which is responsible for the exchange of intracellular Na^+ with extracellular K^+.[3,4] It is thus responsible for maintaining the intracellular/extracellular K^+ and Na^+ gradients. When it is inhibited, intracellular Na^+ levels increase. The increased intracellular Na^+ is an increased chemical potential for driving the Ca^{2+}/Na^+ exchanger, an ion exchange mechanism in which intracellular Na^+ is removed from the cell in exchange for Ca^{2+}. The net effect is an increase in intracellular Ca^{2+} with an enhancement of the inotropic state.

The most commonly used positive inotropic agents are the beta-adrenergic agonists. The $beta_1$ receptor is part of a complex consisting of the receptor on the outer surface of the cell membrane and membrane-spanning G-proteins (so named because they bind GTP), which, in turn, stimulate adenylate cyclase on the inner surface of the membrane, catalyzing the formation cyclic adenosine monophosphate (cAMP). The inotropic state is modulated by cAMP via its catalysis of phosphorylation reactions by protein kinase A. These phosphorylation reactions "open" Ca^{2+} channels on the cell membrane and lead to greater release and uptake of Ca^{2+} from the sarcoplasmic reticulum.[3,4]

There are many drugs that stimulate $beta_1$ receptors and have a positive inotropic effect, including epinephrine, norepinephrine, dopamine, isoproterenol, and dobutamine, the most commonly used catecholamines in the perioperative period. While there are differences in their binding at the $beta_1$ receptor, the most important differences between the various catecholamines are their relative effects on alpha- and $beta_2$-adrenergic receptors. In general, alpha stimulation of receptors on the peripheral vasculature causes vasoconstriction, whereas $beta_2$ stimulation leads to vasodilation (see the discussion elsewhere in this chapter). For some time it was believed that $beta_2$ and alpha receptors were found only in the peripheral vasculature, as well as a few other organs, but not in the myocardium. However, alpha receptors are found in the myocardium and mediate a positive inotropic effect.[5,6] The mechanism for this positive inotropic effect is probably the stimulation of phospholipase C, leading to hydrolysis of phosphatidyl inositol to diacylglycerol and inositol triphosphate, compounds that increase Ca^{2+} release from the sarcoplasmic reticulum and increase myofilament sensitivity to Ca^{2+}. It is also possible that alpha-adrenergic agents increase intracellular Ca^{2+} by prolonging action potential duration by inhibition of outward K^+ currents during repolarization or by activating the Na^+/H^+ exchange mechanism, increasing intracellular pH and increasing myofilament sensitivity to Ca^{2+}. Just as the exact mechanism is uncertain, the exact role of alpha-adrenergic stimulation in control of the inotropic state is unclear, although it is apparent that onset of the effect is slower than that of $beta_1$ stimulation.

Besides the discovery of alpha receptors in the myocardium, $beta_2$ receptors are present in the myocardium.[74] The fraction of $beta_2$ receptors (compared with $beta_1$ receptors) is increased in chronic heart failure, possibly explaining the efficacy of drugs with $beta_2$ activity in this setting. This phenomenon is part of the general observation of $beta_1$-receptor downregulation (decrease in receptor density) and desensitization (uncoupling of effect from receptor binding) that is observed in chronic heart failure.[75] Interestingly, it has been demonstrated in a dog model that this same phenomenon occurs with cardiopulmonary bypass (CPB).[76] In this situation, a newer class of drugs, the phosphodiesterase inhibitors, may be of benefit. These drugs, typified by the agents available in the United States, amrinone and milrinone, increase cAMP levels independently of the beta receptor by selectively inhibiting the myocardial enzyme responsible for the breakdown of cAMP.[3,4]

In clinical use, selection of a particular inotropic agent usually is based more on its side effects than on its direct inotropic properties. Of the commonly used catecholamines, norepinephrine has alpha and $beta_1$ but little $beta_2$ activity and is both an inotrope and a vasopressor. Epinephrine and dopamine are mixed agonists with alpha, $beta_1$, and $beta_2$ activity. At lower doses, they are primarily inotropes and not

vasopressors, although vasopressor effects become more pronounced at higher doses. This is especially true for dopamine, which achieves effects at higher doses by stimulating the release of norepinephrine.[77] Dobutamine is a more selective beta$_1$ agonist, in contrast to isoproterenol, which is a mixed beta agonist. Selection of a drug depends on the particular hemodynamic problem at hand. For example, a patient with depressed myocardial function in the presence of profound vasodilation may require a drug with both positive inotropic and vasopressor effects, whereas a patient who is vasoconstricted may benefit from some other choice. We recommend an empirical approach to selecting inotropic agents with careful monitoring of the response to the drug and selection of the agent that achieves the desired effect.

Clinical experience suggests that phosphodiesterase inhibitors can be effective when catecholamines do not produce an acceptable cardiac output.[78–80] There are few differences in the hemodynamic effects of the two drugs available for use in the United States, amrinone and milrinone. Both agents increase contractility with little effect on heart rate, and both are vasodilators. There is significant venodilation, as well as arteriodilation, and maintaining adequate preload is important in avoiding significant hypotension.[81,82] If amrinone is used, the bolus dose recommended in the product insert, 0.75 mg/mL, is inadequate to maintain therapeutic plasma levels, and a loading dose of 1.5 to 2.0 mg/mL should be used.[83] With either drug, administering the loading dose over 15 to 30 minutes may attenuate possible hypotension. Plasma levels drop rapidly after a loading dose because of redistribution, and the loading dose should be followed immediately by a continuous infusion.[83,84] Because of their longer half-lives, it is rather more difficult to readily titrate plasma levels than with catecholamines (which have plasma half-lives of a few minutes).

Phosphodiesterase inhibitors, specifically milrinone, facilitate separation from CPB with biventricular dysfunction and are used for treating low-cardiac-output syndrome after cardiac surgery.[82,85–87] Doolan and colleagues also demonstrated that milrinone, in comparison with placebo, significantly facilitated separation of high-risk patients from CPB.[88]

Levosimendan

Levosimendan is a new class of drugs known as *calcium sensitizers*. The molecule is a pyridazinone-dinitrile derivative with additional action on adenosine triphosphate (ATP)–sensitive potassium channels.[67,89,90] Levosimendan is used intravenously for the treatment of decompensated cardiac failure, demonstrating enhanced contractility with no increase in oxygen demands, and produces antistunning effects without increasing myocardial intracellular calcium concentrations or prolonging myocardial relaxation. Levosimendan also causes coronary and systemic vasodilation. In patients with decompensated congestive heart failure, IV levosimendan reduced the incidence of worsening congestive heart failure (CHF) or death significantly. IV levosimendan significantly increased cardiac output or cardiac index and decreased filling pressure in the acute treatment of stable or decompensated CHF in large, double-blind, randomized trials and after cardiac surgery in smaller trials. Levosimendan is well tolerated and has not been shown to be arrhythmogenic. In addition to sensitizing troponin to intracellular calcium, levosimendan has been shown to inhibit phosphodiesterase III and open ATP-sensitive potassium channels (K_{ATP}), which may produce vasodilation. Unlike currently available intravenous inotropes, levosimendan does not increase myocardial oxygen use, has not been shown to be proarrhythmic, and has been used effectively in the presence of beta-blocking medications. Levosimendan also has not been shown to impair ventricular relaxation, which was an initial concern with this class of drugs. Clinical studies have demonstrated short-term hemodynamic benefits of levosimendan over both placebo and dobutamine. While large-scale, long-term morbidity and mortality data are scarce, the Levosimendan Infusion versus Dobutamine in Severe Low-Output Heart Failure (LIDO) study suggested a mortality benefit of levosimendan over dobutamine up to 180 days after treatment. Clinical studies comparing levosimendan with other positive inotropes, namely, milrinone, are lacking. Levosimendan treatment appears to be well tolerated, with the primary adverse events being headache and hypotension.

Clinical Trials

Despite their common use after cardiac surgery, there have been relatively few comparative studies of inotropic agents in the perioperative period. In 1978, Steen and colleagues reported the hemodynamic effects of epinephrine, dobutamine, and epinephrine immediately after separation from CPB.[91] The largest mean increase in cardiac index was achieved with dopamine at 15 μg/kg per minute. However, it should be noted that the only epinephrine dose studied was 0.04 μg/kg per minute. In a later comparison of dopamine and dobutamine, Salomon and colleagues concluded that dobutamine produced more consistent increases in cardiac index, although the hemodynamic differences were small, and all patients had good cardiac indices at the onset of the study.[92] Fowler and colleagues also found insignificant differences in the hemodynamic effects of dobutamine and dopamine, although they reported that coronary flow increased more in proportion to myocardial oxygen consumption with dobutamine.[93] While neither of these groups reported significant increases in heart rate for either dopamine or dobutamine, clinical experience has been otherwise. This is supported by a study by Sethna and colleagues, who found that the increase in cardiac index with dobutamine occurs simply because of increased heart rate, although they found that myocardial oxygen was maintained.[94] Butterworth and colleagues subsequently demonstrated that the older and much cheaper agent, epinephrine, effectively increased stroke volume without as great an increase in heart rate as dobutamine.[95] More recently, Feneck and colleagues compared dobutamine and milrinone and found them to be equally effective in treating low-cardiac-output syndrome after cardiac surgery.[96] This study was a comparison of two drugs,

and the investigators emphasized that the most efficacious therapy is probably a combination of drugs. In particular, phosphodiesterase inhibitors require the synthesis of cAMP to be effective, and thus use of a combination of a $beta_1$-adrenergic agonist and a phosphodiesterase inhibitor would be predicted to be more effective than either agent alone.

Finally, while global hemodynamic goals (i.e., heart rate, blood pressure, filling pressures, and cardiac output) may be achieved with inotropic agents, this does not guarantee adequate regional perfusion, in particular renal and mesenteric perfusion. So far there have been few investigations of regional perfusion after cardiac surgery. There has been more interest in regional (especially mesenteric) perfusion in the critical-care medicine literature, and some of the studies may be relevant to postoperative care of the cardiac surgical patient. Two studies have indicated that epinephrine may impair splanchnic perfusion, especially in comparison with combining norepinephrine and dobutamine.[97,98] Norepinephrine alone has variable effects on splanchnic blood flow in septic shock,[99] although adding dobutamine can improve splanchnic perfusion significantly when blood pressure is supported with norepinephrine.[98] Low-dose dopamine improves splanchnic blood flow,[100] but there is evidence that dopamine in higher doses impairs gastric perfusion.[101] The relevance of these studies of septic patients for the cardiac surgical patient is unclear, although there are similarities between the inflammatory responses to CPB and to sepsis.

VASOPRESSORS

CPB often is characterized by derangements of vascular tone. Sometimes CPB induces elevations in endogenous catecholamines, as well as other mediators, such as serotonin and arginine vasopressin (AVP), leading to vasoconstriction. However, often CPB is characterized by endothelial injury and a systemic inflammatory response, with a cascade of cytokine and inflammatory mediator release and profound vasodilation. The pathophysiology has a striking resemblance to that of sepsis or an anaphylactic reaction. Further, vasodilation after cardiac surgery may be exacerbated by the preoperative use of angiotensin-converting enzyme (ACE) inhibitors and post-CPB use of milrinone.

The mechanisms of vasodilatory shock have been reviewed recently.[102] Vascular tone is modulated by intracellular Ca^{2+}, which binds calmodulin. The Ca^{2+}-calmodulin complex activates myosin light-chain kinase, which catalyzes the phosphorylation of myosin to facilitate the interaction with actin. Conversely, intracellular cGMP activates myosin phosphatase (also via a kinase-mediated phosphorylation of myosin phosphatase), which dephosphorylates myosin and inhibits the interaction of actin and myosin. A primary mediator of vasodilatory shock is nitric oxide (NO), which is induced by cytokine cascades. NO activates guanylate cyclase, with resulting loss of vascular tone. Another mechanism of vasodilation that may be particularly relevant to prolonged CPB is activation of ATP-sensitive potassium (K_{ATP}) channels. These channels are activated by decreases in cellular ATP or increases in hydrogen ion or lactate. All these could result from the abnormal perfusion associated with CPB and/or hypothermia. Increases in potassium channel conductance result in hyperpolarization of the vascular smooth muscle membrane, which decreases Ca^{2+} flux into the cell, leading to decreased vascular tone. A third mechanism of vasodilatory shock that also may be particularly relevant to cardiac surgery is deficiency of vasopressin. As noted earlier, CPB often induces the release of vasopressin, and this may contribute to the excessive vasoconstriction sometimes seen after CPB. However, it has been observed in several experimental models of shock that the initially high levels of vasopressin decrease as shock persists, leading some investigators to suggest that vasopressin stores are limited and are depleted by the initial response to hypotension.

Excessive vasodilation during shock usually is treated with catecholamines, most typically phenylephrine, dopamine, epinephrine, or norepinephrine.[103] Although catecholamines produce both alpha- and beta-adrenergic effects, $alpha_1$-adrenergic receptor stimulation produces vasoconstriction. As noted earlier, stimulation of these receptors activates membrane phospholipase C, which, in turn, hydrolyzes phosphatidylinositol 4,55 diphosphate.[7] This leads to the subsequent generation of two second messengers, including diacyl glycerol and inositol triphosphate. Both these second messengers increase cytosolic Ca^{2+} by different mechanisms, which include facilitating release of calcium from the sarcoplasmic reticulum and potentially increasing the calcium sensitivity of the contractile proteins in vascular smooth muscle.

Mediator-induced vasodilation often is poorly responsive to catecholamines,[103] and the most potent pressor among catecholamines, norepinephrine, is required frequently. Some clinicians are concerned about renal, hepatic, and mesenteric function during norepinephrine administration. However, in septic patients, norepinephrine can improve renal function,[102–107] and there is evidence that it may improve mesenteric perfusion as well.[108] Given the hemodynamic similarities between septic patients and some patients at the end of CPB, these results often are extrapolated to the cardiac surgical patient but have not been confirmed by a systematic study. In some cases of profound vasodilatory shock, even norepinephrine is inadequate to restore systemic blood pressure. In this situation, low doses of vasopressin may be useful. Argenziano and colleagues[109] studied 40 patients with vasodilatory shock (defined as a mean arterial blood pressure of less than 70 mm Hg with a cardiac index greater than 2.5 L/m^2 per minute) after cardiac surgery. Arginine vasopressin levels were inappropriately low in this group of patients, and low-dose vasopressin infusion ($\leq$0.1 units/min) effectively restored blood pressure and reduced norepinephrine requirements without significantly changing cardiac index. These observations were similar to an earlier report of the use of vasopressin in vasodilatory septic shock.[110] Vasopressin also has been reported to be useful in treating milrinone-induced hypotension.[111] In this latter report, vasopressin was reported

to increase urine output, presumably via glomerular efferent arteriole constriction. However, the overall effects on renal function are unclear. In addition, there are still important unanswered questions about vasopressin and mesenteric perfusion. While vasopressin effectively may restore blood pressure in vasodilatory shock, it must be remembered that in physiologic concentrations it is a mesenteric vasoconstrictor, and mesenteric hypoperfusion may be a factor in developing sepsis and multiorgan dysfunction syndrome.

VASODILATORS

Different pharmacologic approaches are available to produce vasodilation (Table 4-1). Potential therapeutic approaches include (1) blockade of alpha$_1$-adrenergic receptors, ganglionic transmission, and calcium channel receptors, (2) stimulation of central alpha$_2$-adrenergic receptors or vascular guanylate cyclase and adenylate cyclase, and (3) inhibition of phosphodiesterase enzymes and angiotensin-converting enzymes.[112] Adenosine in low concentrations is also a potent vasodilator with a short half-life, but it is used, as noted earlier, for its ability to inhibit atrioventricular conduction. Losartan, a novel angiotensin II (AII) antagonist, has just been released for treating hypertension but is not available for intravenous use.

Stimulation of Adenylate Cyclase (Cyclic AMP)

Prostacyclin, prostaglandin E$_1$, and isoproterenol increase cyclic nucleotide formation (e.g., adenosine-3′,5′-monophosphate and cyclic AMP) in vascular smooth muscle to produce calcium mobilization out of vascular smooth muscle. Inhibiting the breakdown of cyclic AMP by phosphodiesterase also will increase cyclic AMP.[112] Increasing cyclic AMP in vascular smooth muscle facilitates calcium uptake by intracellular storage sites, thus decreasing calcium available for contraction. The net effect of increasing calcium uptake is to produce vascular smooth muscle relaxation and hence vasodilation. However, most catecholamines with beta$_2$-adrenergic activity (e.g., isoproterenol) and phosphodiesterase inhibitors have positive inotropic and other side effects that include tachycardia, glycogenolysis, and kaluresis.[113] Prostaglandins (i.e., prostacyclin and prostaglandin E$_1$) are potent inhibitors of platelet aggregation and activation. Catecholamines with beta$_2$-adrenergic activity, phosphodiesterase inhibitors, and prostaglandin E$_1$ and prostacyclin have been used to vasodilate the pulmonary circulation in patients with pulmonary hypertension and right ventricular failure.[113]

Table 4–1.

Vasodilators Used in the Treatment of Hypertension, Pulmonary Hypertension, and Heart Failure

Angiotensin-converting enzyme inhibitors
Angiotensin II Antagonists
Alpha$_1$-adrenergic antagonists (prazosin)
Alpha$_2$-adrenergic agonists (clonidine)
Nitrates
Nitric oxide
Hydralazine
Prostacyclin
Calcium channel blockers
Dihydropyridine agents (nifedipine, nicardipine, felodipine, amlodipine)

Nitrates, Nitrovasodilators, and Stimulation of Guanylyl Cyclase (Cyclic GMP)

The vascular endothelium modulates vascular relaxation by releasing both nitric oxide and prostacyclin.[114–116] Inflammatory mediators also can stimulate the vascular endothelium to release excessive amounts of endothelium-derived relaxing factor (EDRF, or nitric oxide), which activates guanylyl cyclase to generate cyclic GMP.[89,90] Nitrates and sodium nitroprusside, however, generate nitric oxide directly, independent of vascular endothelium.[115,116] The active form of any nitrovasodilator is nitric oxide (NO), in which the nitrogen is in a +2 oxidation state. For any nitrovasodilator to be active, it first must be converted to nitric oxide. For nitroprusside, this is easily accomplished because nitrogen is in a +3 oxidation state, with the nitric oxide molecule bound to the charged iron molecule in an unstable manner, allowing nitroprusside to readily donate its nitric oxide moiety. For nitroglycerin, nitrogen molecules exist in a +5 oxidation state, and thus they must undergo significant metabolic transformations before they are converted to an active molecule. Nitroglycerin is a selective coronary vasodilator and does not produce coronary steal compared with nitroprusside because the small intracoronary resistance vessels, those less than 100 μm thick, lack whatever metabolic transformation pathway is required to convert nitroglycerin into its active form of nitric oxide.[115,116] Chronic nitrate therapy can produce tolerance through different mechanisms, as shown in Table 4-2.[114–118] Sodium nitroprusside and nitroglycerin are effective vasodilators that produce venodilation that contributes significantly to the labile hemodynamic state.[114] Intravenous volume administration often is required with nitroprusside owing to the relative intravascular hypovolemia.

Dihydropyridine Calcium Channel Blockers

Dihydropyridine calcium channel blockers are direct arterial vasodilators.[119] Nifedipine was the first dihydropyridine calcium channel blocker, and the newer second-generation water-soluble agents that are available in intravenous form include isradipine and nicardipine. Isradipine and nicardipine produce arterial vasodilation without any effects on the vascular capacitance bed, no effects on atrioventricular nodal conduc-

Table 4–2.

Mechanisms of Nitrate Tolerance

Classic
Decreased bioconversion to nitric oxide
Desensitization of guanylyl cyclase
Neurohumoral adaptations
Renin-angiotensin system activation
Increased vasopressin, catecholamines
Novel
Increased superoxide anion production
Increased production of endothelin-1 via protein kinase C–mediated mechanisms

tion, and no depression of ventricular function (i.e., contractility).[120–125] Nicardipine is the first intravenous drug of this class to be available in the United States, and it offers a novel and important therapeutic option to treat perioperative hypertension following cardiac surgery. Because currently available intravenous calcium channel blockers have longer half-lives than nitrovasodilators, rapid loading infusion rates or bolus loading doses need to be administered to obtain therapeutic levels. Bolus nicardipine administration also can be used to treat acute hypertension that occurs during the perioperative period (i.e., intubation, extubation, cardiopulmonary bypass–induced hypertension, and aortic cross-clamping). Clevidipine, a new short-acting agent of this class, is under investigation.

Phosphodiesterase Inhibitors

The phosphodiesterase inhibitors currently available for use produce both positive inotropic effects and vasodilation.[126] When administered to patients with ventricular dysfunction, they increase cardiac output while decreasing pulmonary artery occlusion pressure, systemic vascular resistance, and pulmonary vascular resistance. Because of their unique mechanisms of vasodilation, they are especially useful for patients with acute pulmonary vasoconstriction and right ventricular dysfunction. Multiple forms of the drug are currently under investigation. The bipyridines (e.g., amrinone and milrinone), the imidazolones (e.g., enoximone), and the methylxanthines (e.g., aminophylline) are the ones most widely available. Papaverine, a benzyl isoquinolinium derivative isolated from opium, is a nonspecific phosphodiesterase inhibitor and vasodilator used by cardiac surgeons for its ability to dilate the internal mammary artery.[126]

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors have growing use in managing heart failure, and more patients are receiving these drugs. The ACE inhibitors prevent the conversion of angiotensin I to angiotensin II by inhibiting an enzyme called *kininase* in the pulmonary and systemic vascular endothelium. This enzyme is also important for the metabolism of bradykinin, a potent endogenous vasodilator, and for release of EDRF. Although there are little data in the literature regarding the preoperative management of patients receiving these drugs, withholding them on the day of surgery has been our clinical practice based on their potential to produce excessive vasodilation during CPB. Although Tuman was unable to find any difference in blood pressure during CPB in patients receiving ACE inhibitors, contact activation during CPB has the ability to generate bradykinin and thus amplify the potential for vasodilation.[127] The vasoconstrictor requirements were increased after bypass in his study.

Angiotensin II–Receptor Blockers

ACE inhibitors may not be tolerated in some patients owing to cough (common) and angioedema (rare). Inhibition of kininase II by ACE inhibitors leads to bradykinin accumulation in the lungs and vasculature, which probably causes cough and vasodilation. Alternative treatment with angiotensin II–receptor blockers (ARBs) may be associated less frequently with these side effects because ARBs do not affect kinin metabolism. Six ARBs are currently available for antihypertensive therapy in the United States: losartan (Cozaar), valsartan (Diovan), irbesartan (Avapro), candesartan (Atacand), eprosartan (Teveten), and telmisartan (Micardis). Mortality in chronic heart failure is related to activation of the autonomic nervous and renin-angiotensin systems, and ACE inhibitor therapy seems to attenuate progression of myocardial dysfunction and remodeling. ACE inhibitors do not completely block angiotensin II (A-II) production[128] and even may increase circulating A-II levels in patients with heart failure.[129] It was thought initially that ARBs might offer advantages over ACE inhibitors for heart failure therapy in terms of tolerability and more complete A-II blockade. Although ARBs were better tolerated,[130] all-cause mortality and the number of sudden deaths or resuscitated cardiac arrests were not different when losartan (Cozaar) and captopril (Capoten) were compared in patients (>60 years old, NYHA classes II to IV, LVEF < 40%).[131] Thus the long-term benefits from ACE inhibitor therapy are, at least in part, attributable to increased bradykinin formation.[132,133] For the treatment of heart failure, combination therapies with ACE inhibitors and ARBs are currently being investigated.[134,135] Perioperative hypotension may be encountered in ARB-treated patients as well as ACE inhibitor–treated patients, and increased inotropic support may be required.[136–138]

PHARMACOLOGIC MANIPULATION OF THE HEMOSTATIC SYSTEM DURING CARDIAC SURGERY

Numerous pharmacologic approaches to manipulate the hemostatic system in cardiac surgery include attenuating hemostatic system activation, preserving platelet function,

Table 4–3.

Novel Anticoagulant Agents Affecting the Hemostatic System

Therapeutic class	Agents	Indications
Anti-inflammatory	Adhesion molecule inhibitors Aprotinin complement inhibitors (pexelizumab) Interleukin antagonists P-selection inhibitors	All agents except aprotinin are in clinical development
Antiplatelet inhibitors (intravenous)	Abciximab (ReoPro) Eptifibatide (Integrelin) Tirofiban (Aggrastat)	Percutaneous coronary interventions
Antiplatelet inhibitors (oral)	Clopidogrel (Plavix)	Reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death)
Antithrombotic	Argatroban (Novastan) Bivalirudin (Angiomax) Dermatan surfate (Orgaran) Pentasaccharide (Fondaparinux) Recombinant hirudin (lepirudin)	Anticoagulation in patients with heparin-induced thrombocytopenia (except for pentacaccharide, which is in phase 3 clinical studies)
Broad-spectrum biologicals	Activated protein C Antithrombin Aprotinin (Trasylol)	In phase 3 studies for sepsis For antithrombin-deficiency states Prophylactic use to reduce blood loss and transfusions in patients undergoing CPB

Source: Reproduced with permission from Levy JH: Pharmacologic preservation of the hemostatic system during cardiac surgry. Ann Thorac Surg 2001; 72:1815S

and decreasing the need for transfusion of allogeneic blood products.[139–141] Different approaches currently available or under investigation are shown in Tables 4-3 and 4-4. Pharmacologic approaches to reduce bleeding and transfusion requirements in cardiac surgical patients are based on either preventing or reversing the defects associated with the CPB-induced coagulopathy.

Pharmacology of Anticoagulation

Anticoagulation therapy is based on inhibiting thrombus formation; however, thrombus is due to both thrombin activation and platelet activation (Table 4-5). Because of the complex humoral amplification system linking both hemostatic and inflammatory responses, there are multiple pathways to generate thrombin and platelet activation. During cardiac surgery, multiple aspects of the extracorporeal system can generate thrombin.

Heparin

Heparin is purified from either porcine intestine or beef lung. Heparin that is used for cardiac surgery includes fragments that range from 3000 to 30,000 Da and is also called *unfractionated*.[141] Heparin acts as an anticoagulant by binding to antithrombin III (AT III), enhancing the rate of thrombin–AT III complex formation and also inhibiting other clotting factors.[142] One major advantage of unfractionated heparin is that it can be reversed immediately by protamine. Because heparin also binds to other proteins, it can produce platelet dysfunction. Heparin dosing for CPB ranges from 300 to 500 units/kg. Despotis reported that the maintenance of patient-specific heparin concentrations during CPB was associated with more effective suppression of hemostatic activation.[143,144] Further, Mochizuki has shown that excess protamine can further alter coagulation and coagulation tests, and the careful, exactly titrated reversal of heparin, avoiding excess protamine, may be an important contribution by Despotis.[145] Heparin-induced thrombocytopenia (HIT) is an adverse effect of heparin produced by antibodies (IgG) to the composite of heparin–platelet factor 4 (PF4) that leads to the formation of immune complexes.[146] These immune complexes bind to platelets via platelet Fc-receptors (CD32), producing intravascular platelet activation, thrombocytopenia, and platelet activation with potential thromboembolic complications that can result in limb loss or death.

Table 4–4.

Agents That Improve Hemostatic Function in the Bleeding Patient

Therapeutic class	Agents	Indications
Blood components	Fresh-frozen plasma	Factor deficiency, reversal of warfarin, increased prothrombin time
	Cryoprecipitate	Von Willebrand's disease, hypofibrinogenemia
	Platelets	Thrombocytopenia, platelet dysfunction
Factor concentrates	Recombinant factor VIII	Hemophilia
	Recombinant factor IX	Hemophilia
	Recombinant factor VIIa (NovoSeven)	Hemophilia with factor inhibitors; use reported with intractable, life-threatening bleeding
Fibrinolytic inhibitors	Aprotinin (Trasylol)	All agents used to decrease bleeding during cardiac surgery, but aprotinin is the only drug FDA approved to reduce bleeding
	Epsilon-aminocaproic acid	
	Tranexamic acid	
Pharmacologic agents	Desmopressin	Hemophilia A with factor VIII coagulant activity levels greater than 5%, used also to improve platelet function in renal failure
Protease inhibitors	Protinin (Trasylol)	Prophylactic use to reduce blood loss and transfusions in patients undergoing CPB
Topical agents	Fibrin glue/fibrin tissue adhesives	Tissue sealant applied for refractory bleeding

Source: Reproduced with permission from Levy JH: Pharmacologic preservation of the hemostatic system during cardiac surgry. Ann Thorac Surg 2001; 72:1814S

Low-Molecular-Weight Heparin

Low-molecular0weight heparin (LMWH) is manufactured by depolymerizing unfractionated heparin to produce a mean molecular weight of approximately 5000.[147] A pentasaccharide sequence is required for attachment of a heparin fragment to antithrombin, and additional 13-saccharide residues are necessary to allow the heparin fragment to attach itself simultaneously to the heparin-binding domain of thrombin.[147] LMWH fragments of less than 18 saccharides retain the critical pentasaccharide sequence required for formation of a factor Xa–antithrombin complex; LMWH inhibits both factor Xa and thrombin, but the ratio of factor Xa to thrombin is increased.[147] LMWH is used widely in cardiovascular medicine but poses a problem for cardiac surgical

Table 4–5.

Preoperative Anticoagulants Used in Cardiac Surgical Patient

	Heparin	LMWH	Warfarin
Chemistry	Glycosaminoglycan MW = 15.000	MW = 5.000	4-Hydroxy-coumarin
Mechanism of action	Binds to antithrombin 111 to inhibit thrombin	Inhibition Ila-Xa	Vitamin K antagonist (factors II, VII, IX, X)
Bioavailability	30%	100%	
Half-life	IV: 45–60 min	SC: 4–7 h	40 h
Laboratory evaluation	Act–APTT	Anti-Xa	PT/INR
Reversal	Protamine, 1 mg/100 units heparin	Protamine reverses 60–80%	Vitamin K, FFP (2–4 units)

patients because of its long half-life. Partial thromboplastin time and activated clotting time are not affected by LMWH, and LMWH is not readily reversible with protamine.

Antithrombin

Antithrombin (AT) levels normally are present as approximately 100% activity but decrease approximately 30% in patients receiving heparin.[147] Following initiation of CPB, AT decreases by 40 to 50%, an important consideration that may be critical in determining the extent of thrombin inhibition, especially during CPB.[148] Despotis suggested better anticoagulation during CPB may be associated with less bleeding postprocedure, presumably related to preservation of critical coagulation components. One promising therapy currently under investigation is the use of purified antithrombin III (AT III).[150] Supplemental AT, through improved heparin sensitivity and enhanced anticoagulation, may preserve hemostasis during CPB.[151]

New Anticoagulants

The new intravenous antithrombins recombinant hirudin (Refludan), bivalirudin (Hirulog), and argatroban inhibit fibrin-bound thrombin independent of AT.[152–158] The direct thrombin inhibitors do not require AT or access to the heparin-binding site of thrombin and inhibit fibrin-bound as well as fluid-phase thrombin.[41] Recombinant hirudin (lepirudin), a 65-amino-acid polypeptide, is the most potent antithrombin. Although lepirudin has been used for cardiac surgical patients with HIT, it is nonreversible, its effect is difficult to monitor, it is eliminated by renal mechanisms, and it has been replaced by other agents. Argatroban is a synthetic intravenous direct thrombin inhibitor with a relatively short elimination half-life that is approved for use in patients with HIT and is used in critically ill patients, especially in ICU settings. Argatroban requires hepatic elimination and can be used in patients with renal failure.

When patients with HIT require CPB, although danaparoid (Orgaran), ancrod, recombinant hirudin (Refludan), and several other drug combinations have been used with various degrees of success, one of the major problems with these drugs is their lack of reversibility and thus potential to produce bleeding. Danaparoid has a long half-life ($t_{1/2}$ of anti–factor Xa activity of 24 hours), and monitoring is complicated by the need to measure anti–factor Xa. Recombinant hirudin, a direct thrombin inhibitor modified from a leech salivary protein, is the most potent and specific thrombin inhibitor currently known. Bivalirudin (Angiomax) is a short-acting hirudin analogue that requires infusions to be effective and is the most studied agent in patients with HIT both on pump and off pump for cardiac surgery.[161,162]

Aprotinin

Aprotinin is a naturally occurring polypeptide with a molecular weight of 6512 that reversibly complexes with the active serine site in various proteases in plasma to inhibit the serine proteases trypsin, kallikrein, plasmin, and elastase reversibly. Multiple mechanisms are responsible for aprotinin's ability to reduce bleeding after CPB.[163–170] Aprotinin is the most potent antifibrinolytic agent. The propagation of the "intrinsic" fibrinolysis through factor XII–mediated kallikrein activation and the generation of plasmin through "extrinsic" or tissue plasminogen activator (tPA)–mediated activation of plasminogen is effectively inhibited by approximately 4 μmol/L of aprotinin, which is maintained in plasma with the high-dose regimen. Aprotinin also has multiple anti-inflammatory effects, and inflammation and hemostasis are closely linked. Finally, aprotinin has been studied in multiple placebo-controlled studies and is the only agent approved by the Food and Drug Administration (FDA) to reduce bleeding in cardiac surgical patients.[167–171]

ANTIFIBRINOLYTIC AGENTS AND DESMOPRESSIN

The synthetic lysine analogues epsilon aminocaproic acid (EACA, Amicar) and tranexamic acid inhibit fibrinolysis by attaching to the lysine-binding site of the plasmin(ogen) molecule, displacing plasminogen from fibrin. Levi and colleagues reported a meta-analysis of all randomized, controlled trials of the three most frequently used pharmacologic strategies to decrease perioperative blood loss [aprotinin, lysine analogues (aminocaproic acid and tranexamic acid), and desmopressin].[170] Studies were included if they reported at least one clinically relevant outcome (e.g., mortality, rethoracotomy, proportion of patients receiving a transfusion, or perioperative myocardial infarction) in addition to perioperative blood loss. In addition, a separate meta-analysis was done for studies concerning complicated cardiac surgery. A total of 72 trials (8409 patients) met the inclusion criteria. Treatment with aprotinin decreased mortality almost twofold [odds ratio (OR) = 0.55; 95% confidence interval (CI) = 0.34–0.90] compared with placebo. Treatment with aprotinin and with lysine analogues decreased the frequency of surgical reexploration (OR = 0.37; 95% CI = 0.25–0.55 and OR = 0.44; 95% CI = 0.22–0.90, respectively). These two treatments also decreased significantly the proportion of patients receiving any allogeneic blood transfusion. The use of desmopressin resulted in a small decrease in perioperative blood loss but was not associated with a beneficial effect on other clinical outcomes. Aprotinin and lysine analogues did not increase the risk of perioperative myocardial infarction; however, desmopressin was associated with a 2.4-fold increase in the risk of this complication. Studies in patients undergoing complicated cardiac surgery showed similar results.

Acquired Platelet Dysfunction

Acquired functional platelet disorders are caused by the multitude of potent antiplatelet agents that patients receive for atherosclerotic vascular disease or during percutaneous interventions.[172–173] Clopidogrel (Plavix), a drug that selectively

interferes with ADP-induced platelet aggregation, is used commonly in patients with ischemic heart disease and those undergoing angioplasty.[172] Clopidogrel requires 3 to 5 days for the onset to occur and a similar length of time for the effect to disappear.[172] Because of the pivotal role of the platelet glycoprotein (GP) IIb/IIIa complex in platelet-mediated thrombus formation, three different GP IIb/IIIa antagonists are available currently, but they differ in antagonist affinity, reversibility, and receptor specificity.[172] GP IIb/IIIa (IIbβ3) is a receptor on platelets that binds to key hemostatic proteins, including fibrinogen and von Willebrand factor (vWF), to allow cross-linking of platelets and platelet aggregation. By blocking this final common pathway using GP IIb/IIIa antagonists, these drugs function as inhibitors of platelet participation in acute thrombosis. Various antagonists of GP IIb/IIIa are available and include the monoclonal antibody abciximab (ReoPro); tirofiban (Aggrastat), a nonpeptide fiban molecule; and eptifibatide (Integrelin), a cyclic peptide. Tirofiban and eptifibatide are cleared predominantly through renal mechanisms and have a circulating plasma half-life of approximately 2 to 4 hours, and while abciximab has a relatively short plasma half-life, the monoclonal antibody avidly binds to platelets with a relatively longer duration of action.[171]

Antiplatelet agents are used primarily to treat and prevent arterial thrombosis. Ticlopidine and clopidogrel are believed to inhibit the binding of adenosine 5′-diphosphate (ADP) to its platelet receptor; this ADP-receptor blockade leads to direct inhibition of the binding of fibrinogen to the GP IIb/IIIa complex.[172] Clopidogrel was approved by the FDA for the reduction of ischemic events in patients with recent myocardial infarction, stroke, or peripheral arterial disease with no added risk for neutropenia. Use of the combination of clopidogrel and aspirin, as well as the use of clopidogrel in coronary stenting, is growing rapidly. Many heart centers now administer clopidogrel before anticipated stenting procedures. The variability in bleeding in patients receiving these agents for cardiac surgery may relate to the time and duration of therapy.

Previous recommendations for managing patients receiving antiplatelet agents and requiring cardiac surgery are summarized in Table 4-6. The fact that a patient is receiving antiplatelet agents should not preclude urgent revascularization. Platelets may be needed and should be available when operating on abciximab-treated patients. Platelets should not be administered prophylactically. Although recommendations have been made on reducing heparin dosing, we believe that there are no data to support reductions in heparin dosing during CPB and cardiac surgery. Therefore, standard loading doses should be considered, and additional heparin doses, based on time and duration of bypass or on actual heparin levels, should be maintained. Further, the heparin is reduced at the end of CPB.

Table 4–6.

Recommendations for Managing Patients Receiving Platelet Inhibitors for Cardiac Surgery

Stop therapy.
Do not give platelet transfusions prior to surgery or revascularization.
Give normal doses of heparin.
Platelet transfusions as needed after cardiopulmonary bypass.

Protamine

One of our most unusual clinical practices is to anticoagulate patients with heparin, an extract from bovine lung or porcine intestine, and reverse the heparin with protamine, which is a histone and a basic arginine-rich polypeptide extracted from salmon sperm. Protamine immediately reverses heparin by nonspecific polyionic-polycationic (acid-base) interactions. There are different methods to determine the amount of protamine to be administered: Use a ratio of 1.3 mg protamine per 100 units of heparin administered, determine heparin levels based on heparin-protamine titrations, or use a dose based on the total amount of heparin administered over time.[174]

Protamine, a polypeptide isolated from fish sperm, does have the potential to produce anaphylactic reactions and other potential adverse drug reactions.[175,176] Although rapid protamine administration has the potential to produce hemodynamic instability, the life-threatening reactions to protamine seen clinically represent immediate hypersensitivity reactions.[175,176] The incidence of anaphylaxis appears to be higher in certain patient groups, including patients with diabetes receiving protamine-containing insulin such as neutral protamine Hagedorn (NPH). We have reported that the incidence of anaphylaxis to protamine in NPH insulin–dependent diabetics is 0.6 to 2% compared with 0.06% in most other patients.[175,176] Other patient groups may be at an increased risk for adverse reactions to protamine, including patients with a prior vasectomy or previous fish allergy; however, data do not support this contention.[175,176]

New methods for reversing anticoagulation were once under investigation but may never come to market and include heparin-binding filters, recombinant platelet factor 4, and heparinase.[177]

Antifibrinolytics

As discussed earlier, patients following fibrinolytic therapy have a complex coagulopathic state. Because of the potential half-lives of the fibrinolytic agents, drugs that counteract their effects are potentially useful. Epsilon-aminocaproic acid (EACA, Amicar) and its analogue, tranexamic acid, are derivatives of the amino acid lysine. Both these drugs inhibit the proteolytic activity of plasmin and the conversion of plasminogen to plasmin by plasminogen activators. Although

Table 4–7.

Indications for Blood Product Administration in the Bleeding Cardiac Surgical Patient

Blood product	Indication	Doses
Red blood cells	Low Hct	
Fresh-frozen plasma	Warfarin therapy Documented coagulation factor deficiency Abnormal PT	2–4 units
Platelets	Low platelet count, e.g., <50,000–100,000 Platelet dysfunction, e.g., abnormal TEG	1 unit/10 kg
Cryoprecipitate	Low fibrinogen, e.g., <150 mg/dL Fibrin glue	1–1.5 units/10 kg
Bovine Antithrombin III	Fibrin glue Inadeguate ACT (pt on heparin)	500–1000 units

aprotinin in concentrations used clinically is the most potent inhibitor of fibrinolysis and would represent a useful therapy, it is not approved for this use.[170] Additional coagulation factors and platelets may be required besides to inhibiting fibrinolysis to reverse the coagulopathy.

Blood Products

Blood products are administered widely in cardiac surgical patients and represent a major utilization for hospitals. Once widely administered as part of empirical therapy, specific indications for coagulation factors need to be determined prior to their administration (Table 4-7). In addition to cost, blood products carry significant risks. Although the risk of viral-induced transmission is low, immunosuppressive effects, transfusion-related acute lung injury, and cost need to be considered when administering blood products. The role of fresh-frozen plasma needs to be considered because it represents an often inappropriately used product. Specific indications for blood products are listed in Table 4-7. Each institution needs to develop its own algorithm for blood product administration in cardiac surgical patients. With the use of specific therapies, excessive and inappropriate transfusions can be avoided.

Recombinant Coagulation Products

Coagulation products used to manage bleeding in patients with hemophilia, von Willebrand's disease (vWD), or acquired inhibitors to antihemophilic factor include antihemophilic factor concentrates, factor IX concentrates, factor VIIa concentrate, factor IX complexes, anti-inhibitor coagulant complexes, and desmopressin acetate. These commercially available products are used to manage acute bleeding or to prevent excessive bleeding during cardiac and noncardiac surgery in patients with hematologic disorders. Recombinant activated factor VIIa (rFVIIa, NovoSeven, Novo Nordisk A/S) has been used as a novel and effective treatment for patients with hemophilia with inhibitors for the treatment of bleeding and to secure hemostasis in complex clinical situations.[178–181]

The role of rFVIIa in the treatment of bleeding as a therapeutic approach has been addressed in multiple reports and in a study of high-risk patients. Further, the use of rFVIIa has been reported in patients who refused allogeneic blood products.[181]

The modes of action of rFIIa are multiple, including tissue-factor-dependent mechanisms and generation of factors Xa and IXa on the surfaces of activated platelets. These studies relate thrombin generation on activated platelets to the high level of rFVIIa binding to platelet surfaces. Therapeutic doses of rFVIIa are not established; different doses have been used during surgery in patients with hemophilia and inhibitors and in those with refractory bleeding following cardiac surgery. The off-label use of rFVIIa has been reported to control bleeding in patients with refractory bleeding undergoing cardiac surgery, although current studies are underway to better define its application, especially in relation to its cost. Recommended dose ranges for rFVIIa usually vary from 30 to 90 μg/kg.[178]

Fibrinolytics

Patients also may have received fibrinolytic drugs, including tissue plasminogen activator (tPA), streptokinase, and urokinase. These drugs inactivate fibrinogen and other adhesive proteins and have the potential to affect platelets as well.[181] Patients receiving these drugs within 24 hours of surgery should be considered to be at high risk for coagulopathy, and fibrinogen levels should be measured.

BETA-ADRENERGIC RECEPTOR BLOCKERS

Not surprisingly, most of the effects observed after administration of a beta-adrenergic receptor blocker reflect the

reduced responsiveness of tissues containing beta-adrenergic receptors to cathecholamines present in the vicinity of those receptors. Hence the intensity of the effects of beta blockers depends on both the dose of the blocker and the receptor concentrations of catecholamines, primarily epinephrine and norepinephrine. In fact, a purely competitive interaction of beta blockers and catecholamines can be demonstrated in normal human volunteers as well as in isolated tissues studied in the laboratory. The presence of disease and other types of drugs modifies the responses to beta blockers observed in patients, but the underlying competitive interaction is still operative. The key to successful use of beta-adrenergic receptor blockers is to titrate the dose to the desired degree of effect and to remember that excessive effects from larger than necessary doses of beta-adrenergic receptor blockers can be overcome by (1) administering a catecholamine to compete at the blocked receptors and/or (2) administering other types of drugs to reduce the activity of counterbalancing autonomic mechanisms that are unopposed in the presence of beta-receptor blockade. An example of the latter is propranolol-induced bradycardia, which reflects the increased dominance of the vagal cholinergic mechanism on cardiac nodal tissue. Excessive bradycardia may be relieved by administering atropine to block the cholinergic receptors, which are also located in the sinoatrial (SA) and atrioventricular (AV) nodes.

Table 4–8.

Location and Actions of Beta-Adrenergic Receptors

Tissue	Receptor	Action	Opposing actions
Heart			
Sinus and AV nodes	1	↑ Automaticity	Cholinergic receptors
Conduction pathways	1	↑ Conduction velocity	Cholinergic receptors
		↑ Automaticity	Cholinergic receptors
Myofibils	1	↑ Contractility	—
		↑ Automaticity	—
Vascular smooth muscle (Arterial, venous)	2	Vasodilation	Alpha-adrenergic receptors
Bronchial smooth muscle	2	Bronchodilation	Cholinergic receptors
Kidneys	1	↑ Renin release (juxtaaglomerular cells)	$Alpha_1$-adrenergic receptors
Liver	2	↑ Glucose metabolism ↑ Lipolysis	$Alpha_1$-adrenergic receptors
Fat/adipose tissue	3	↑ Lipolysis	—
Skeletal muscle	2	↑ Potassium uptake glyccogenolysis	—
Eye, ciliary muscle	2	Relaxation	Cholinergic receptors
GI tract	2	↑ Motility	Cholinergic receptors
Gallbladder	2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	2	Relaxation	Cholinergic receptors
Uterus	2	Relaxation	Oxytocin
Platelets	2	↓ Aggregation	$Alpha_2$-adrenergic receptors (aggregation)

Source: Reproduced with permission from Lefkowitz RH, Hoffman BB, Taylor P: Neurotransmission: The autonomic and somatic motor nervous system, in Hardman JL, Molinoff BB, Ruddon RW, Gilman AG (eds): The Pharmacological Basis of Therapeutics. New York, McGraw-Hill, 1996; p 84.

Knowledge of the type, location, and action of beta receptor is fundamental to understanding and predicting effects of beta-adrenergic receptor–blocking drugs[183] (Table 4-8). Beta-adrenergic receptor blockers are competitive inhibitors; hence the intensity of blockade depends on both the dose of the drug and the receptor concentrations of catecholamines, primarily epinephrine and norepinephrine.

Beta-adrenergic receptor antagonists (blockers) include many drugs (Table 4-9) that typically are classified by their relative selectivity for $beta_1$ and $beta_2$ receptors (i.e., cardioselective or nonselective), the presence or absence of agonistic activity, membrane-stabilizing properties, alpha-receptor-blocking efficacy, and various pharmacokinetic features (e.g., lipid solubility, oral bioavailability, and elimination half-time).[184] The practitioner must realize that the selectivity of individual drugs for $beta_1$ and $beta_2$ receptors is relative, not absolute. For example, the risk of inducing bronchospasm with a $beta_1$-adrenergic (cardioselective) blocker (e.g., esmolol or metoprolol) may be relatively less than with a nonselective blockers (e.g., propranolol); however, the risk is still present.

Acute Myocardial Infarction

Clinical trials of intravenous beta-adrenergic blockers in the early phases of acute myocardial infarction suggest that mortality decreases by 10%. Following myocardial infarction, chronic oral beta-blocking agents reduce the incidence of recurrent myocardial infarction. A randomized, controlled trial of atenolol (Tenormin) in the perioperative period was performed by Mangano and his group. In their study, the incidence of myocardial ischemia was reduced by 50% in patients receiving atenolol. Overall mortality after discharge was lower in the atenolol group than in the control group over a 2-year period (10% versus 21%).[185] However, atenolol did not result in reducing death during hospitalization or perioperative myocardial infarction. Poldermans and colleagues performed another randomized, controlled perioperative trial using bisoprolol (Zebeta) in high-risk vascular surgical patients. Bisoprolol therapy, started 1 week before a major surgery and continued for 30 days postoperatively, has reduced the rate of death and nonfatal myocardial infarction significantly.[186] The follow-up of this study showed that the

Table 4–9.

Beta-Adrenergic Receptors Blockers

Generic name	Trade name	Dosage forms	β_1-Selective
Acebutolol	Sectral	PO	Yes
Atenolol	Tenormin	IV, PO	Yes
Betaxolol	Kerlone	PO	Yes
Bisoprolol	Zebeta	PO	Yes
Esmolol	Brevibloc	IV	Yes
Metoprolol	Lopressor, Toprol-XL	IV, PO	Yes
Carvedilol*	Coreg	PO	No
Carteolol	Cartrol	PO	No
Labetalol*	Normodyne, Trandate	IV, PO	No
Nadolol	Corgard	PO	No
Penbutolol	Levatol	PO	No
Pindolol	Visken	PO	No
Propranolol	Inderal	IV, PO&	No
Sotalol	Betapace	PO	No
Timolol	Blocadren	PO	No

$Alpha_1$: beta-adrenergic blocking ratio; carvedilol 1:10, labetalol 1:3 (oral)/1:7 (IV).

Source: Reproduced with permission from Hug CJ: Beta-adrenergic blocking drugs, in Drug Evaluations Annual 1994. Chicago, American Medical Association, 1993; p 539.

reduction in cardiac events persisted over 2 years in the bisoprolol-treated group (12% versus 32%).[187]

Supraventricular Tachycardias and Ventricular Dysrhythmias

Beta-adrenergic blocking agents are Vaughan Williams class II antidysrhythmics that primarily block cardiac responses to catecholamines. Propranolol (Inderal), esmolol (Brevibloc), and acebutolol (Sectral) are used commonly for this indication. Beta-blocking agents decrease spontaneous depolarization in the SA and AV nodes, decrease automaticity in Purkinje fibers, increase AV nodal refractoriness, increase threshold for fibrillation (but not for depolarization), and decrease ventricular slow responses that depend on catecholamines. Amiodarone, a class III agent, also exerts noncompetitive alpha- and beta-adrenergic blockade, which may contribute its antidysrhythmic and antihypertensive actions.[188] Sotalol is another class III antidysrhythmic with nonselective beta-blocking action. There is evidence that beta-blocking agents also decrease intramyocardial conduction in ischemic tissue and reduce the risks of dysrhythmias to the extent that they decrease myocardial ischemia. Beta-adrenergic blockers are not particularly effective in controlling dysrhythmias that are not induced or maintained by catecholamines.

Hypertension

Hypertension is a major risk factor for developing heart failure and other end-organ damage. Beta blockers, along with diuretics, are considered to be the initial drug of choice for uncomplicated hypertension in patients aged less than 65 years.[189]

During the early phases of therapy, there is a decrease in cardiac output, a rise in systemic vascular resistance (SVR), and relatively little change in mean arterial blood pressure. Within hours to days, SVR normalizes, and blood pressure declines. In addition, the release of renin from the juxtaglomerular apparatus in the kidney is inhibited ($beta_1$ blockade). Beta-blocking agents with intrinsic agonistic activity reduce systemic vascular resistance below pretreatment levels presumably by activating $beta_2$ receptors in vascular smooth muscle. Most beta-adrenergic blockers are used with other agents in treating chronic hypertension. When combined with a vasodilator, beta blockers limit reflex tachycardia. For example, when propranolol is combined with intravenous nitroprusside (a potent arterial dilator), it prevents reflex release of renin and reflex tachycardia induced by nitroprusside.

Acute Dissecting Aortic Aneurysm

The primary goal in managing dissecting aneurysms is to reduce stress on the dissected aortic wall by reducing the systolic acceleration of blood flow. Beta blockers reduce cardiac inotropy and ventricular ejection fraction. Beta blockers also may limit reflex sympathetic responses to vasodilators that are used to control systemic arterial pressure.

Pheochromocytoma

The presence of catecholamine-secreting tissue is tantamount to the continuous or intermittent infusion of a varying mixture of norepinephrine and epinephrine. It is absolutely essential that virtually complete alpha-adrenergic receptor blockade be established prior to administering the beta blocker to prevent exacerbation of hypertensive episodes by unopposed alpha-adrenergic receptor activity in vascular smooth muscle.

Chronic Heart Failure

It is now understood that activation of the autonomic nervous system (ANS) and renin-angiotensin system (RAS) as compensatory mechanisms for the failing heart actually may contribute to deterioration of myocardial function. Mortality in chronic heart failure seems related to activation of ANS and RAS. Progression of myocardial dysfunction and remodeling may be attenuated by the use of beta-blocking agents and ACE inhibitors. Carvedilol (Coreg) is a beta blocker approved by the FDA to treat patients with heart failure. It has an $alpha_1$- and nonselective beta-blocking activity (alpha:beta = 1:10). It is contraindicated in severe decompensated heart failure and asthma. In patients with atrial fibrillation and left-sided heart failure treated with carvedilol, improved ejection fraction and a trend toward a decreased incidence of death and chronic heart failure hospitalization were observed in a retrospective analysis of a U.S. carvedilol study.[190] There are several ongoing clinical trials with carvedilol, metoprolol (Toprol), and bisoprolol (Zebeta). The results of these studies may provide answers as to which beta-blocking agent would be most successful in the treatment of specific patient populations.

Other Indications

The other clinical applications of beta-adrenergic receptor blockers listed in Table 4-10 are based on largely symptomatic treatment or empirical trials of beta-adrenergic antagonists.

Side Effects and Toxicity

The most obvious and immediate signs of a toxic overdose of a beta-adrenergic receptor blocker are hypotension, bradycardia, congestive heart failure, decreased AV conduction, and a widened QRS complex on the electrocardiogram. Treatment is aimed at blocking the cholinergic receptor responses to vagal nerve activity (e.g., atropine) and administering a sympathomimetic to compete with the beta blockers at adrenergic receptors. In patients with asthma and chronic obstructive pulmonary disease (COPD), beta blockers may cause bronchospasm. Beta blockers may increase levels of plasma triglycerides and reduce levels of high-density lipoprotein (HDL) cholesterol.[191] Rarely, beta blockers may mask the symptoms of hypoglycemia in diabetic patients. Other side effects include mental depression, physical fatigue, altered sleep patterns, sexual dysfunction, and gastrointestinal symptoms, including indigestion, constipation, and diarrhea.

Table 4–10.

Clinical Applications of Beta-Adrenergic Receptor Blockers
Angina pectoris
Accute myocardial infarction (prophylaxis)
Supraventricular tachycardia
Ventricular dysrhythmias
Hypertension (usually in combination with other drugs)
Pheochromocytoma (after alpha-receptor blockade is established)
Acute dissecting aortic aneurysm
Hyperthyroidism
Hypertrophic obstructive cardiomyopathy (IHSS)
Dilated cardiomyopathy (selected patients)
Migraine prophylaxis
Acute panic attack
Alcohol withdrawal syndrome
Glaucoma (topically)

Source: Reproduced with permission from Hug CJ: Beta-adrenergic blocking drugs, in Drug Evaluations Annual 1994. Chicago, American Medical Association, 1993; p 539.

Drug Interactions

Pharmacokinetic drug interactions include reduced gastrointestinal absorption of the beta blocker (e.g., aluminum-containing antacids and cholestyramine), increased biotransformation of the beta blocker (e.g., phenytoin, phenobarbital, rifampin, and smoking), and increased bioavailability owing to decreased biotransformation (e.g., cimetidine and hydralazine). Pharmacodynamic interactions include an additive effect with calcium channel blockers to decrease conduction in the heart and a reduced antihypertensive effect of beta blockers when administered with some of the nonsteroidal anti-inflammatory drugs (NSAIDs).

DIURETICS

Diuretics are drugs that act directly on the kidneys to increase urine volume and produce a net loss of solute (principally sodium and other electrolytes) and water. Diuretics and beta blockers are initial drugs of choice for uncomplicated hypertension in patients younger than 65 years.[189] The currently available diuretic drugs have a number of other uses in medicine (e.g., glaucoma and increased intracranial pressure). The principal indications for the use of diuretics by intravenous administration in the perioperative period are (1) to increase urine flow in oliguria, (2) to reduce intravascular volume in patients at risk for acute congestive heart failure from excessive fluid administration or acute heart failure, and (3) to mobilize edema.

Renal function depends on adequate renal perfusion to maintain the integrity of renal cells and to provide the hydrostatic pressure that produces glomerular filtration. There are no drugs that act directly on the renal glomerulus to affect glomerular filtration rate (GFR). In the normal adult human of average size, GFR averages 125 mL/min, and urine production approximates 1 mL/min. In other words, 99% of the glomerular filtrate is reabsorbed. Diuretics act primarily on specific segments of the renal tubule to alter reabsorption of electrolytes, principally sodium, and water.

There are two basic mechanisms behind the renal tubular reabsorption of sodium. First, sodium is extruded from the tubular cell into peritubular fluid primarily by active transport of the sodium ion, which reflects the action of the Na^+,K^+-ATPase pump as well as the bicarbonate reabsorption mechanism (see below). This extrusion of sodium creates an electrochemical gradient that causes diffusion of sodium from the tubular lumen into the tubular cell. Second, sodium moves from the glomerular filtrate in the tubular fluid into the peritubular fluid by several different mechanisms. The most important quantitatively is the sodium electrochemical gradient created by the active extrusion of sodium from the tubular cell into the peritubular fluid. In addition, sodium is coupled with organic solutes and phosphate ions, exchanged for hydrogen ions diffusing from the tubular cell into the tubular lumen, and coupled to the transfer of a chloride ion or a combination of a potassium and two chloride ions (Na^+-K^+-$2Cl^-$ cotransport) from the tubular fluid into the tubular cell. Diuretics are classified by their principal site of action in the nephron and by the primary mechanism of their naturetic effect (Table 4-11).

Osmotic Diuretics

Mannitol is the principal example of this type of diuretic, which is used for two primary indications: (1) prophylaxis and early treatment of acute renal failure that is characterized by a decrease in GFR leading to a decreased urine volume and an increase in the concentration of toxic substances in the renal tubular fluid and (2) to enhance the actions of other diuretics by retaining water and solutes in the tubular lumen, thereby providing the substrate for the action of other types of diuretics. Normally, 80% of the glomerular filtrate is reabsorbed isosmotically in the proximal tubules. By its osmotic effect, mannitol limits the reabsorption of water and dilutes the proximal tubular fluid. This reduces the electrochemical gradient for sodium and limits its reabsorption so that more is delivered to the distal portions of the nephron. Mannitol produces a prostaglandin-mediated increase in renal blood flow that partially washes out the medullary hypertonicity, which is essential for the countercurrent mechanism promoting the reabsorption of water in the late distal tubules and collecting

Table 4–11.

Classification of Diuretics

Site of action	Mechanism	
Osmotic	Proximal convoluted and late proximal for NA^+ diffusion from tubular fluid into tubular cell	↓ Eleectrochemical gradient
	Late proximal tubule	↓ Gradient for Cl^- (accompanying NA^+ diffusion)
	Thick ascending loop of Henle	↓ Na^+-K^+-$2Cl^-$ cotransport
Carbonic	Proximal convoluted tubule anhydrase inhibitors	↓ Na^+-H^+ exchange$^+$
Thiazides	Distal convoluted tubule	↓ Na^+-Cl^- cotransport
High-ceiling loop diuretics	Thick ascending loop of Henle	↓ Na^+-K^+-$2Cl^-$ cotransport
Potassium-sparing diuretics	Late distal tubule and collecting duct	↓ Electrogeenic Na^+ entry into cells (driving force for K^+ ssectretion)

Source: Reproduced with permission from Wener IM: Drugs affecting renal function and electrolyte metabolism, in Gilman AG, Rall TW, Nies AS, Taylor P (eds): The Pharmacological Basis of Therapeutics, 8th ed. New York, Pergamon Press, 1990; p 708.

system under the influence of antidiuretic hormone (ADH). Mannitol is used often (25 to 50 g) as part of the priming solution of cardiopulmonary bypass for the above-mentioned indications. The principal toxicity of mannitol is acute expansion of the extracellular fluid volume leading to CHF in the patient with compromised cardiac function.

High-Ceiling (Loop) Diuretics

Furosemide (Lasix), bumetanide (Bumex), and ethacrynic acid (Edecrin) are three chemically dissimilar compounds that have the same primary diuretic mechanism of action. They act on the tubular epithelial cell in the thick ascending loop of Henle to inhibit the Na^+-K^+-$2Cl^-$ cotransport mechanism. Their peak diuretic effect is far greater than that of the other diuretics currently available. Administered intravenously, they have a rapid onset and relatively short duration of action, the latter reflecting both the pharmacokinetics of the drugs and the body's compensatory mechanisms to the consequences of diuresis. These three diuretics increase renal blood flow without increasing GFR and redistribute blood flow from the medulla to the cortex and within the renal cortex. These changes in renal blood flow are also short-lived, reflecting the reduced extracellular fluid volume resulting from diuresis. Minor actions, including carbonic anhydrase inhibition by furosemide and bumetanide and actions on the proximal tubule and on sites distal to the ascending limb, remain controversial. All three of the loop diuretics increase the release of renin and prostaglandin, and indomethacin blunts the release as well as the augmentation in renal blood flow and naturesis. All three of the loop diuretics produce an acute increase in venous capacitance for a brief period of time after the first intravenous dose is administered, and this effect is also blocked by indomethacin.

Potassium, magnesium, and calcium excretion is increased in proportion to the increase in sodium excretion. In addition, there is augmentation of titratable acid and ammonia excretion by the distal tubules leading to metabolic alkalosis, which is also produced by contraction of the extracellular volume. Hyperuricemia can occur but usually is of little physiologic significance. The nephrotoxicity of cephaloridine, and possibly other cephalorsporins, is increased. A rare but serious side effect of the loop diuretics is deafness, which may reflect electrolyte changes in the endolymph.

Because of their high degree of efficacy, prompt onset, and relatively short duration of action, the high-ceiling or loop diuretics are favored for intravenous administration in the perioperative period to treat the three principal problems cited earlier. Dosage requirements vary considerably among patients. Some may only require furosemide 3 to 5 mg IV to produce a good diuresis. And for some patients, the less potent benzothiazides may be sufficient.

Benzothiazides

Hydrochlorothiazide (HCTZ) is the prototype of more than a dozen currently available diuretics in this class. Although the drugs differ in potency, they all act by the same mechanism of action and have the same maximum efficacy. All are actively secreted into the tubular lumen by tubular cells and act in the early distal tubules to decrease the electroneutral Na^+-Cl^- cotransport reabsorption of sodium. Their moderate efficacy probably reflects the fact that more than 90% of the filtrated sodium is reabsorbed before reaching the distal tubules. Their action is enhanced by their combined administration with an osmotic diuretic such as mannitol. The benziothiazides increase urine volume and the excretion of

sodium, chloride, and potassium. The decreased reabsorption of potassium reflects the higher rate of urine flow through the distal tubule (diminished reabsorption time).

This class of diuretics produces the least disturbance of extracellular fluid composition, reflecting their moderate efficacy as diuretics and perhaps suggesting their usefulness when a moderate degree of diuretic effect is indicated. Their principal side effects include hyperuricemia, decreased calcium excretion, and enhanced magnesium loss. Hyperglycemia can occur and reflects multiple variables. With prolonged use and development of a contracted extracellular fluid volume, urine formation decreases (i.e., tolerance develops to their diuretic actions). These agents also have a direct action on the renal vasculature to decrease GFR.

Carbonic Anhydrase Inhibitors

Acetazolamide (Diamox) is the only diuretic of this class available for intravenous administration. Its use is directed primarily toward alkalinization of urine in the presence of metabolic alkalosis, which is a common consequence of prolonged diuretic therapy. It acts in the proximal convoluted tubule to inhibit carbonic anhydrase in the brush border of the tubular epithelium, thereby reducing the destruction of bicarbonate ions (i.e., conversion to CO_2 that diffuses into the tubular cell). The carbonic anhydrase enzyme in the cytoplasm of the tubular cell is also inhibited, and as a consequence, conversion of CO_2 to carbonic acid is reduced markedly, as is the availability of hydrogen ions for the Na-H exchange mechanism. Hence the reabsorption of both sodium and bicarbonate in the proximal tubules is diminished. However, more than half the bicarbonate is reabsorbed in more distal segments of the nephron, thereby limiting the overall efficacy of this class of diuretics.

Potassium-Sparing Diuretics

Spironolactone (Aldactone) is a competitive antagonist of aldosterone. Spironolactone binds to the cytoplasmic aldosterone receptor and prevents its conformational change to the active form, thereby aborting the synthesis of active transport proteins in the late distal tubules and collecting system where the reabsorption of sodium and secretion of potassium are reduced.

Triamterene (Dyrenium) and amiloride (Midamor) are potassium-sparing diuretics with a mechanism of action independent of the mineralocorticoids. They have a moderate natriuretic effect leading to an increased excretion of sodium and chloride with little change or a slight increase in potassium excretion when the latter is low. When potassium secretion is high, they produce a sharp reduction in the electrogenic entry of sodium ions into the distal tubular cells and thereby reduce the electrical potential that is the driving force for potassium secretion.

Both types of potassium-sparing diuretics are used primarily in combination with other diuretics to reduce potassium loss. Their principal side effect is hyperkalemia. It is appropriate to limit the intake of potassium when using this type of diuretic. It is also appropriate to use this type of diuretic cautiously in patients taking ACE inhibitors, which decrease aldosterone formation and consequently increase serum potassium concentrations.

Other Measures to Enhance Urine Output and Mobilization of Edema Fluid

The infusion of albumin (5 to 25% solutions) or other plasma volume expanders (e.g., hetastarch) is often employed in an attempt to draw water and its accompanying electrolytes (i.e., edema fluid) osmotically from the tissues into the circulating blood and thereby enhance their delivery to the kidney for excretion. In the presence of a reduced circulating blood volume, this approach seems to be a logical method to increase the circulating blood volume and renal perfusion. The limiting feature of this approach to enhancing diuresis relates to the fact that the osmotic effect of albumin and plasma expanders is transient because they can diffuse (at a rate slower than water) from blood through capillary membranes into tissue. The albumin or plasma expander then tends to hold water and its accompanying electrolytes in tissue (i.e., rebound edema). The same limiting feature applies to osmotic diuretics such as mannitol, which may transiently draw water and its accompanying electrolytes from tissues into the circulating blood for delivery to the kidney, where the mannitol passes through the glomerulus and delays the reabsorption of water and its accompanying electrolytes from the proximal tubular fluid. While this mechanism may enhance the actions of other diuretics, it is a transient effect that is limited by the diffusion of mannitol from blood into tissues with the production of rebound edema.

Dopamine (Intropin), at doses 1 to 3 μg/kg per minute, has been used conventionally to support mesenteric and renal perfusion. Its vascular action is mediated via vascular dopamine 1 (D_1) receptors in coronary, mesenteric, and renal vascular beds. By activating adenyl cyclase and raising intracellular concentrations of cyclic AMP, D_1-receptor agonists cause vasodilatation. There are also dopamine 2 (D_2) receptors that antagonize D_1-receptor stimulation. Fenoldopam (Corlopam), a parenteral D_1-receptor-specific agonist, was approved by the FDA recently. The Joint National Commissions VI and VII recommendations include this drug for hypertensive emergencies.[192,193] Infusion of fenoldopam (0.1 to 0.3 μg/kg per minute) causes an increase in GFR, renal blood flow, and Na^+ excretion.

Clinical trials of dopamine failed to show improvement in renal function, which probably is due to the nonspecificity of dopamine. As a catecholamine and a precursor in the metabolic synthesis of norepinephrine and epinephrine, dopamine has inotropic and chronotropic effects on the heart. The inotropic effect is mediated by beta$_1$-adrenergic receptors and usually requires infusion rates higher than those able to produce enhanced renal perfusion and diuresis. However, there are varied pharmacokinetic responses to dopamine infusion even in healthy subjects[194]; therefore, the use of a "renal dose" dopamine regimen may not always result in the desirable effects. Stimulation of catecholamine receptors and D_2 receptors antagonizes the effects of

D_1-receptor stimulation. There are a small number of studies where improved renal outcome was shown with use of the D_1-receptor-specific agonist fenoldopam.[195–197] A further large-scale study is needed to answer whether prophylactic use of fenoldopam reduces the incidence of perioperative renal insufficiency.

HERBAL MEDICINE

A large number of Americans take herbal remedies for their health. Most of these herbal therapies are not supported by clear scientific evidence and are not under rigorous control by the FDA.[198] Patients who take alternative remedies may not necessarily disclose this information to their physicians.[199] There are increasing concerns regarding serious drug interactions between herbal therapy and prescribed medication. Some of the most common herbal remedies and drug interactions are summarized in Table 4-12.[200]

Drugs for airway management

Airway management in cardiovascular surgical patients is very important because these patients often present with coexisting conditions that may complicate endotracheal intubation. For example, a patient with morbid obesity and sleep apnea may require awake intubation with a fiberoptic bronchoscope, or a history of smoking and COPD may make the patient susceptible to rapid desaturation and/or bronchospasm. Airway management in the perioperative period is a primary responsibility of the anesthesiologist, but the surgeon becomes involved in the absence of the anesthesiologist or in assisting the anesthesiologist in difficult situations. Airway management involves instrumentation and mechanics (not discussed here) and employs drugs to overcome pathophysiologic problems that contribute to airway obstruction and to facilitate manipulation and instrumentation of the airway. Most of the drugs used for these purposes are taken from drug classes that have other important therapeutic applications (e.g., sympathomimetics).

Five major challenges may be encountered in airway management. Each of these is described succinctly below to facilitate understanding of the roles that drugs play in meeting the challenges. For the most part, details of pharmacology such as doses, side effects, and toxicity are left to standard textbooks of pharmacology and drug compendia. The five challenges are (1) overcoming airway obstruction, (2) preventing pulmonary aspiration, (3) performing endotracheal intubation, (4) maintaining intermittent positive-pressure ventilation (IPPV), and (5) reestablishing spontaneous ventilation and airway protective reflexes.

Airway Obstruction

Obstruction to gas flow can occur from the entry of a foreign object (including food) into the airway and as a result of pathophysiologic processes involving airway structures (e.g., trauma and edema). In the anesthetized or comatose patient, the loss of muscle tone can allow otherwise normal tissues (e.g., tongue and epiglottis) to collapse into the airway and cause obstruction. The first measure in relieving such obstructions involves manipulation of the head and jaw, insertion of an artificial nasal or oral airway device, and evacuation of obstructing objects and substances (e.g., blood, secretions, or food particles). Except for drugs used to facilitate endotracheal intubation (see below), the only drug useful to improve gas flow through a narrowed airway is a mixture of helium and oxygen (heliox), which has a much reduced viscosity resulting in reduced resistance to gas flow.

Aspiration

The upper airway (above the larynx/epiglottis) is a shared porthole to the lungs (gas exchange) and gastrointestinal tract (fluids and nutrition). Passive regurgitation or active vomiting resulting in accumulation of gastric contents in the pharynx places the patient at risk of pulmonary aspiration, especially under circumstances in which airway reflexes (e.g., glottic closure and coughing) and voluntary avoidance maneuvers are suppressed (e.g., anesthesia or coma). Particulate matter can obstruct the tracheobronchial tree, and acidic fluid ($pH < 2.5$) can injure the lung parenchyma. The resulting pneumonitis can cause significant morbidity (e.g., acute respiratory distress syndrome) and has a high mortality rate. Preoperative restriction of fluids and food (NPO status) does not guarantee the absence of aspiration risks. Similarly, the advance placement of a naso- or orogastric tube may serve to reduce intragastric pressure but does not guarantee complete removal of gastric contents. Nevertheless, both NPO orders and the insertion of a naso- or orogastric tube under some circumstances are worthwhile measures to reduce the risks of pulmonary aspiration. In some circumstances, the deliberate induction of vomiting in a conscious patient may be indicated, but this is done rarely and almost never involves the use of an emetic drug. In fact, more often antiemetic drugs are employed to reduce the risks of vomiting during airway manipulation and induction of anesthesia.

Drug therapy to reduce the risks of pulmonary aspiration is focused on decreasing the quantity and acidity of gastric contents and on facilitating endotracheal intubation (see below). Nonparticulate antacids [e.g., sodium citrate (Bicitra)] are used to neutralize the acidity of gastric fluids. Drugs to reduce gastric acid production include H_2-receptor blockers [e.g., cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid)] and inhibitors of gastric parietal cell hydrogen-potassium ATPase [proton pump inhibitors, e.g., omeprazole (Prilosec), lansoprazole (Prevacid), and esomeprazole (Nexium)]. Metoclopramide (Reglan) enhances gastric emptying and increases gastroesophageal sphincter tone. Cisapride (Propulsid) also increases gastrointestinal motility via the release of acetylcholine at the myenteric plexus.

Antiemetic drugs are used more commonly in the postoperative period and include several different drug classes: anticholinergics [e.g., scopolamine (Transderm Scop)],

Table 4–12.

Commonly Used Herbal Remedies

Name	Common uses	Side effects/drug interactions
Cayenne (paprika)	Muscle spasm, GI disorders	Skin ulcers/blistering
		Hypothermia
Echinacea	Common cold antitussive urinary tract infections	May cause hepatotoxicity May decrease effects of steroids and cyclosporine
Ephedra (ma-huang)	Antitussive, bacteriostatic	Enhanced sympathomimetic effects with guanethedine or monoamine oxidase inhibitor (MAOI)
		Arrhythmias with halothane or digoxin
		Hypertension with oxytocin
Feverfew	Migraine, antipyretic	Platelet inhibition, rebound headache, aphthous ulcers, GI irritation
Garlic	Lipid lowering, antihypertensive antithrombotic	May potentiate warfarin
Ginger	Antinausseant antispasmodic	May potentiate aspirin and warfarin
Gingko	Improve circulation	May potentiate aspirin and warfarin
Ginseng	Adaptogenic enhace energy level, antioxidant	Ginseng abuse synddrome: sleepiness, hypertonia, edema May cause mania in patients on phynelzine
		May decrease effects of warfarin
		Postmenopausal bleeding
		Mastalgia
Glodenseal	Diuretic, anti-inflammatory, laxative hemostatic	Overdose may cause paralysis; aquaretic (no sodium excretion); may worsen edema/hypertension
Kava-kava	Anxiolytic	Potentiates barbiturates and benzodiazepines
		Potentiates ethanol
		May increase suicide risk in depression
Licorice	Antitussive gastric ulcers	High blood pressure, hypokalemia, and edema
Saw palmetto	Benign prostatic hypertrophy, antiandrogenic	Additive effects with other hormone therapy (e.g., HRT)
St. John's wort	Antidepressant, anxiolytic	Possible interaction with MAOIs
		Deecreases metabolism of fentanyl and ondansetron
Valerian	Mild sedative, anxiolytic	Potentiates barbiturates and benzodiazepines

antihistamines [e.g., hydroxyzine (Vistaril) and, promethazine (Pherergan)], and antidopaminergics [e.g., droperidol (Inapsine) and prochlorperazine (Compazine)]. Antidopaminergic agents may cause extrapyramidal side effects in elderly patients. More costly but effective alternatives include the use of antiserotoninergics [e.g., ondansetron (Zofran) and dolasetron (Anzmet)].

Of course, the most widely used measure to minimize the risks of pulmonary aspiration in the anesthetized or comatose patient is endotracheal intubation.

Endotracheal Intubation

Drugs are employed for three purposes in facilitating endotracheal intubation: (1) to improve visualization of the larynx during laryngoscopy, (2) to prevent closure of the larynx, and (3) to facilitate manipulation of the head and jaw.

For bronchoscopy, laryngoscopy, or fiberoptic endotracheal intubation, the reflex responses to airway manipulation can be suppressed by several different methods alone or in combination. Topical anesthesia (2% or 4% lidocaine spray) can be used to anesthetize the mucosal surfaces of the nose, oral cavity, pharynx, and epiglottis. Atomized local anesthetic can be inhaled to anesthetize the mucosa below the vocal cords. The subglottic mucosa also can be anesthetized topically by injecting local anesthetic into the tracheal lumen through the cricothyroid membrane. A bilateral superior laryngeal nerve block eliminates sensory input from mechanical contact or irritation of the larynx above the vocal cords. It must be remembered that anesthesia of the mucosal surfaces to obtund airway reflexes compromises the reflex protective mechanisms of the airway and increases the patient's vulnerability to aspiration of substances from the pharynx. Improvement of visualization of the larynx includes decreasing salivation and tracheal bronchial secretions by administration of an anticholinergic drug (e.g., glycopyrrolate), reducing mucosal swelling by topical administration of a vasoconstrictor (e.g., phenylephrine), and minimizing bleeding owing to mucosal erosion by instrumentation, which also is minimized by topical vasoconstrictors. The use of steroids in minimizing acute inflammatory responses in the airway may have some delayed benefit, but steroids usually are not indicated just before intubation.

Systemic drugs, usually administered intravenously, can be used to obtund the cough reflex. Intravenous lidocaine (1 to 2 mg/kg) transiently obtunds the cough reflex without affecting spontaneous ventilation to any significant degree. The risks of central nervous system (CNS) stimulation and seizure-like activity have to be kept in mind and can be reduced by the prior administration of an intravenous barbiturate or benzodiazepine in small doses. Intravenous opioids are effective in suppressing cough reflexes, but the doses required impair spontaneous ventilation to the point of apnea. A combination of an intravenous opioid and a major tranquilizer (e.g., neuroleptanalgesia) allows the patient to tolerate an endotracheal tube with much smaller doses of the opioid and less embarrassment of spontaneous ventilation. Small doses of opioids are also useful in obtunding airway reflexes during general anesthesia provided either by intravenous (e.g., thiopental) or inhaled anesthetics (e.g., isoflurane). Not only do the opioids obtund the cough reflex that results in closure of the larynx, but they also are useful in limiting the autonomic sympathetic response to endotracheal intubation that typically leads to hypertension and tachycardia.

Skeletal muscle relaxants are used most commonly in conjunction with a general anesthetic to allow manipulation of the head and jaw and to prevent reflex closure of the larynx. Of course, they also render the patient apneic, and two procedures are used commonly to maintain oxygenation of the patient's blood. First, the patient breathes 100% oxygen by mask while still awake to eliminate nitrogen from the lungs, and then a rapid-sequence administration of an intravenous anesthetic (e.g., thiopental) is followed immediately by a rapid-acting neuromuscular blocker [e.g., succinylcholine or rocuronium (Zemuron)], and cricoid pressure is applied (Sellick maneuver). As soon as the muscle relaxation is apparent (30 to 90 seconds), laryngoscopy is performed, an endotracheal tube is inserted, the tracheal tube cuff is inflated, and the position of the tube in the trachea is verified. Second, when there is minimal risk of pulmonary aspiration (e.g., presumed empty stomach), the patient is anesthetized and paralyzed while ventilation is supported by intermittent positive pressure delivered via a face mask. At the appropriate time, laryngoscopy is performed, and the endotracheal tube is inserted.

Normalizing Pulmonary Function during Positive-Pressure Ventilation

Once an endotracheal tube is in place, it is common practice in the operating room to maintain general anesthesia and partial muscular paralysis in order to facilitate positive-pressure ventilation and continued toleration of the endotracheal tube by the patient. Postoperatively, in the PACU and ICU, general anesthesia and partial muscular paralysis may be continued if prolonged positive-pressure ventilation is anticipated, or sedatives may be administered by intravenous infusion to allow toleration of the endotracheal tube in anticipation of recovery of spontaneous ventilation and tracheal extubation.

Three other problems are encountered in the patient whose ventilation is supported mechanically by an endotracheal tube: (1) poor ventilatory compliance, (2) bronchoconstriction, and (3) impaired gas exchange. Poor ventilatory compliance can reflect limited compliance of the chest wall and diaphragm, limited compliance of the lungs per se, or both. Deepening general anesthesia and administration of a skeletal muscle relaxant can be used to reduce intercostal and diaphragmatic muscle tone, but they obviously cannot improve the chest cavity compliance that is fixed by disease (e.g., scoliosis or emphysema).

Poor lung compliance may reflect pulmonary interstitial edema, consolidation, bronchial obstruction (e.g., mucus plugs), bronchoconstriction, or compression of the lung by

intrathoracic substances (e.g., pneumothorax, hemothorax, or tumor mass). Treatment of these involves drug therapy of heart failure and infection and procedures such as bronchoscopy, thoracentesis, etc.

Bronchoconstriction may exist chronically (e.g., asthma or reactive airways disease), and these conditions can be exacerbated by the collection of tracheobronchial secretions in the presence of an endotracheal tube, which reduces the effectiveness of coughing in clearing the airway. Occasionally bronchoconstriction can be induced by mechanical stimulation of the airway by an endotracheal tube or other object in an otherwise normal patient. Drug treatment is focused on reducing bronchial smooth muscle tone (e.g., $beta_2$ sympathomimetic or anticholinergic agents), minimizing tracheal bronchial secretions, and decreasing sensory input from the tracheal bronchial tree (e.g., topical anesthetic, deeper general anesthesia, intravenous lidocaine, or an opioid). Acute treatment of bronchoconstriction may involve any combination of the following: (1) an aerosolized $beta_2$ sympathomimetic and/or anticholinergic agent and (2) systemic intravenous administration of a $beta_2$ sympathomimetic agent, a phosphodiestrerase inhibitor [e.g., theophylline salts (aminophylline)], and/or an anticholinergic agent.

Intravenous steroids are indicated in severe bronchoconstriction, especially in asthmatic patients, for whom they have been effective in the past. With the administration of 100% oxygen, blood oxygenation usually is not the main problem in patients with bronchoconstriction; it is the progressive development of hypercarbia and the trapping of air in lung parenchyma that reduce ventilatory compliance and increase intrathoracic pressure. These, in turn, reduce venous return and may cause a tamponade-like impairment of cardiac function.

Impaired alveolar-capillary membrane gas exchange can result from alveolar pulmonary edema (treated by diuretics, inotropes, and vasodilators), decreased pulmonary perfusion (treated by inotropes and vasodilators), and lung consolidation (antibiotic therapy for infection).

Restoration of Spontaneous Ventilation and Airway Protective Mechanisms

The anesthesiologist attempts to tailor the anesthetic plan according to postoperative expectations for the patient. In the relatively healthy patient for whom tracheal extubation can be anticipated in the operating room, the goal is to have the patient breathing spontaneously with airway reflexes intact and the patient arousable to command immediately on completion of the operation. The challenge for the anesthesiologist is to maintain satisfactory general anesthesia through the entire course of the operation and yet have the patient sufficiently recovered from anesthetic drugs, including hypnotics and opioids, shortly after conclusion of the operation. If this is not possible, then the patient is transferred to the PACU to allow additional time for elimination of drugs that depress spontaneous ventilation and cough reflexes. Another possibility is to administer antagonists to opioids (e.g., naloxone) and benzodiazepines (e.g., flumazenil), but this approach risks sudden awakening, pain, and uncontrolled autonomic sympathetic activity leading to undesirable hemodynamic changes. And there is the risk of recurrent ventilatory depression because it is difficult to match the doses of the antagonists to the residual amounts of anesthetic drugs. On the other hand, it is fairly routine for the effects of neuromuscular blockers to be antagonized by administration of an anticholinesterase (e.g., neostigmine) in combination with an anticholinergic agent (e.g., atropine) to limit the autonomic cholinergic side effects of the anticholinesterase.

When the expectation is for maintenance of mechanical ventilation for some time in the postoperative period, then the patient's tolerance of the endotracheal tube is facilitated by the persistent effect of residual anesthetic drugs subsequently supplemented by administration of intravenous hypnotics (e.g., propofol) and opioids (e.g., fentanyl or morphine). These agents can be associated with side effects, including respiratory depression, especially when they are used concurrently. Dexmedetomidine (Precedex), an $alpha_2$-adrenergic agonist, may offer advantages for sedation during weaning from mechanical ventilation because it provides sedation, pain relief, anxiety reduction, stable respiratory rates, and predictable cardiovascular responses.[201–203] Dexmedetomidine facilitates patient comfort, compliance, and comprehension by offering sedation with the ability to rouse patients. This "rousability" allows patients to remain sedated yet communicate with health care workers.

When the appropriate time comes to have the patient take over his or her own ventilation completely, these sedative and analgesic drugs are weaned to a level allowing satisfactory maintenance of blood oxygenation and carbon dioxide removal, easy arousal of the patient, and at least partial restoration of airway reflex mechanisms.

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CHAPTER 5

Pathology of Cardiac Surgery

Robert F. Padera, Jr. • Frederick J. Schoen

In the past several decades, the virtual explosion in the number and scope of surgical and interventional diagnostic and therapeutic procedures performed on patients with cardiovascular diseases has launched cardiovascular pathology into the forefront of high-quality patient care.[1] Quality patient care is informed by the results of pathologic examinations and clinicopathologic studies of patients, procedures, and devices that facilitate informed choices among surgical or catheter-based interventional options and optimize short- and long-term patient management, including recognition of complications. Importantly, beyond implicit clinical benefit, studies of cardiac pathology and pathobiology serve as the cornerstones of modern cardiovascular research and the development of innovative medical devices and other therapeutic options.

This chapter summarizes pathologic considerations most relevant to surgery in the major forms of acquired cardiovascular disease, emphasizing pathologic anatomy, clinicopathologic correlations, and pathophysiologic mechanisms. In view of space limitations, several areas (e.g., aortic disease) are necessarily omitted from discussion and others (e.g., cardiac assist devices) are attenuated, as they are discussed in greater detail elsewhere in the text. Moreover, although we have not included the key pathologic considerations herein, we are mindful that the number of adults with congenital heart disease is increasing rapidly and that they have unique and important clinical and pathologic concerns.[2–4]

GENERAL CONSIDERATIONS

Myocardial Hypertrophy

Hypertrophy is the compensatory response of the cardiac muscle, the myocardium, to increased work (Fig. 5-1).[5] Myocardial hyperfunction induces an increase in the overall mass and size of the heart that reflects increased size of myocytes through addition of contractile elements (sarcomeres) and mitochondria. Since cardiac myocytes are terminally differentiated cells that cannot divide, functionally beneficial augmentation of myocyte number (hyperplasia) in response to stress or injury occurs either little or not at all in the adult heart. Since the vasculature does not proliferate commensurate with increased cardiac mass, hypertrophied myocardium is usually relatively deficient in blood vessels and thereby particularly vulnerable to ischemic damage. Moreover, myocardial fibrous tissue is often increased.

The pattern of hypertrophy reflects the nature of the stimulus. Pressure-overloaded ventricles (e.g., resulting from systemic hypertension or aortic stenosis) develop concentric hypertrophy with an increased ventricular mass, wall thickness, and ratio of wall thickness to cavity radius, without appreciable dilation. In contrast, volume-overloaded ventricles (e.g., resulting from chronic aortic or mitral regurgitation) develop hypertrophy with chamber dilation in which both ventricular radius and wall mass are increased. Pressure-overload hypertrophy is accomplished predominantly by augmentation of cell width via parallel addition of sarcomeres; in contrast, volume overload and/or dilation stimulate augmentation of both cell width and length via both parallel and series addition of sarcomeres. In situations such as myocardial infarction (MI), where there is local myocyte necrosis, the noninfarcted regions of myocardium not only hypertrophy (termed *compensatory hypertrophy*) but also may be overwhelmed by mechanical disadvantage and degenerative changes. The constellation of changes that occur in both infarcted and noninfarcted myocardium is called *ventricular remodeling*.[6] In contrast to the regional changes resulting from MI, the chamber wall is affected globally by the increased chamber pressure of hypertension, the increased pressure or volume workload of valvular heart disease, and in dilated cardiomyopathy.

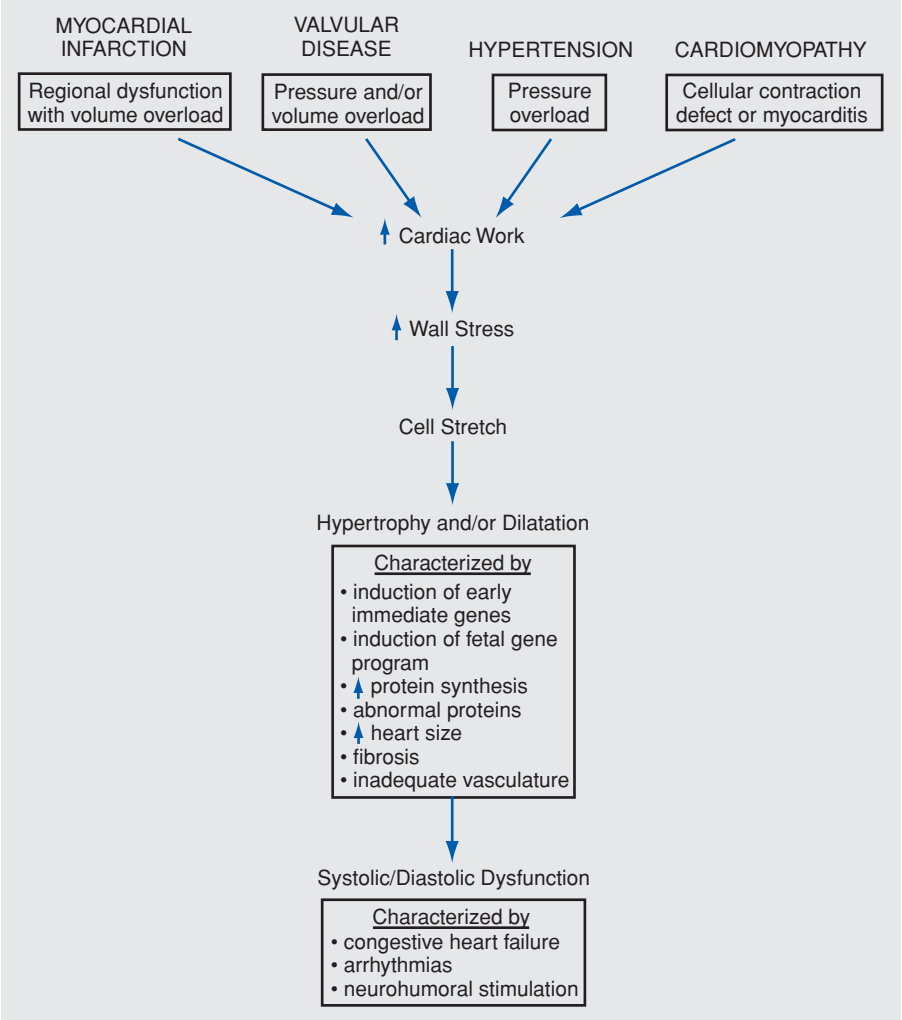


Figure 5-1. Summary of the macroscopic, cellular, and extracellular changes in cardiac hypertrophy and heart failure. (*Modified with permission from Schoen.*[5])

Molecular changes that initially mediate enhanced function in hypertrophied hearts may subsequently contribute to the development of heart failure.[7] Hemodynamic overload alters myocardial gene expression, leading to re-expression of a pattern of protein synthesis similar to that of proliferating cells in general and of fetal cardiac myocytes during development. Proteins comprising contractile elements and those involved in excitation-contraction coupling and energy utilization are altered quantitatively or through production of different isoforms; the variant proteins may be less functional than the normal proteins. Hypertrophied and/or failing myocardium may have additional abnormalities that include reduced adrenergic responsiveness, decreased calcium availability, impaired mitochondrial function, and microcirculatory spasm. Apoptosis of cardiac myocytes, potentially triggered by the same mechanical forces, neurohormonal activation, hypoxia, or cytokines that prompted the adaptive changes, also plays a role in the development of heart failure, and may provide a therapeutic strategy for heart failure treatment.[8]

The changes in the heart described above initially enhance function and are thereby adaptive, but they may ultimately become deleterious and contribute to cardiac failure. Thus, cardiac hypertrophy comprises a tenuous balance between adaptive characteristics and potentially deleterious structural, functional, and biochemical/molecular alterations including enlarged muscle mass with alterations in the cardiac configuration, enhanced metabolic requirements, synthesis of abnormal proteins, decreased capillary:myocyte ratio, fibrosis, microvascular spasm, and impaired contractile mechanisms. Hypertrophy (with or without chamber dilation) also decreases myocardial compliance and may thereby hinder diastolic filling. In addition, left ventricular hypertrophy (LVH) is an independent risk factor for cardiac mortality and morbidity, especially for sudden death.[9,10]

Left ventricular hypertrophy regresses in many cases following removal of the stimulus, but it is uncertain to what extent hypertrophy is capable of resolution in individual patients. Moreover, progressive cardiac failure may ensue following and despite hemodynamic adjustment by valve replacement or repair (Fig. 5-2). In addition, in cardiac surgery with its attendant global ischemia, markedly increased cardiac muscle mass may compromise intraoperative myocardial preservation and render the heart particularly susceptible to ischemic damage.

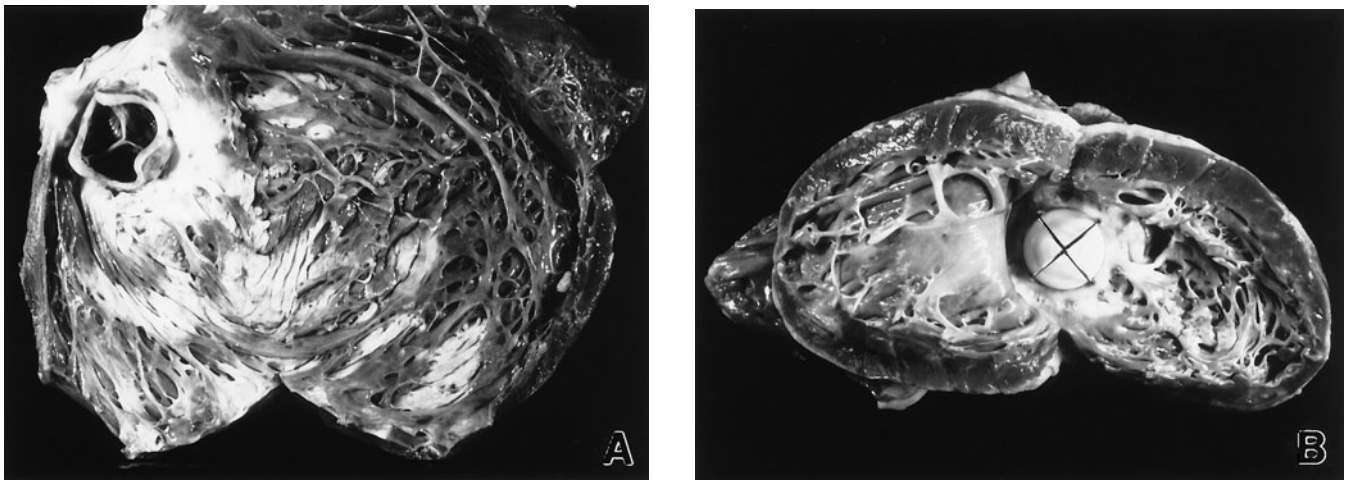


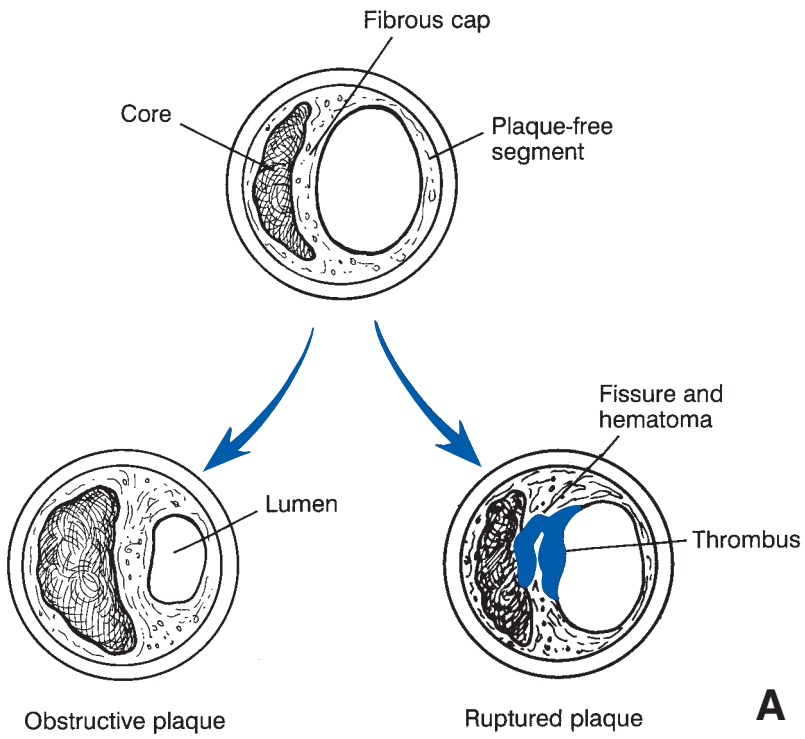
Figure 5-2. Late postoperative cardiac failure necessitating heart transplantation. (A) Four years following mitral valve replacement with a porcine bioprosthesis for congenital deformity causing mitral regurgitation. (B) Twenty-eight years following mitral valve replacement with a caged-disk valve for rheumatic mitral stenosis. In both cases the myocardial degradation secondary to the underlying disease progressed despite an intact valve prosthesis.

Atherosclerosis

Atherosclerosis is a chronic, progressive, multifocal disease of the vessel wall intima whose characteristic lesion is the atheroma or plaque that forms through the key processes of intimal thickening (mediated predominantly by smooth muscle cell proliferation) and lipid accumulation (mediated primarily by monocyte phagocytosis).[11,12] Atherosclerosis primarily affects the large elastic arteries and large and medium-sized muscular arteries of the systemic circulation, particularly at points of branches, sharp curvatures, and bifurcations. Atherosclerosis of native coronary arteries involves the large epicardial vessels, especially the proximal portions of the left anterior descending and circumflex arteries, and the right coronary artery diffusely, and generally not their intramural branches. In contrast, the arteriosclerosis that affects the coronary arteries of transplanted hearts is a diffuse process that affects distal, intramural vessels as well as the larger epicardial vessels (see later in this chapter). Although normal veins are usually spared from atherosclerosis, venous bypass grafts interposed within branches of the arterial system frequently develop rapidly progressive intimal thickening and ultimately atherosclerotic obstructions. Paradoxically, arterial grafts such as the internal mammary artery are largely spared. Most atheromas in the coronary arteries are eccentric, with a plaque-free segment often occupying a substantial fraction of the vessel wall. In early lesions, the plaque bulges outward at the expense of the media with the arterial lumen remaining circular in cross-section at essentially the same original diameter (a process termed *vascular remodeling*).[13]

The prevailing theory of atherogenesis and atherosclerosis centers around interactions between endothelial cells and smooth muscle cells of the arterial wall, monocytes and platelets in the bloodstream, and plasma lipoproteins. Endothelial cell injury from chronic hypercholesterolemia, homocystinemia, chemicals in cigarette smoke, viruses, localized hemodynamic forces, systemic hypertension, hyperglycemia, or the local effects of cytokines causes phenotypic and hence functional changes in endothelial cells, called *endothelial dysfunction*, which can also contribute to atherosclerosis. Endothelial dysfunction is manifested by: (1) vasoconstriction due to decreased production of the vasodilator nitric oxide, (2) increased permeability to lipoproteins, (3) expression of tissue factor leading to thrombosis, and (4) expression of certain injury-induced adhesion molecules leading to adherence of platelets and inflammatory cells.[14] Progression through an early, subendothelial lesion (often called a fatty streak) to a mature, complex atheromatous plaque involves the following events: (1) monocyte adherence to endothelial cells, migration into the subendothelial space, and transformation into tissue macrophages; (2) smooth muscle cell migration from the media into the intima, and proliferation and secretion of collagen and other extracellular matrix constituents; (3) lipid accumulation, both intracellularly (foam cells) in macrophages and smooth muscle cells as well as extracellularly; (4) lipoprotein oxidation in the vessel wall leading to generation of potent biologic stimuli such as chemoattractants and cytotoxins; (5) persistent chronic inflammation, especially at the junction with the uninvolved arterial wall (the "shoulder"); (6) cell death with release of intracellular lipids (mostly cholesterol esters); and often (7) calcification.

Mature atherosclerotic plaques consist of a central core of lipid and cholesterol crystals and cells such as macrophages, smooth muscle cells, and foam cells along with necrotic debris, proteins, and degenerating blood elements.[15] This core is separated from the lumen by a fibrous cap rich in collagen. The configuration and composition of atheromas



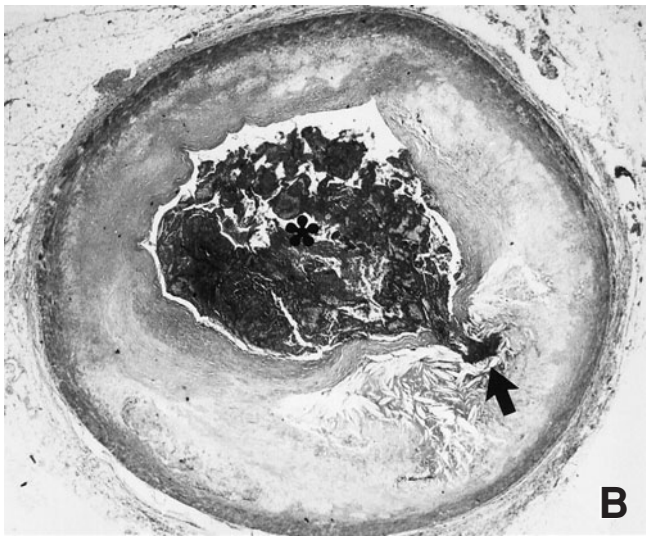


Figure 5-3. Consequences of coronary arterial atherosclerosis. (A) Progression of fibrous atheromatous plaque with a core of extracellular lipid and necrotic debris covered by intact fibrous cap (top) to either severe chronic stenosis (lower left) or acute plaque rupture, fissuring, or erosion, resulting in a complicated lesion with a surface defect, hematoma, or mural thrombus (lower right). (B) Coronary thrombosis, superimposed on atherosclerotic plaque, triggering fatal myocardial infarction. A fissure breaching the fibrous cap and extending into the plaque necrotic core (arrow) presumably initiated the occlusive thrombus (asterisk). Hematoxylin and eosin 15x. (*B: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

can vary considerably among individuals, among arteries in the same individual, or among regions of one artery, especially with regard to the proportion of lipid to connective tissue. The natural history of atheromatous plaque and the efficacy and safety of interventional therapies depend on relative plaque composition, the spatial distribution of the constituents, the integrity of the fibrous cap, and the local mechanical environment.[16–18] These features of plaque structure can be evaluated using intravascular ultrasound and potentially novel imaging methods, including noninvasive molecular imaging.[19,20]

The clinical manifestations of advanced atherosclerosis in the coronary arteries are generally due to their encroachment of the lumen, leading to progressive stenosis, or to acute plaque disruption with thrombosis (see later discussion in section on ischemic heart disease) (Fig. 5-3). However, slowly developing occlusions over time may stimulate the formation of collateral vessels that protect against distal myocardial ischemia and infarction despite high-grade stenosis. Aneurysms may form secondary to atherosclerosis as a result of atrophy or necrosis of the media, a process more common in the aorta than in the coronary circulation.[21]

The natural history, morphologic features, key pathogenetic events, and clinical complications of atherosclerosis are summarized in Fig. 5-4.

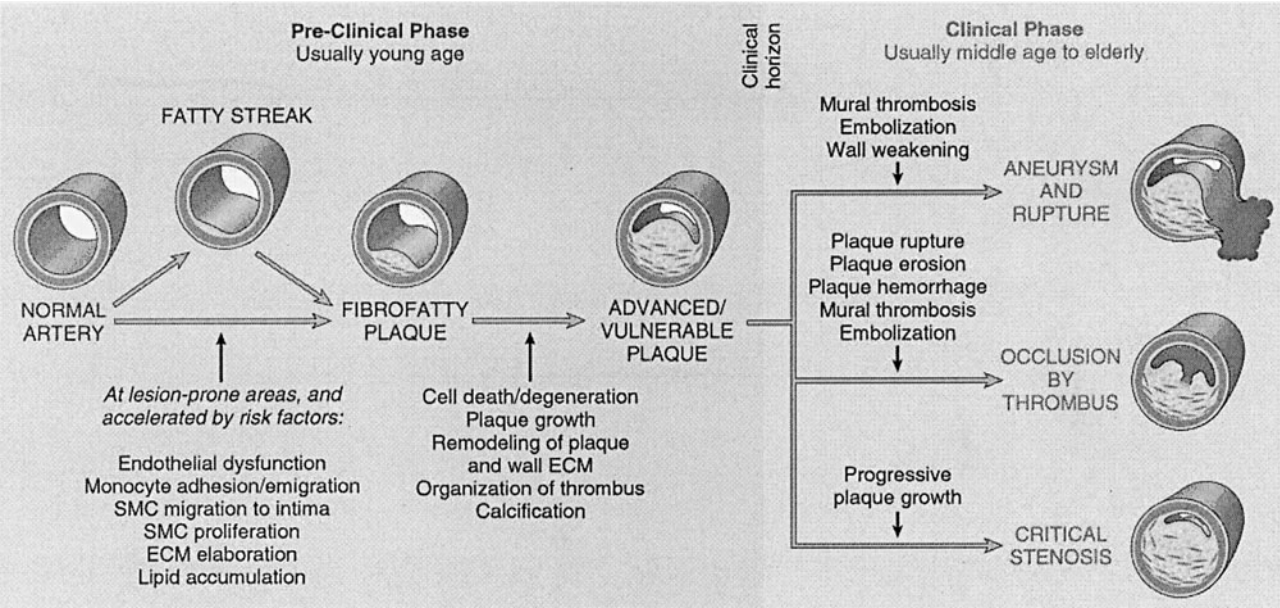


Figure 5-4. Summary of the pathology, pathogenesis, complications, and natural history of atherosclerosis. Plaques usually develop slowly and insidiously over many years, beginning in childhood or shortly thereafter and exerting their clinical effects in middle age or later. As described in the text, they may progress from a fatty streak to a fibrous plaque, and then to plaque complications that lead to disease. The schematic diagram interrelates the morphology, pathogenesis, and complications of atherosclerosis and provides a unified approach to this serious disease process. SMC = smooth muscle cell; ECM = extracellular matrix. (*Modified with permission from Schoen FJ: Blood vessels, in Kumar V, Fausto N, Abbas A [eds]: Robbins & Cotran Pathologic Basis of Disease, 7th ed. Philadelphia, WB Saunders, 2004; p 511.*)

Ischemic Myocardial Injury

Cardiac *ischemia* occurs when perfusion is inadequate to meet the metabolic needs of the tissue.[22] Ischemia is most often caused by inadequate local coronary blood flow resulting from obstruction or narrowing secondary to atherosclerosis, thrombosis, embolism, or spasm. Decreased coronary flow leading to global hypoperfusion also follows systemic hypotension, in shock, and during cardiopulmonary bypass. Ischemia can also result from increased cardiac demand secondary to exercise, tachycardia, hyperthyroidism, or ventricular hypertrophy and/or dilation. The effects of ischemia are potentiated when the oxygen supply is decreased secondary to anemia, hypoxia, or cardiac failure.

Progression of damage

The severity and duration of ischemia determine the consequences. The pre-existing adaptive and nutritional/metabolic state of the affected cells and tissues is also a factor.

Intracellular changes following the onset of myocardial ischemia are sequential and complex (Table 5-1). Ischemia induces anaerobic glycolysis in cardiac myocytes within seconds, leading to inadequate production of high-energy phosphates such as adenosine triphosphate and the accumulation of metabolites such as lactic acid, leading to intracellular acidosis. Myocardial function is exquisitely sensitive to these biochemical consequences of severe ischemia; indeed, following the onset of ischemia, a contractility defect is evident within seconds, leading to total loss of contraction within 2 minutes. Ischemic changes in an individual cell are initially sublethal and potentially reversible if the duration of ischemic injury is short and perfusion is restored prior to the onset of irreversible changes (15 to 20 minutes). Irreversible (lethal) injury of cardiac myocytes marked by cell membrane structural defects occurs only after 20 to 40 minutes within the most severely ischemic area. When ischemic injury is of sufficient severity and duration in groups of involved cells, the affected cells die, and *myocardial infarction* results.

Within the region of myocardium made vulnerable by loss of perfusion, termed the *area at risk*, not all cells are equally injured. In particular, a gradient of ischemia exists across the myocardium. The most severely affected regions, and therefore the first to become necrotic, are the subendocardium and papillary muscles in the center of the perfusion defect. However, the myocytes immediately beneath the endocardium to a depth of approximately several hundred microns may be effectively perfused by the well-oxygenated blood in the left ventricular chamber and therefore protected from ischemic damage. As uninterrupted ischemia progresses, there is a *wavefront* of cell death outward from the mid-subendocardial region toward and eventually encompassing the lateral borders and less ischemic subepicardial and peripheral regions. The predominant mechanism of cell

Table 5–1.

Approximate Time of Onset and Recognition of Key Features of Ischemic Myocardial Injury

Event/process	Time of onset
Onset of anerobic metabolism	Within seconds
Loss of contractility	<2 min
ATP* reduced to 50% of normal to 10% of normal	 10 min 40 min
Irreversible cell injury	20–40 min
Microvascular injury	>1 h
Pathologic feature	**Time of recognition**
Ultrastructural features of reversible injury	5–10 min
Ultrastructural features of irreversible damage	20–40 min
Wavy fibers Staining defect with tetrazolium dye Classic histologic features of necrosis	1–3 h 2–3 h 6–12 h
Gross alterations	12–24 h

**ATP = adenosine triphosphate.*

death in MI has traditionally been thought of as coagulation necrosis; however, apoptosis may also play a role.[23,24] In human MI, approximately 50% of the area that has impaired perfusion (i.e., the area at risk) becomes necrotic in approximately 3 to 4 hours. The final transmural extent of an infarct is generally established within 6 to 12 hours. Restoration of flow to a severely ischemic area via therapeutic intervention can alter the outcome depending on the interval between the onset of ischemia and reperfusion.

Within a few minutes of the onset of ischemia, reversible ultrastructural changes can be observed using transmission electron microscopy, including glycogen depletion, cellular and mitochondrial swelling, myofibrillar relaxation, and margination of nuclear chromatin. This is followed by the development of amorphous mitochondrial densities and sarcolemmal disruption as evidence of necrosis. However, neither reversible ischemia nor necrosis existing less than 6 or more hours before patient death can be detected by gross or microscopic analysis. On gross examination at autopsy of a patient who died at least 2 to 3 hours following the onset of infarction, the presence of a necrotic region may often be indicated as a staining defect with triphenyl tetrazolium chloride, a dye that turns viable myocardium a brick-red color on reaction with intact myocardial dehydrogenases.[25] The earliest light microscopic features include clusters of necrotic myocytes that exhibit intense eosinophilia, nuclear pyknosis and loss, and stretched and wavy myocytes. Short-term ischemia short of necrosis cannot be reliably demonstrated by gross or microscopic examination.

The subsequent morphologic changes in the infarcted region follow a largely stereotyped sequence. Inflammatory exudation with polymorphonuclear leukocytes can usually be seen after 6 to 12 hours and peaks within 1 to 3 days. The inflammatory reaction continues with removal of necrotic tissue by macrophages (3 to 5 days) and is followed by a fibroblastic reparative response accompanied by neovascularization (granulation tissue) beginning after approximately 7 to 10 days at the margins of preserved tissue. The infarcted tissue is replaced by scar that reaches maturity by about 6 to 8 weeks. Therefore, neither gross nor microscopic examination can distinguish a scar that is 8 weeks old from one that formed many years before.

The repair sequence following an infarct is similar to that which follows tissue injury of diverse causes and at various noncardiac anatomic sites. However, healing of MI may be altered by reperfusion (see below), mechanical stress, gender, and neurohumoral and other factors.[26] For example, healing of myocardial ischemic injury may be slowed by anti-inflammatory agents administered following MI,[27] or as a component of immunosuppressive therapy following transplantation.[28] Sublethal but chronic ischemic injury is often manifest as myocyte vacuolization, usually most prevalent in the subendocardium.[29]

Although cardiac myocytes are traditionally thought incapable of regeneration, a growing body of evidence suggests that regeneration of cardiac myocytes can occur under certain circumstances at the viable borders of myocardial infarcts.[30,31] Whether this capacity for renewal can be harnessed to therapeutic advantage is not yet known, and is a rapidly evolving and controversial area (discussed later in this chapter).

Effects of reperfusion

The progression of myocardial ischemic injury can be modified by restoration of blood flow (reperfusion) to jeopardized myocardium, since ischemic injury to myocytes is progressive and initially reversible.[32] Reperfusion occurring before the onset of irreversibility (about 20 minutes in the most severely ischemic regions) can prevent cell death, which may substantially limit infarct size or prevent infarction altogether.[33] Later reperfusion after up to 6 to 12 hours does not prevent infarction entirely, but may salvage myocytes located at the leading edge of the "wavefront" that are only reversibly injured.[34] The potential for recovery decreases with increasing severity and duration of ischemia (Fig. 5-5). Whether late

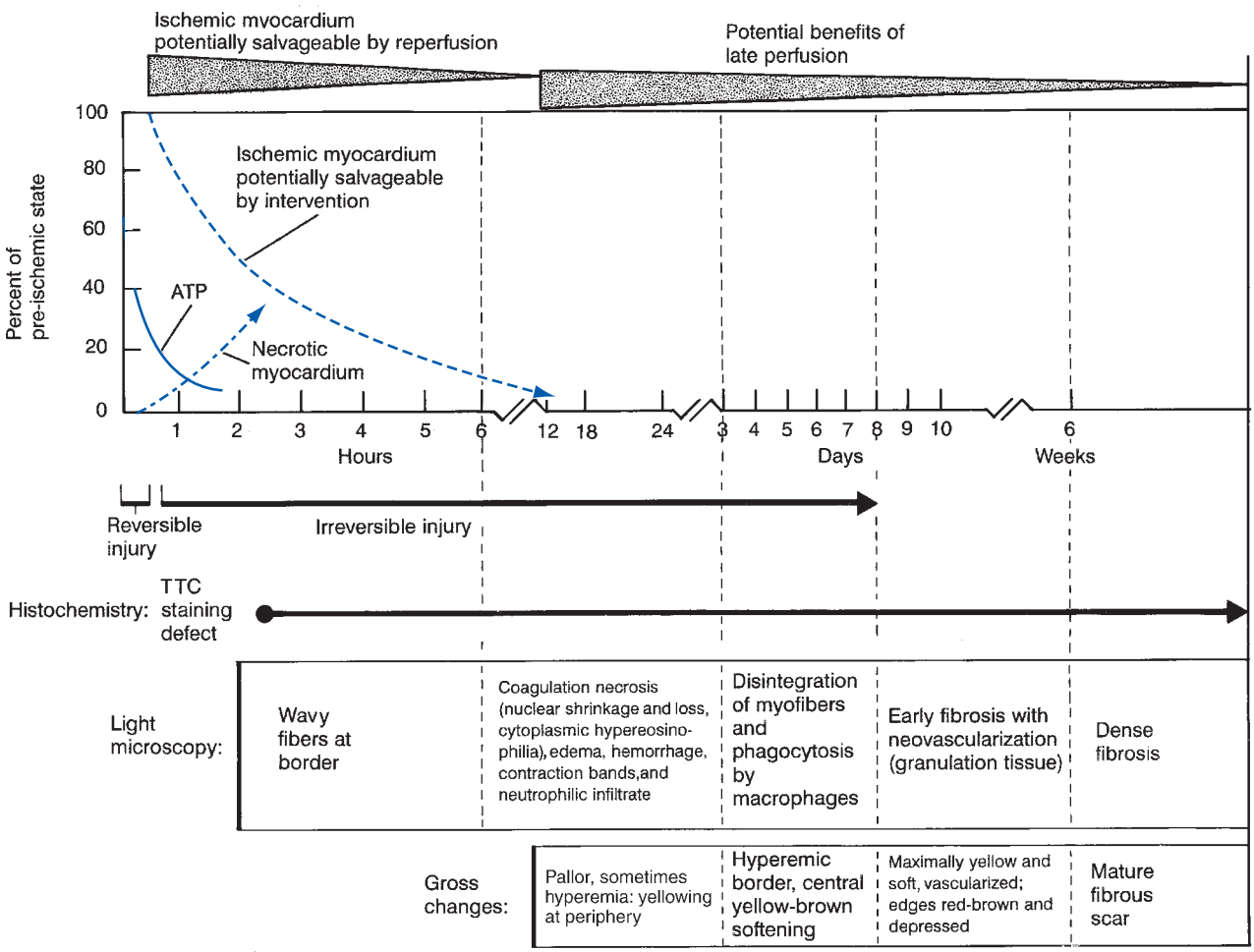


Figure 5-5. Temporal sequence of early biochemical, ultrastructural, histochemical, and histologic findings after onset of severe myocardial ischemia. The time frames for early and late reperfusion of the myocardium supplied by an occluded coronary artery are schematically shown at the top of the figure. For approximately one-half hour following the onset of even the most severe ischemia, myocardial injury is potentially reversible. Thereafter, progressive loss of viability occurs to completion by 6 to 12 hours. The benefits of reperfusion are greatest when it is achieved early, with progressively smaller benefit occurring as reperfusion is delayed. ATP = adenosine triphosphate; TTC = triphenyl tetrazolium chloride. (*Reproduced with permission from Antman and Braunwald*[104] *and Schoen.*[5])

reperfusion beyond the interval at which myocyte salvage continues to be possible may also lead to improved clinical outcomes is not yet resolved.[35]

The gross and microscopic findings of reperfusion of ischemic myocardium are summarized in Fig. 5-6. The microscopic pattern of reperfusion includes hemorrhage and necrotic myocytes with contraction bands, which are transverse eosinophilic lines across the cell that represent clusters of hypercontracted sarcomeres. Contraction bands are a distinct manifestation of irreversible myocyte injury caused by ischemic cell membrane damage followed by a massive influx of calcium from the restored blood flow. This leads to intense sarcomeric contraction.[36] In some cases of reperfusion after severe global ischemia, the left ventricle may undergo a massive tetanic contraction to a small, hard mass; this is termed the stone heart syndrome.[37]

Restoration of systemic pressure to an artery supplying a healthy microvasculature will often restore adequate blood flow. However, microvascular damage often follows severe, prolonged myocardial ischemia and ischemic necrosis, and the effects of ischemic vascular injury followed by reperfusion may include: (1) hemorrhage, visible grossly and microscopically, due to vascular wall incompetence; or (2) microvascular occlusion due to endothelial or interstitial edema, hypercontracted ischemic myocytes, and/or plugging by platelet or neutrophil aggregates, which can cause the *no-reflow phenomenon.* Thus, microvascular occlusions may inhibit the reperfusion of damaged regions.[38]

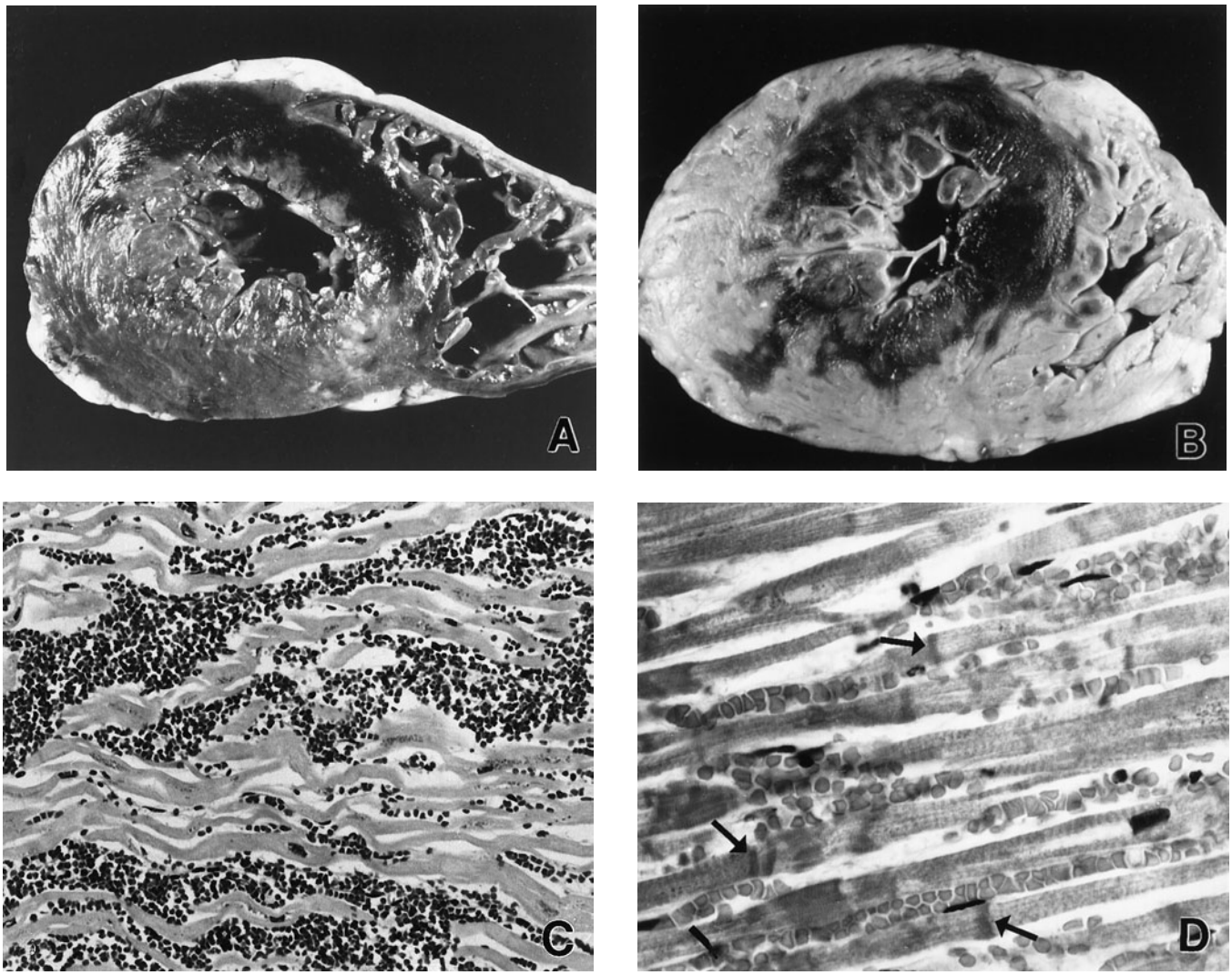


Figure 5-6. Morphologic effects of reperfusion following severe myocardial ischemia. (A) Large, densely hemorrhagic anteroseptal acute myocardial infarct from patient treated by streptokinase intracoronary thrombolysis for left anterior descending artery thrombus, approximately 4 hours following onset of chest pain. (B) Subendocardial circumferential hemorrhagic acute myocardial necrosis in a large hypertrophied heart 2 days postcardiac transplantation. (C) Photomicrograph of myocardial interstitial hemorrhage from heart shown in (A). Hematoxylin and eosin 375x. (D) Photomicrograph of myocardial necrosis with contraction bands (contraction band necrosis). Contraction bands are noted by arrows. Hematoxylin and eosin 375x. (*A, C, and D: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

Reperfusion may actually damage some of the ischemic but still viable myocytes that have not been irreversibly injured (*reperfusion injury*). However, the amount of salvaged myocardium likely outweighs the extent of this damage. Reperfusion injury is thought to be mediated by toxic oxygen species (such as free radicals) that are overproduced by myocytes, infiltrating polymorphonuclear leukocytes, or complement activation.[39] Arrhythmias also may occur after reperfusion, possibly secondary to myocyte damage by oxygen free radicals and/or increased intracellular calcium.

Although reperfusion may accomplish salvage of myocardial cell viability, metabolic and functional recovery of successfully reperfused myocardium is usually not instantaneous, with contractile dysfunction persisting for hours to days following brief periods of ischemia. Reversible postischemic myocardial dysfunction is termed *myocardial stunning*. Myocardial stunning may occur after percutaneous coronary interventions, cardiopulmonary bypass, or even ischemia related to unstable angina or stress. The use of cardiac assist devices may allow the stunned myocardium to recover in situations of reversible cardiac failure.[40,41]

Viable regions of myocardium with chronically impaired function in the setting of chronically reduced coronary blood flow are termed *hibernating myocardium*.[42,43] Myocardial hibernation is characterized by: (1) persistent wall motion abnormality; (2) low myocardial blood flow; and (3) evidence of viability of at least some of the affected areas. Contractile function of hibernating myocardium can improve if blood flow returns toward normal or if oxygen demand is reduced. Correction of this abnormality is likely responsible for the reversal of long-standing defects in ventricular wall motion that may be observed following coronary bypass graft (CBG) surgery or percutaneous coronary intervention (PCI). Assessment of viable but poorly perfused myocardium may identify those patients who would benefit from restoration of adequate coronary blood flow.[44]

Adaptation to short-term transient ischemia (i.e., duration insufficient to cause cell death) may induce tolerance against subsequent, more severe ischemic insults in a process termed *ischemic preconditioning*.[45,46] Thus, a short (5-minute) period of cardiac ischemia followed by reperfusion may be capable of protecting the affected myocardium against injury from a more intense period of subsequent ischemia. The mechanism of this protection is uncertain, but stimulation of adenosine receptors when adenosine is released during ischemia, enhanced expression of heat-shock proteins (which makes the heart more resistant to prolonged ischemia), and involvement of protein kinase C and adenosine triphosphate–dependent potassium channels have been suggested.[47] Pharmacologic stimulation of these pathways may potentially induce the benefits of preconditioning without actually subjecting the myocardium to dangerous ischemia.

Biomaterials and Tissue Engineering

Biomaterials are synthetic or modified biologic materials that are used in implanted or extracorporeal medical devices to augment or replace body structures and functions.[48,49] Biomaterials include polymers, metals, ceramics, carbons, processed collagen, and chemically treated animal or human tissues, the latter exemplified by glutaraldehyde-preserved heart valves and pericardium. The first generation of biomedical materials (e.g., metals used for early valve substitutes) was generally designed to be inert; the goal was to reduce the host inflammatory responses to the implanted material. By the mid-1980s, bioactive biomaterials were emerging that could interact with the host in a beneficial manner (e.g., biodegradable polymer sutures and drug delivery systems). With a greater understanding of material-tissue interactions at the cellular and molecular levels, advanced materials are being designed to stimulate specific cellular and tissue responses at the molecular level.[50,51]

Biomaterial-tissue interactions comprise effects of both the implant on the host tissues and the host on the implant, and are important in mediating prosthetic device complications (Fig. 5-7).[52] Major morphologic effects of biomaterials on tissues are illustrated in Fig. 5-8. Complications of cardiovascular medical devices, regardless of anatomic site of implantation, can be grouped into six major categories: (1) thrombosis and thromboembolism; (2) device-associated infection; (3) exuberant or defective healing; (4) degeneration, fracture, or other biomaterials failure; (5) adverse local tissue interaction, such as toxicity or traumatic hemolysis; and (6) adverse effects distant from the intended site of the device, such as biomaterial/device migration or systemic hypersensitivity.

Blood-surface interaction

Thromboembolic complications of cardiovascular devices can cause significant mortality and morbidity. Thrombotic deposits can impede the function of a prosthetic heart valve, vascular graft, or blood pump, or cause distal emboli. As in the cardiovascular system in general, surface thrombogenicity, hypercoagulability, and locally static blood flow (called *Virchow's triad*), present individually or in combination, determine the relative propensity toward thrombus formation and location of thrombotic deposits with specific devices. No known synthetic or modified biologic surface is as thromboresistant as the normal, unperturbed endothelium. Like a blood vessel denuded of endothelium, foreign materials in contact with blood spontaneously and rapidly (within seconds) absorb a film of plasma components, primarily protein, followed by platelet adhesion.[53] If conditions of relatively static flow are present, macroscopic thrombus can ensue. Considerable evidence implicates a primary role for blood platelets in the thrombogenic response to artificial surfaces (see Fig. 5-8A).[54] Nevertheless, the clinical approach to control of thrombosis in cardiovascular devices is generally through systemic anticoagulants, particularly warfarin. This agent inhibits thrombin formation but does not inhibit platelet-mediated thrombosis. Antiplatelet agents, such as aspirin or clopidogrel, may also be helpful. The specific physical and chemical characteristics of materials that regulate the outcomes of blood-surface interaction are clearly important but incompletely understood.

Coagulation proteins, complement products, other proteins, and platelets are activated, damaged, and consumed by blood-material interactions. For example, blood contact with the large areas of synthetic surfaces during the extracorporeal perfusion of cardiopulmonary bypass may have at least four consequences: (1) activation and resultant dysfunction of platelets; (2) progressive denaturation of plasma proteins and lipoproteins; (3) activation of coagulation proteins and the fibrinolytic system, and through interaction with inflammatory pathways, production of various bioactive molecules, including bradykinin, a potent vasodilator; and (4) activation of complement through the alternative pathway, with production of C3a and C5a, inducing polymorphonuclear leukocyte stasis in the pulmonary circulation with the occasional sequelae of acute pulmonary hypertension and inflammatory lung injury.[55]

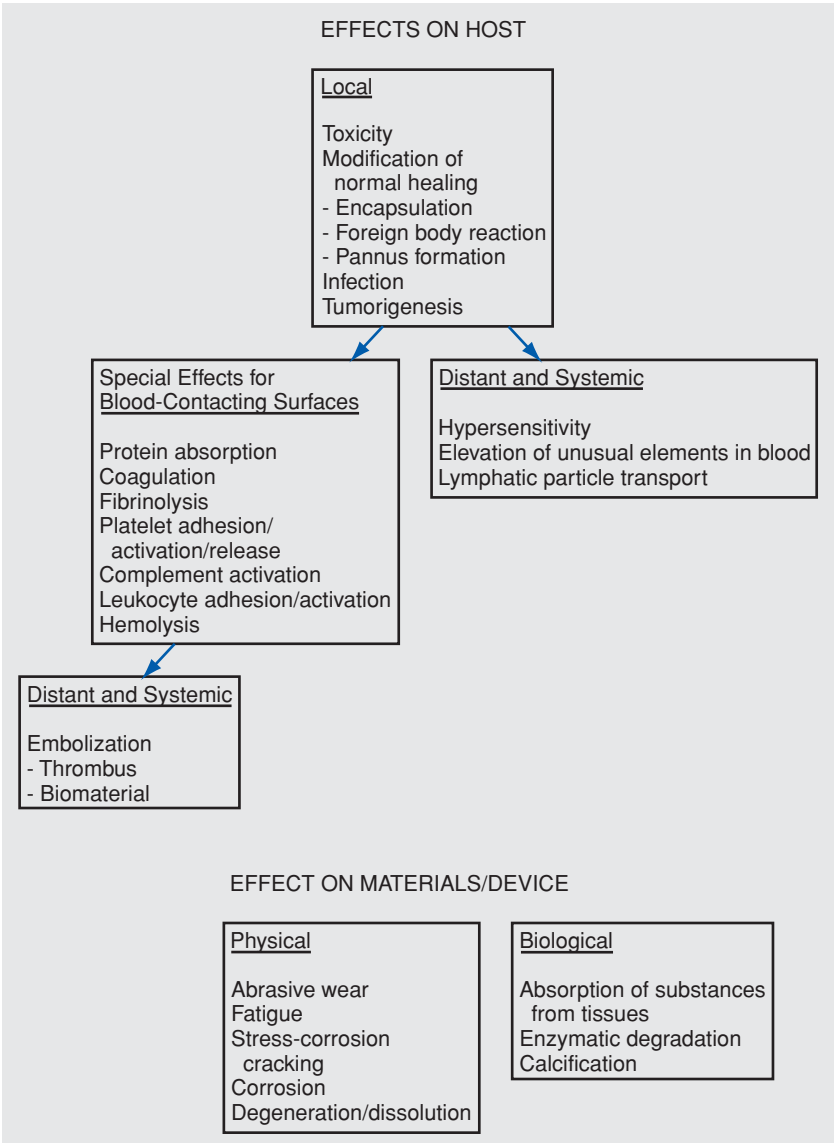


Figure 5-7. Overview of potential interactions of biomaterials with tissue, comprising local, distant, and systemic effects of the biomaterial on the host tissue, as well as the physical and biologic effects of the environment on the materials and the device. These interactions comprise the pathophysiologic basis for device complications and failure modes. (*Modified with permission from Schoen FJ: Introduction to host reactions to biomaterials and their evaluation, in Ratner BD, Hoffman AS, Schoen FJ, Lemons JE, [eds]: Biomaterials Science: An Introduction to Materials in Medicine, 2nd ed. Orlando, Elsevier, Academic Press, 2004; p 293.*)

Hemolysis (damage to red blood cells) in implants and extracorporeal circulatory systems results from both blood-surface interactions and turbulence. Erythrocytes have reduced survival following cardiopulmonary bypass. Also, with earlier model heart valve prostheses, renal tubular hemosiderosis or cholelithiasis occurred in many patients, indicative of chronic hemolysis. With contemporary valves, hemolysis generally is modest and well compensated, but may be accentuated by valve dysfunction.

Tissue-biomaterials interaction

Synthetic biomaterials typically are not immunogenic, but they elicit a foreign body reaction, a special form of nonimmune inflammatory response with an infiltrate predominantly composed of macrophages.[56,57] Nevertheless, immunologic reactions have been proposed rarely for synthetic biomaterial-tissue interactions,[58] and they are possible with tissue-derived biomaterials. Indeed, antibodies can be elicited by implantation of some materials in finely pulverized form. Nevertheless, proven clinical cardiovascular device failure owing to immunologic reactivity is rare. For most biomaterials implanted into solid tissue, encapsulation by a relatively thin fibrous tissue capsule (composed of collagen and fibroblasts) resembling a scar ultimately occurs, often with a fine capillary network at its junction with normal tissue (see Fig. 5-8B). An ongoing inflammatory infiltrate consisting of monocytes/macrophages and multinucleated foreign body giant cells in the vicinity of a foreign body generally suggests persistent tissue irritation (see Fig. 5-8C).

Vascular graft healing

The healing of fabric prostheses or components within the cardiovascular system can yield exuberant fibrous tissue at the anastomosis as an overactive physiologic repair response to vascular injury (Fig. 5-9). Synthetic and biologic vascular grafts often fail because of generalized or anastomotic narrowing mediated by connective tissue

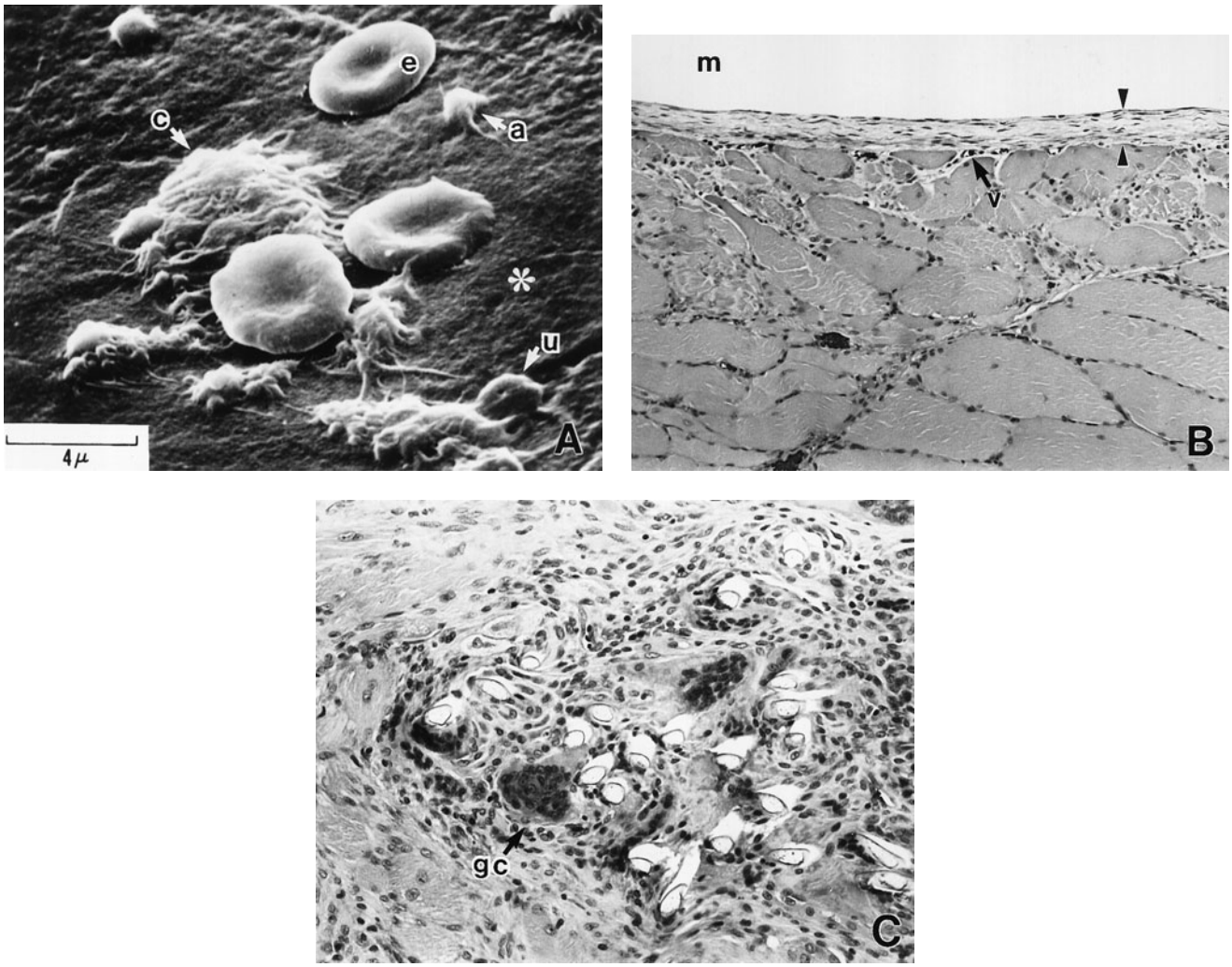
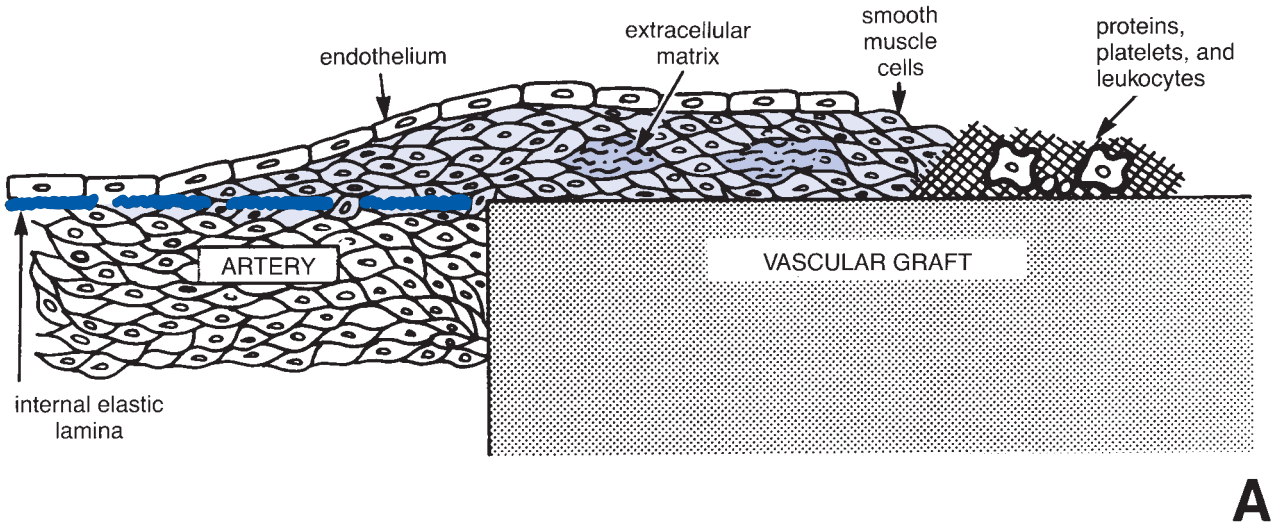
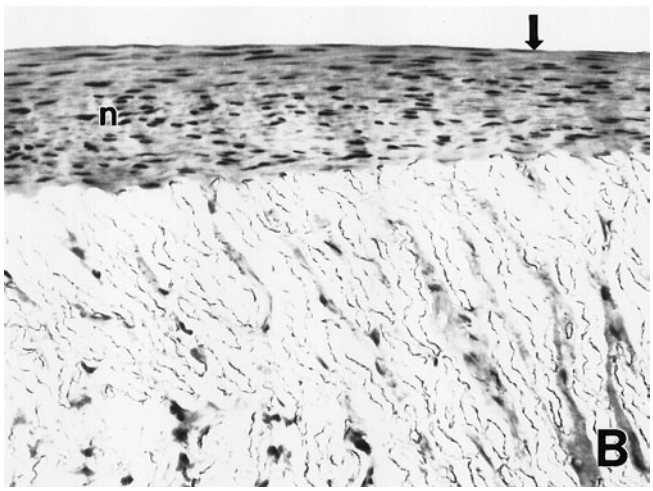


Figure 5-8. Morphology of biomaterials-tissue interactions. (A) Scanning electron photomicrograph of early thrombotic deposits on heart valve material exposed to calf blood for a few minutes in an extracorporeal experiment. Numerous platelets in various stages of adhesion ranging from relatively unaffected (u) to adherent activated (a) forms, some aggregated in clumps (c), are adherent to a background of protein absorption (asterisk). Erythrocytes (e) are probably passively adsorbed in early surface-induced thrombus formation. (B) Photomicrograph of experimental tissue reaction to relatively inert biocompatible material (m), implanted into rabbit muscle. A thin discrete fibrous capsule with virtually no inflammatory cell infiltrate is adjacent to the implant (between arrowheads). Fine vascularity (v) is noted at the interface between the fibrous capsule and the surrounding muscle. Hematoxylin and eosin 150x. (C) Granulomatous inflammatory response to surgically implanted Dacron mesh. This is an intense inflammatory response that includes abundant foreign body giant cells (gc). Hematoxylin and eosin 200x. (*A: Reproduced with permission from Schoen FJ: Cardiac valve prostheses: pathological and bioengineering considerations. J Card Surg 1987; 2:265. B and C: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

proliferation in the intima, and heart valve prostheses can elicit excessive pannus that occludes the orifice. Intimal hyperplasia results primarily from smooth muscle cell migration, proliferation, and extracellular matrix elaboration following and possibly mediated by acute or ongoing endothelial cell injury. Contributing factors to an exuberant response include: (1) surface thrombogenesis; (2) delayed or incomplete endothelialization of the fabric; (3) disturbed flow across the anastomosis; and (4) mechanical "mismatch" at the junction of the implant and host tissues.

Tissue lining a vascular graft or coating a heart valve sewing cuff derives principally from overgrowth from the host vessel across anastomotic sites. However, tissue ingrowth through the fabric of a graft with interstices large enough to permit ingrowth of fibrovascular elements can arise from capillaries extending from outside to inside the graft. This may permit endothelial cells to migrate to the luminal surface at a large distance from the anastomosis. However, since most clinical vascular grafts are impervious in order to obviate hemorrhage, existing grafts (and other





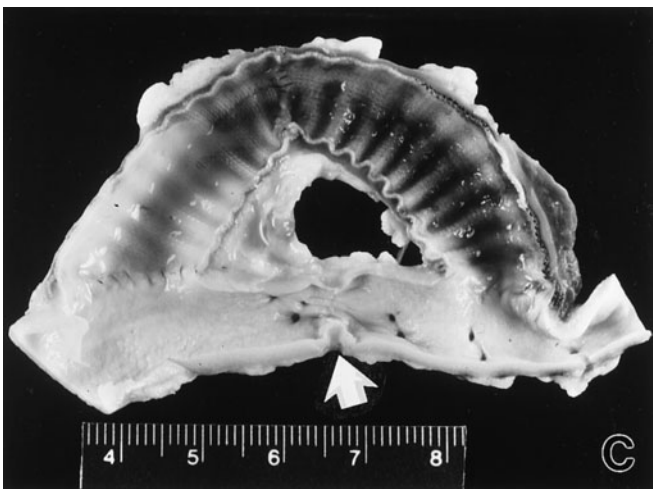


Figure 5-9. Vascular graft healing. (A) Schematic diagram of pannus formation, the major mode of graft healing with currently available vascular grafts. Smooth muscle cells migrate from the media to the intima of the adjacent artery and extend over and proliferate on the graft surface. The thin smooth muscle cell layer is covered by a proliferating layer of endothelial cells. (B) Neointima (n), consisting of smooth muscle cells and extracellular matrix covered by endothelium in an experimental expanded polytetrafluoroethylene graft in the rabbit aorta. The blood-contacting surface is indicated by the arrow. Hematoxylin and eosin 150x. (C) Experimental composite vascular graft composed of dissimilar grafts anastomosed together, used to bypass a surgically-created stenotic segment in the sheep aorta (arrow), from a study of variables in graft healing. The extent of healing is vastly different between the gelatin-coated graft (left) and the albumin-coated graft (right). (*A and B: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989. C: Reproduced with permission from Kadoba K, Schoen FJ, Jonas RA: Experimental comparison of albumin-sealed and gelatin-sealed knitted Dacron conduits. J Thorac Cardiovasc Surg 1992; 103:1059.*)

fabrics used as cardiovascular implants) heal primarily by ingrowth of endothelium and smooth muscle cells from the cut edges of the adjacent artery or other tissue (*pannus*). A third mechanism exists, deposition of functional endothelial cell progenitors from the circulating blood, but the extent of functional endothelialization via this route is not yet known.[59]

Humans have a limited ability to spontaneously endothelialize cardiovascular prostheses, and full endothelialization of clinical grafts (yielding an intact *neointima*) usually does not occur. For uncertain reasons, endothelial cell coverage generally is restricted to a zone near an anastomosis, typically 10 to 15 mm, thereby allowing healing of intracardiac fabric patches and prosthetic valve sewing rings, but not long vascular grafts. Thus, except adjacent to an anastomosis, a compacted platelet-fibrin aggregate (*pseudointima*) comprises the inner lining of clinical fabric grafts, even after long-term implantation.

Because firm adherence of such linings to the underlying graft may be impossible, dislodgment of the lining and formation of a flap-valve can occur and cause obstruction.[60] Current research centers on the design of novel vascular graft materials that enhance endothelial cell attachment, grafts preseeded with unmodified or genetically engineered endothelial cells, attempts to block smooth muscle cell proliferation, and tissue engineered vascular grafts (see below).[61]

Infection

Infection is a common complication of implanted prosthetic devices and is a frequent source of morbidity and mortality.[62,63] Early implant infections (less than 1 to 2 months postoperatively) most likely result from intraoperative contamination or early postoperative wound infection. In contrast, late infections generally occur by a hematogenous route, and can be initiated by bacteremia induced by therapeutic dental or genitourinary procedures. Antibiotics given prophylactically at device implantation and shortly before subsequent diagnostic and therapeutic procedures may protect against implant infection.

Infections associated with medical devices are characterized microbiologically by a high prevalence of organisms capable of forming a protective *biofilm*.[64] These organisms include gram-positive bacteria such as *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Enterococcus faecalis,* and viridans streptococci, gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, and fungi such as *Candida albicans*. Some of these organisms, especially *S. epidermidis* and viridans streptococci, are organisms of relatively low virulence in the absence of a foreign body, but are frequent causes of medical device infection.

The presence of a foreign body potentiates infection in several ways. Microorganisms may inadvertently be introduced into deep tissue locations by contamination at device implantation, bypassing natural barriers against infection during implantation. Some devices, such as many of the current left ventricular assist devices (LVADs), require a percutaneous driveline, providing a continuous potential means of entry for microorganisms. The production of a biofilm (a multicellular film of microbial cells that is irreversibly associated with a material surface and enclosed in a self-produced extracellular matrix composed primarily of polysaccharides) by the organisms is protective against the humoral and cellular immune response of the host.[65] The penetration of opsonizing antibodies is delayed by the biofilm, resulting in ineffective uptake and killing by phagocytes. The biofilm also slows the penetration of antibiotics. Moreover, an implanted foreign body could limit phagocyte migration into infected tissue or interfere with inflammatory cell phagocytic mechanisms by release of soluble implant components or surface-mediated interactions with the extracellular matrix of the biofilm. Consequently, an implant-associated infection generally persists until the device is removed.

Tissue engineering and cardiovascular regeneration

As a logical extension of biomaterials science, *tissue engineering* comprises medical devices and therapeutic approaches that use living cells together with natural materials or synthetic polymers to develop or regenerate functional tissues.[66–68] In the most widely used approach to engineering tissues, the first step involves the seeding of cells on a synthetic polymer or natural material (such as collagen or chemically treated tissue) scaffold, and a tissue is matured in vitro. A typical scaffold is a bioresorbable polymer in a porous configuration, adhesive for cells in the desired geometry for the engineered tissue. The cells are either differentiated cells or stem cells. When placed in a metabolically and mechanically supportive environment with growth media (in a *bioreactor*), the cells proliferate and elaborate extracellular matrix in the form of a "new" tissue (the *construct*). In the second step, the construct is implanted in the appropriate anatomic location. Remodeling of the construct in vivo following implantation is intended to replicate the normal functional architecture of an organ or tissue. Key processes occurring during the in vitro and in vivo phases of tissue formation and maturation are (1) cell proliferation, sorting, and differentiation; (2) extracellular matrix production and organization; (3) degradation of the scaffold; and (4) remodeling and potential growth of the tissue.

Progress has been made toward tissue engineered vascular grafts, myocardium, and heart valves. Details are discussed below.

ENGINEERED VASCULAR GRAFTS: Human implantation of a tissue engineered blood vessel (pulmonary artery segment) constructed from cells and polymer has been reported.[69] Engineered tissue blood vessels of small caliber are actively being investigated.[70,71] Clinically employed conventional extended polytetrafluoroethylene vascular grafts have been seeded with endothelial cells at the time of implantation.[72]

A vessel "equivalent" composed of collagen and cultured bovine fibroblasts, smooth muscle, and endothelial cells was unable to withstand burst strengths for in vivo applications, despite reinforcement with a Dacron mesh.[73] Other investigators have improved the mechanical performance of engineered tissue vascular grafts by constructing a cohesive cellular sheet of smooth muscle cells, rolling this sheet to form the media (analogous to a "jelly roll"), and wrapping this sheet of human fibroblasts around the media to serve as an adventitia, and seeding endothelial cells in the lumen.[74] In other work in this area, cultured smooth muscle and endothelial cells isolated from bovine aorta were applied onto tubular scaffolds composed of polyglycolic acid and placed in a bioreactor.[75] Exposure to pulsatile physical forces enhanced the properties of the graft vessels; pulsed grafts were thicker, had greater suture retention, and had higher cell and collagen density than nonpulsed engineered grafts, as well as a histologic appearance similar to that of native arteries. Another approach to vascular graft engineering utilizes naturally derived matrices with or without cell repopulation prior to implantation.[76] Vascular grafts fabricated

from small intestine submucosa used as experimental vascular grafts in dogs were reported to be completely endothelialized and histologically similar to arteries.[77]

Another approach to vascular engineering extends the concept of Sparks' silicone mandril-grown graft used clinically in the 1970s.[78] Sparks grew a vessel substitute inside the subject's own body adjacent to the diseased vessel as the fibrous capsule that forms adjacent to an implanted foreign body (silicone mandril); the mandril was subsequently removed yielding an autologous tissue tube. However, owing to the variability of the quality of tissue generated in older patients in areas of circulatory insufficiency, such vascular replacements developed aneurysms when used clinically. Grafts were recently grown as the tissue that forms around silicone tubing inserted into the peritoneal cavity of rats, rabbits, and dogs.[79] The tissue was removed from the tubing, completely everted (so that mesothelial cells become the blood-contacting surface), grafted into the carotid artery of the same animal, and remained patent up to 4 months.

REGENERATION OF CARDIAC TISSUE: The classic view is that the adult heart responds to mechanical overload by hypertrophy (increase in cell size) and to severe ischemic or other injury by cell death (see earlier). Functional increase in cardiac myocyte number by cell regeneration or hyperplasia has generally not been considered possible. Nevertheless, three lines of research create enthusiasm that clinically-important cardiac regeneration may indeed be possible, including (1) cell-based therapies in which fetal or adult cardiomyocytes, skeletal myoblasts, or nonmuscle stem or differentiated cells are injected into the heart; (2) the possibility that the heart may have endogenous mechanisms of repair; and (3) experimental generation of functional myocardium by tissue engineering approaches, in which cells are seeded on a resorbable biomaterial scaffold, cultured in vitro, and implanted as a prosthetic myocardial patch.

Recent experiments and some early-phase clinical trials lend credence to the notion that cell-based cardiac repair may be an achievable therapeutic target.[80–82] Therapeutic strategies have explored fetal cardiomyocytes; skeletal myoblasts; embryonic-derived endothelial cells; bone marrow–derived immature myocytes; fibroblasts; smooth muscle cells; endothelial progenitor cells; and hematopoietic, mesenchymal, and embryonic stem cells. Clinical trials have used cells derived from skeletal muscle and bone marrow, and basic researchers are investigating sources of new cardiomyocytes, such as resident myocardial progenitors and embryonic stem cells. Structural and functional integration of the graft with the host myocardium may be attainable. Nevertheless, the most appropriate form of cellular therapy for myocardial injury remains to be identified, and it is unclear at present whether the beneficial effects are a result of functional and electrically-integrated myocytes (the ideal), enhancement of angiogenesis owing to a local and nonspecific inflammatory reaction at the site of injection, or a "paracrine" effect, whereby transplanted cells are proposed to produce growth factors, cytokines, and other local signaling molecules that are beneficial to the infarct through neovascularization and/or scar remodeling.

Recent evidence that myocyte regeneration and death occur physiologically, and that these cellular processes are enhanced in pathologic states, have challenged the view of the heart as a postmitotic organ. Heart homeostasis may be regulated by a stem cell compartment in the heart characterized by multipotent cardiac stem cells that possess the ability to acquire the distinct cell lineages of the myocardium, and are capable of regenerating myocytes and coronary vessels throughout life, and have the capacity to adapt to increases in pressure and volume loads.[83] Moreover, adult bone marrow cells may be able to differentiate into cells beyond their own tissue boundary and create cardiomyocytes and coronary vessels. Indeed, myocytes bearing a Y chromosome have been found in the hearts of female donors transplanted to male recipients, raising the possibility that endogenous primitive stem cells, either circulating or resident, may play a role in repair of myocardial infarcts.[84]

Myocardial tissue generated from cells, scaffolds, and bioreactors has been encouraging with respect to construct survival, vascularization, and integration, but functional improvement in clinical implantation has yet to be demonstrated.[85,86] Application of cyclic mechanical stretch and electrical signals have been shown to enhance cell differentiation and force of contraction.[87]

ENGINEERED HEART VALVES: Recent scientific and technological progress has stimulated the goal of creating a living valve replacement that would obviate the complications of conventional valve replacement, adapt to changing environmental conditions in the recipient, and potentially grow with a growing patient.[88–90] Innovative work toward this objective is active in many laboratories, and may eventually lead to clinical application. The long-term success of a tissue engineered (living) valve replacement will depend on the ability of its living cellular components (particularly valvular interstitial cells) to assume normal function with the capacity to repair structural injury, remodel the extracellular matrix, and potentially grow. Three approaches are under consideration: (1) Use the methodology of tissue engineering, combining cells plus a scaffold in a bioreactor environment to generate tissue formed in vitro, which is then implanted in vivo to form an organ or tissue; (2) recruit endogenous cells through the circulation from bone marrow or other source; and (3) harness the intrinsic regenerative potential of the heart valves.

Tissue engineered heart valves grown as valved conduits from autologous cells (either vascular wall cells or bone marrow–derived mesenchymal stem cells) seeded on biodegradable synthetic polymers grown in vitro have functioned in the pulmonary circulation of growing lambs for up to 5 months (Fig. 5-10),[91,92] and evolved in vivo into a

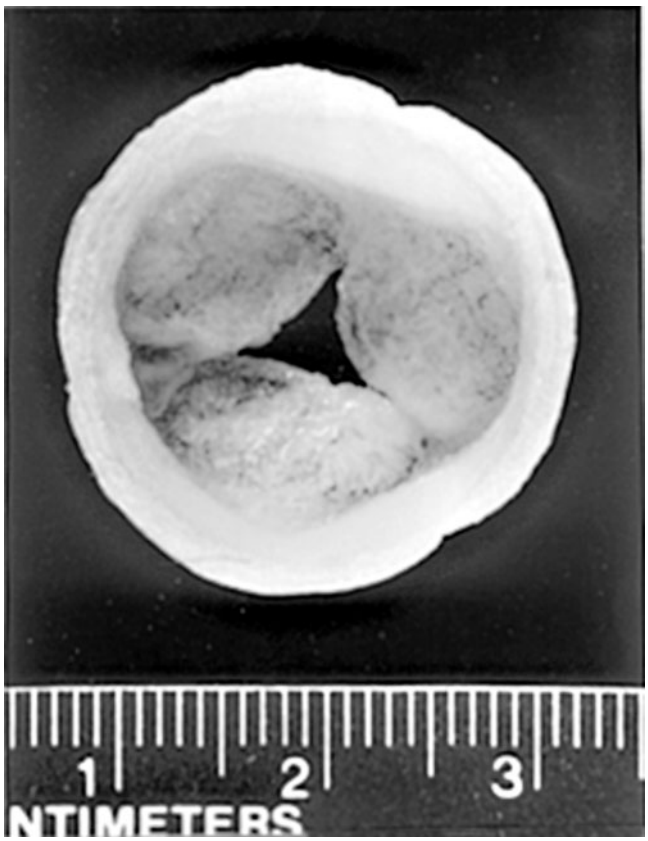


Figure 5-10. Tissue engineered heart valve composed of ovine vascular wall cells seeded on polyglycolic acid polymer scaffold and conditioned in a pulsatile bioreactor in vitro for 14 days. (*Reproduced with permission from Hoerstrup et al.*[91])

specialized layered structure that resembled that of a native semilunar valve. A recent study has shown that pulmonary vascular walls fabricated from vascular wall cells and biodegradable polymer and implanted into very young lambs enlarged proportionally to overall animal growth over a 2-year period.[93]

In an effort to eliminate the need for in vitro cell seeding and culture steps, an alternative tissue engineering strategy has used either a scaffold of a naturally derived biomaterial (such as small intestine submucosa) implanted without prior seeding or a decellularized valve.[94] Tissue-derived valve scaffolds may possess desirable three-dimensional architecture, mechanical properties, and potential adhesion/migration sites for cell attachment and ingrowth. Nevertheless, decellularized porcine valves implanted in humans had a strong inflammatory response and suffered structural failure.[95]

Translation of heart valve tissue engineering and regenerative medicine from the laboratory to the clinical realm has exciting potential, but also formidable challenges and uncertainties. Key hurdles include selection and validation of suitable animal models, development of guidelines for characterization and assurance of the quality of an in vitro fabricated tissue engineered heart valve for human implantation, and strategies to understand, monitor, and potentially control patient variability in wound healing and tissue remodeling in vivo.

ISCHEMIC HEART DISEASE

The ischemic heart disease syndromes are primarily caused by atherosclerosis and its complications, causing diminished coronary perfusion. They are the direct effect on the myocardium of a complex and dynamic interaction among fixed atherosclerotic narrowing of the epicardial coronary arteries, intraluminal thrombosis overlying a ruptured or fissured atherosclerotic plaque, platelet aggregation, and vasospasm.

Pathogenesis

Role of fixed coronary obstructions

In the absence of significant pathology, coronary arterial flow provides adequate myocardial perfusion at rest, and compensatory vasodilation provides flow reserve that is more than sufficient to accommodate the increased metabolic demands during vigorous exertion. When the luminal cross-sectional area is decreased by 75% or more, coronary blood flow generally becomes limited with exertion; with 90% or greater reduction, coronary flow may be inadequate even at rest. Over 90% of patients with ischemic heart disease syndromes have advanced stenosing coronary atherosclerosis (fixed obstructions), and most myocardial infarcts occur in patients with coronary atherosclerosis.

Nonatherosclerotic causes of coronary artery obstruction can also occur. The most common causes are autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), vasculitis (e.g., Buerger disease and Kawasaki disease), fibromuscular dysplasia, dissection, spasm, and embolism. Obstruction of the small intramural coronary arteries is seen in several disease states, including diabetes, deposition diseases such as Fabry disease and amyloidosis, progressive systemic sclerosis (scleroderma), and as a proliferative intimal lesion in the coronary arteries of cardiac allografts (see later).

Role of acute plaque change

The onset and prognosis of ischemic heart disease and other complications of atherosclerosis are not well predicted by the angiographically determined extent and severity of fixed anatomic disease.[96] Dynamic vascular changes are largely responsible for the conversion of chronic stable angina or an asymptomatic state to an *acute coronary syndrome*, most commonly fracture of the fibrous cap leading to hemorrhage into the plaque, followed by platelet aggregation and thrombosis compromising the lumen, and sometimes fissuring and/or ulceration.[97] Plaque alterations precipitating the acute coronary syndrome span a

broad morphologic range from superficial erosion of the intima without a frank rupture through the plaque fibrous cap, to lacerations that extend deep within the plaque.[98] Vasospasm, tachycardia, hypercholesterolemia, and intraplaque hemorrhage are likely contributors, as are stresses induced by blood flow and/or coronary intramural pressure or tone in plaque. Regardless of the extent of injury, the result is flow disruption and exposure of the luminal blood to a thrombogenic surface (collagen, lipid, or necrotic debris), thereby setting the stage for mural or total thrombosis.

Pathologic and clinical studies show that plaques that undergo abrupt disruption leading to coronary occlusion often are those that previously produced only mild to moderate luminal stenosis. Overall, approximately two-thirds of plaques that rupture with subsequent occlusive thrombosis cause occlusion of only 50% or less before plaque rupture, and in 85% of patients, stenosis is initially less than 70%. Thus, there is great interest in predicting plaque disruption or subsequent thrombosis in an individual patient.[99] Although x-ray coronary angiography remains widely used, a noninvasive test is highly desirable. Calcification of the coronary arteries can be detected noninvasively by electron beam computed tomography (CT). Radiographically visible calcium in the epicardial coronary arteries predicts the extent of atherosclerotic disease, but cannot identify features of plaque instability. However, since plaque burden correlates with cardiovascular risk, coronary calcium tends to be a good prognostic indicator of future myocardial ischemic events.[100] Moreover, three-dimensional coronary magnetic resonance angiography (MRA) has the potential to visualize both the coronary lumen and the atherosclerotic plaques in the arterial wall.[101] Intravascular ultrasound also can provide precise information about the degree of stenosis, and the location and nature of atherosclerotic plaque. Molecular imaging techniques that have potential applicability in this setting are emerging.

Plaques considered prone to rupture are termed *vulnerable plaques*. The events that trigger abrupt changes in plaque configuration and superimposed thrombosis of vulnerable plaques are complex and poorly understood. Influences that are both intrinsic to the plaque (e.g., structure and composition) and extrinsic (e.g., blood pressure and platelet reactivity) are important. The fibrous cap is a highly dynamic tissue, and local inflammation regulates the balance of collagen synthetic and degradative activity, which itself determines stability and prognosis. Thus, lesions prone to rupture have a thin collagen layer and few smooth muscle cells (the cells that are responsible for the repair and maintenance of the all-important collagenous matrix and are a rich source of extracellular matrix macromolecules in the artery wall), contain many macrophages which produce matrix metalloproteinases that degrade the collagen that lends strength to the fibrous cap, and contain large areas of foam cells and extracellular lipid.[102] Inflammation also may contribute to coronary thrombosis by altering the balance between prothrombotic and fibrinolytic properties of the endothelium. There is evidence that lipid lowering by diet or drugs such as statins can reduce the onset of coronary thrombotic complications by stabilizing plaque (i.e., increasing the thickness and strength of the fibrous cap) by reducing accumulation of macrophages expressing matrix-degrading enzymes and tissue factor, and reducing activation of smooth muscle cells and endothelial cells.[103]

Potential outcomes for unstable lesions include thrombotic occlusion, nonocclusive thrombosis, healing at the site of plaque erosion, athero- or thromboembolization, organization of mural thrombus (plaque progression), and organization of the occlusive mass with recanalization. Among these outcomes, the most common fate is plaque progression, owing either to resealing of the plaque fissure or to organization of a nonocclusive mural thrombus. Indeed, asymptomatic plaque rupture and its subsequent healing is likely an important mechanism of progressive stenosis.

Coronary and Myocardial Interventions

Revascularization in acute myocardial infarction

The pathophysiologic basis of revascularization in early acute myocardial infarction (AMI) to limit infarct size and improve cardiac function and survival is as follows:[104] (1) Untreated thrombotic occlusion of a coronary artery causes transmural infarction; (2) the extent of necrosis during an evolving MI progresses as a wavefront and becomes complete only 6 hours or more following coronary occlusion (see Fig. 5-5); (3) both early- and long-term mortality following AMI correlate strongly with the amount of residual functioning myocardium; and (4) early reperfusion rescues some jeopardized myocardium. Thus, the benefits of thrombolytic therapy or early percutaneous transluminal coronary angioplasty (PTCA) depend on and are assessed by the amount of myocardium salvaged, recovery of left ventricular function (LVF), and resultant reduction in mortality. These important clinical endpoints are largely determined by the time interval between onset of symptoms and a successful intervention, adequacy of early coronary reflow, and the degree of residual stenosis of the infarct vessel. The maximal time for substantial myocardial salvage is approximately 3 to 4 hours, but some studies suggest that modest benefit can occur following later reperfusion. Spontaneous recanalization, presumably owing to inherent thrombolysis, can be beneficial to LVF but occurs in fewer than 10% of patients within the critical 3 to 4 hours after symptom onset.

Successful thrombolytic therapy or PTCA alone often re-establishes antegrade flow in the infarct-related coronary artery but does not reverse intimal rupture, enhanced platelet adhesiveness, or coronary spasm. Thus, balloon angioplasty with stent placement (see below) or surgical revascularization during infarct evolution constitute more effective management of the underlying disease process than thrombolysis alone.[105]

Angioplasty and stents

PTCA is used in patients with stable angina, unstable angina, or AMI to restore blood flow through a diseased portion of the coronary circulation obstructed by atherosclerotic plaque and/or thrombotic deposits.[106] Angioplasty has also been applied to obstructions in saphenous vein grafts, internal mammary artery (IMA) grafts, and coronary arteries in transplanted hearts. Today, nearly all patients undergoing PTCA will also receive a stent.

ANGIOPLASTY: In PTCA, the plaque splits at its weakest point and enlargement of the lumen and increased blood flow occurs by plaque fracture (the predominant mechanism), and by embolization, compression, redistribution of the plaque contents, and overall mechanical expansion of the vessel wall.[107] The split extends at least to the intimal-medial border and often into the media, with consequent circumferential and longitudinal dissection of the media (Fig. 5-11). Coronary arterial dissection may contribute to the propensity for acute closure that occurs in up to 5% of patients. For example, a dissection that involves a considerable portion of the circumference can generate a flap that may impinge on the lumen. Alternatively, a dissection that involves a substantial proximal-to-distal segment of the vessel, which traverses a large plaque-free wall segment, can induce compression of the vessel at a point of minimal disease. Short-term failure of this procedure (i.e., closure of the treated vessel within hours to days) can occur via several mechanisms, including elastic recoil of the vessel wall, acute thrombosis at the site of ballooning, and acute dissection (i.e., blood within the wall itself) of the vessel beyond the area of angioplasty.

Angioplasty-induced plaque fracture, medial dissection, and stretching of the media beyond the dissection are accompanied by local flow abnormalities and generation of new, thrombogenic blood-contacting surfaces (similar to what is observed with spontaneously disrupted plaque). These features can lead to platelet deposition and occlusive thrombosis. The immediate postangioplasty healing process is not well understood, but dissolution of soft atheromatous material, retraction of the split plaque, thrombus formation, and intimal healing with re-endothelialization likely occur. PTCA is successful in 85 to 95% of cases (including vein grafts and IMAs) and is associated with a mortality rate of 1%.

The long-term success of PTCA is limited by the development of progressive, proliferative restenosis, which occurs in 30 to 40% of patients, most frequently within the first 4 to 6 months[108] (Fig. 5-12). Although vessel wall recoil and organization of thrombus likely contribute, the major process leading to restenosis is excessive medial smooth muscle proliferation as an exaggerated response to angioplasty-induced injury. Medial smooth muscle cells migrate to the intima, where along with existing plaque smooth muscle cells, they proliferate and secrete abundant extracellular matrix. Interest in locally delivered pharmacologic and molecular therapies to mitigate restenosis has been long-standing; regrettably, success has been limited.[109]

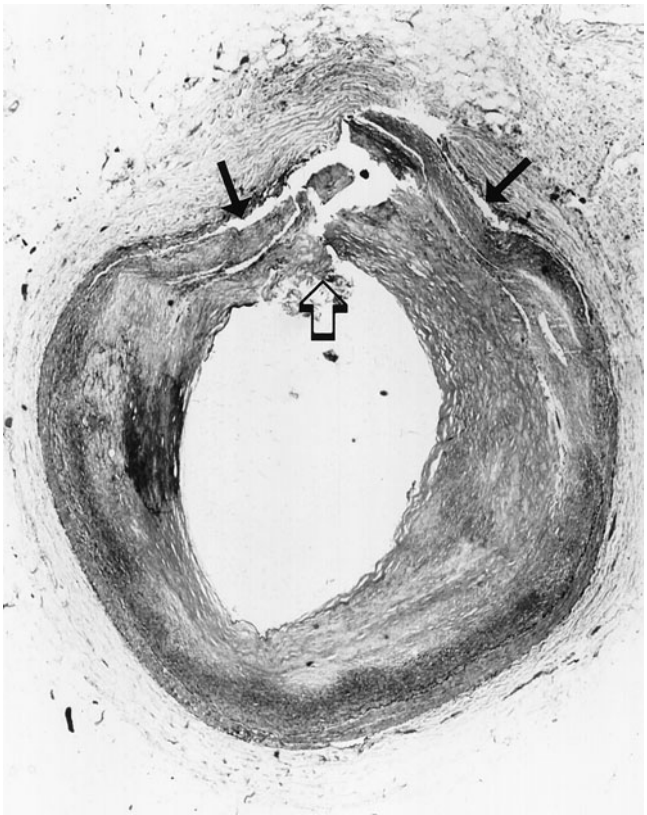


Figure 5-11. Acute changes of percutaneous transluminal coronary angioplasty (PTCA) on coronary arterial atherosclerotic plaque. The changes induced by balloon angioplasty consist of fracture of the plaque (open arrow) with deep extension of the wall defect and partial circumferential dissection (closed arrows). Verhoff van Giesen stain (for elastin) 20x. (*Reproduced with permission from Schoen FJ: Blood vessels, in Kumar V, Fausto N, Abbas A [eds]: Robbins & Cotran Pathologic Basis of Disease, 7th ed. Philadelphia, WB Saunders, 2004; p 511.*)

Coronary atherectomy of primary or restenosis lesions mechanically removes obstructive tissue by excision. Deep arterial resection, including medial and even adventitial elements, occurs frequently but has not been associated with acute symptomatic complications. The morphology of arterial vessel healing after directional or rotational atherectomy is similar to that following angioplasty.

STENTS: Stents are expandable tubes of metallic mesh that are inserted percutaneously at the time of PTCA to preserve luminal patency in both native coronary arteries and vein grafts. They provide a larger and more regular lumen by acting as a scaffold to support the intimal dissections that occur in PTCA, mechanically prevent vascular spasm, and increase blood flow, all of which minimize thrombus formation and reduce the impact of postangioplasty restenosis.

Stenting has been shown to be superior to angioplasty alone in several lesions and situations, including in vessels

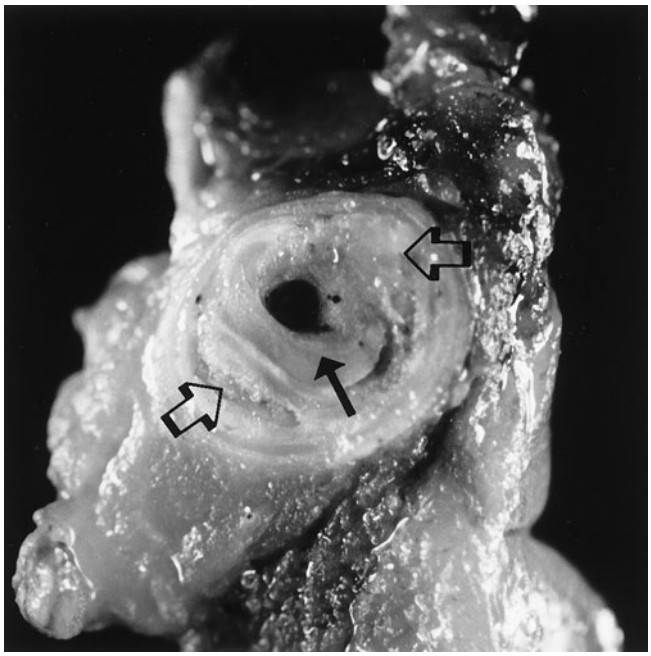


Figure 5-12. Proliferative restenosis after percutaneous transluminal coronary angioplasty. This gross cross-section of a coronary artery from a patient who died several months after angioplasty illustrates both the original, previously disrupted atherosclerotic plaque (open arrows) and markedly occlusive concentric fibrous tissue that formed after the procedure (arrow). (*Reproduced with permission from Schoen FJ: Blood vessels, in Kumar V, Fausto N, Abbas A [eds]: Robbins & Cotran Pathologic Basis of Disease, 7th ed. Philadelphia, WB Saunders, 2004; p 511.*)

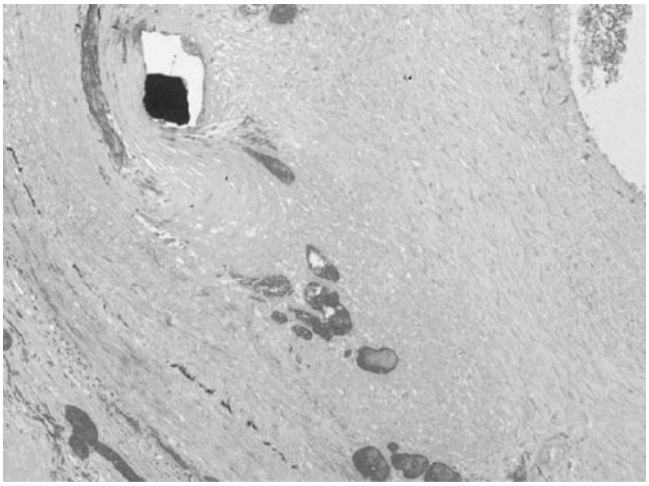


Figure 5-13. Metallic coronary artery stent implanted long-term, demonstrating thickened proliferative neointima separating the stent wires (black structure) from the lumen. Movat stain. (*Reproduced with permission from Schoen and Edwards.*[4])

>3 mm in diameter, in chronic total occlusions, in stenotic vein grafts, in restenotic lesions after angioplasty alone and in patients with AMI. Complications include acute, subacute, or late stent thrombosis and in-stent restenosis.[110]

The reasons for thrombosis and restenosis are complex and are largely due to tissue interactions with an implanted stent.[111,112] There is early damage to the endothelial lining and stretching of the vessel wall, stimulating adherence and accumulation of platelets and leukocytes. Covered initially by a variable platelet-fibrin coating, stent wires may eventually become completely covered by an endothelium-lined neointima, with the wires embedded in a layer of intimal thickening consisting of smooth muscle cells in a collagen matrix (Fig. 5-13). This tissue may thicken secondary to the release of growth factors, chemotactic factors, and inflammatory mediators from platelets and other inflammatory cells that result in increased migration and proliferation of smooth muscle cells, and increased production of extracellular matrix molecules, narrowing the lumen and resulting in restenosis, which may occur in 50% of patients implanted with first-generation (nondrug eluting) stents.

Many approaches have been used in an attempt to reduce in-stent restenosis. Intracoronary radiotherapy is thought to block cell proliferation, induce cell death, and inhibit migration of smooth muscle cells in the area of the stent to reduce neointimal accumulation. Several studies have shown promising initial results in reducing the restenosis rate, but have also shown some long-term complications including late thrombosis, increased restenosis at the edge of the treated field, and damage to the wall.[113]

The most promising results have been attained with polymer-coated drug-eluting stents, which are now widely used, especially with two drugs, rapamycin (sirolimus) and paclitaxel.[114,115] Rapamycin, a drug used for immunosuppression in solid organ transplant recipients, also inhibits proliferation, migration, and growth of smooth muscle cells and extracellular matrix synthesis. Paclitaxel, a drug used in the chemotherapeutic regimens for several types of cancer, also has similar anti–smooth muscle cell activities. These drugs are embedded in a polymer matrix (such as a copolymer of poly-*n*-butyl methacrylate and polyethylene–vinyl acetate or a gelatin-chondroitin sulfate coacervate film) that is coated onto the stent. The drug is released by diffusion and/or polymer degradation over varying periods of time that can be engineered by the specifics of the polymer-drug system. Despite some risk of late stent thrombosis,[116] coated stents have had excellent long-term success, virtually eliminating restenosis for periods of 2 years and longer, and are felt to represent a major breakthrough in the treatment of coronary artery disease (CAD).[117,118] The impact of the current era of coronary stenting on further surgical and medical treatment has recently been reviewed.[119,120]

Coronary artery bypass graft surgery

Coronary artery bypass graft (CABG) surgery improves survival in patients with significant left main coronary artery disease, with three-vessel (and possibly two-vessel) disease, or with reduced ventricular function.[121] CABG surgery

prolongs and improves the quality of life in patients with left main equivalent disease (the proximal left anterior descending and proximal left circumflex arteries), but does not protect them from the risk of subsequent MI. The main mechanism for these benefits is thought to be the reperfusion of hibernating (i.e., viable but poorly perfused and poorly functioning) myocardium, leading to increased LVF.

The hospital mortality rate for CABG surgery is approximately 1% in low-risk patients, with less than 3% of patients suffering perioperative MI. The most consistent predictors of mortality after CABG are urgency of operation, age, prior cardiac surgery, female gender, low left ventricular ejection fraction (LVEF), degree of left main stenosis, and number of vessels with significant stenoses. The benefit of CABG is greatest in the highest-risk patients with the most severe disease; it is not surprising, therefore, that a recently reported increase in morbidity and mortality has accompanied increased utilization of CABG performed in an older and sicker population.

The most common mode of early death after CABG is acute cardiac failure leading to low output or arrhythmias. Although the underlying cause is massive myocardial damage in some cases, other contributory factors may include: (1) evolving myocardial necrosis either undetectable clinically or too recent to detect at autopsy; (2) postischemic dysfunction of viable myocardium, for which no morphologic markers of the dysfunctional state are known; or (3) a metabolic cause, such as hypokalemia, for which there is no morphologic counterpart. Therefore, although established myocardial necrosis causes cardiac dysfunction in some patients with postoperative failure, it may not be the predominant lesion or the cause of death in all such patients.

Perioperative infarction usually is caused by either perioperative hypotensive episodes or inadequate intraoperative myocardial preservation, potentially exacerbated by severe obstruction of feeding arteries and poor collaterals. Such necrosis usually predominates in the subendocardium and often has the morphology of necrosis with contraction bands. As in cardiac surgery in general, perioperative MI is more likely to occur in patients with cardiomegaly than in those with normal-sized hearts, and in patients who have had preoperative infarctions.

Early thrombotic occlusion of the graft vessel may occur, with inadequate distal run-off from extremely small distal native coronaries (often further compromised by atherosclerosis) comprising the major mechanism. Additional factors may include acute graft dissection at the anastomotic site, atherosclerosis or arterial branching at the anastomotic site, distortion of a graft that is too short or too long for the intended bypass, as well as patient factors. In some cases, thrombosis occurring early postoperatively involves only the distal portion of the graft, suggesting that early graft thrombosis is frequently initiated at the distal anastomosis. Antiplatelet therapy has resulted in improved patency rates, and graft thromboses account for only a minority of early cardiac deaths; indeed, most patients who die early have patent grafts.

The patency of saphenous vein grafts is reported as 60% at 10 years; occlusion results from (with increasing postoperative interval) thrombosis, progressive intimal thickening, and/or obstructive atherosclerosis.[122–124] Between 1 month and 1 year, graft stenosis is usually caused by intimal hyperplasia with excessive smooth muscle proliferation and extracellular matrix production similar to that seen following angioplasty. Atherosclerosis becomes the more dominant mechanism in graft occlusion beyond 1 to 3 years after CABG. As in the native coronary arteries, atherosclerosis in bypass grafts can cause myocardial ischemia through progressive luminal stenosis or plaque rupture with secondary thrombotic obstruction. The potential for disruption and embolization of atherosclerotic lesions in vein grafts exceeds that for native coronary atherosclerotic lesions. Plaques in grafts generally often have poorly developed fibrous caps with large necrotic cores, and develop secondary dystrophic calcific deposits that may extend to the lumen (Fig. 5-14). Thus, atheroembolization is a major risk, often with catastrophic results; PCI or intraoperative manipulation of grafts may stimulate atheroembolism.

In contrast, the IMA has a >90% patency rate at 10 years (Fig. 5-15).[125] Multiple factors likely contribute to the remarkably higher long-term patency of IMA grafts compared to vein grafts. Free saphenous vein grafts sustain not only disruption of their vasa vasora and nerves, but also endothelial damage, medial ischemia, and acutely increased internal pressure. In contrast, the IMA generally requires minimal surgical manipulation, maintains its nutrient blood supply, is accustomed to arterial pressures, needs no proximal anastomosis, and has an artery-to-artery distal anastomosis, as well as having minimal pre-existing atherosclerosis in most cases. The sizes of graft and recipient vessels are comparable with the IMA grafts, but disparate (the graft is substantially larger) with saphenous vein grafts. Radial and gastroepiploic arteries are occasionally also used successfully. With the advent of off-pump and minimally invasive CABG, there have been efforts to facilitate anastomosis of the graft to the aorta. Several sutureless anastomotic devices have been developed to facilitate aortocoronary bypass.[126] An anastomotic device should be easy to use, and produce a geometrically optimal anastomosis with minimal endothelial damage and minimal blood-exposed nonintimal surface.

Transmyocardial laser revascularization

Transmyocardial laser revascularization (TMR) has been used in selected patients to manage CAD that is refractory to conventional revascularization techniques and maximal medical therapy. Performed on a beating heart through a left thoracotomy, the operation employs a high-energy laser to bore transmural channels into the left ventricle. The hypothesis is that blood will flow directly from the left ventricular chamber into the channels and then into the intramyocardial

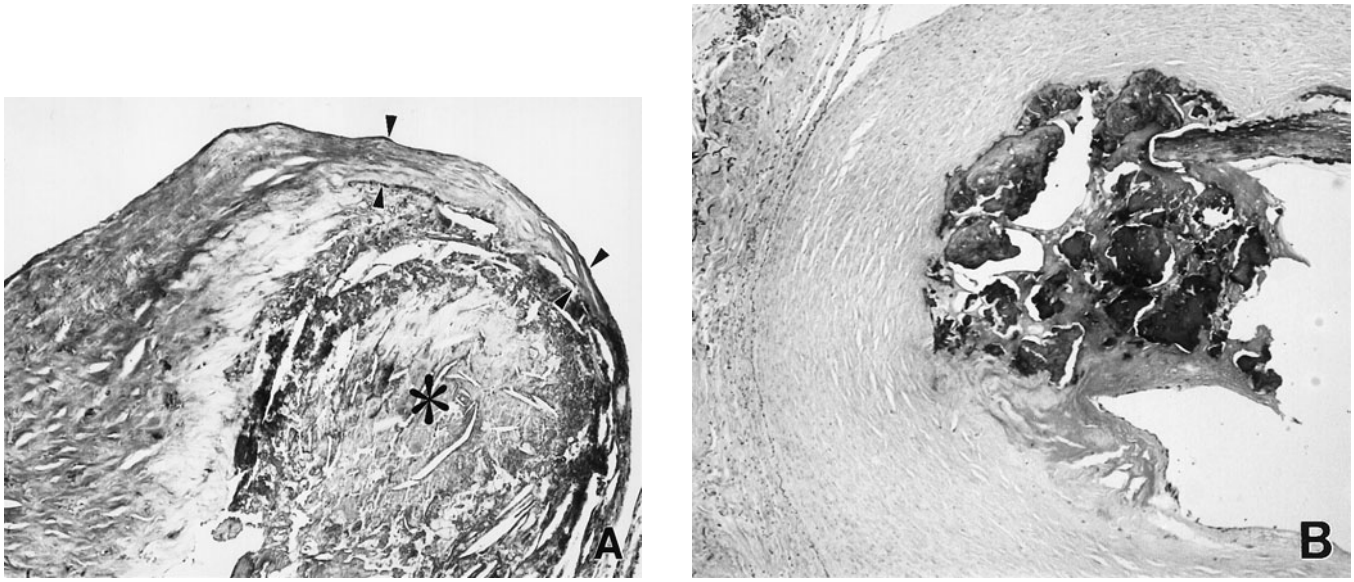


Figure 5-14. Atherosclerosis of saphenous vein bypass grafts. (A) Typical fibrous cap (between arrowheads) is attenuated over the necrotic core (asterisk).100x. (B) Prominent calcification eroding through the luminal surface. Hematoxylin and eosin, 60x. (*Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

vascular plexus, thereby restoring perfusion to potentially viable myocardium in a manner reminiscent of normal reptilian hearts. Although some clinical trials report a decrease in anginal symptoms after TMR, the success of the technique is as yet uncertain.[127,128]

Intramyocardial channels generated by TMR initially have a central region of destroyed myocardium surrounded by a thin rim of necrotic tissue (Fig. 5-16). Over the first 24 hours, the channels fill with blood and fibrin and are surrounded by myocardium with contraction band necrosis (see Fig. 5-16A). After 2 to 3 weeks, the channels are filled with vascularized granulation tissue in keeping with the general time course of wound healing (see Fig. 5-16B). Clinical studies and examination of hearts from patients who have died at various postmortem intervals failed to reveal patent channels.[129] The leading hypothesis for the reported efficacy of TMR is the stimulation of neovascularization in the vicinity of the channels; denervation of these areas may also play a role in the reduction of symptomatic angina.

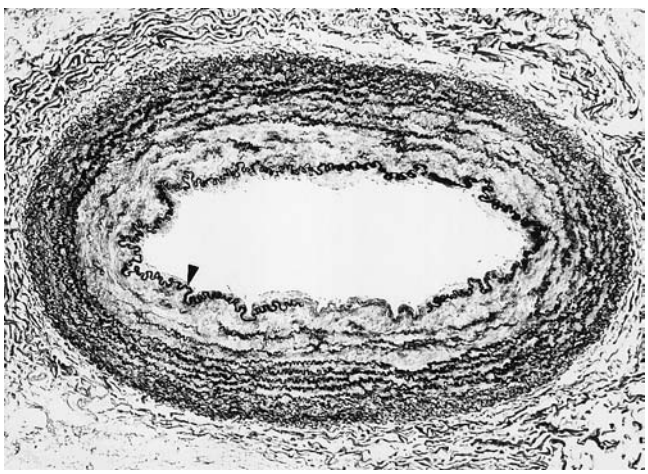


Figure 5-15. Internal mammary artery removed 13 years following function as an aortocoronary bypass, demonstrating near-normal morphology with minimal intimal thickening. The internal elastic lamina is indicated by the arrowhead. Verhoff von Giesen stain (for elastin) 60x. (*Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

Myocardial Infarction and Its Complications

Coronary atherosclerosis with acute plaque rupture and superimposed thrombosis typically results in a transmural infarct, where ischemic necrosis involves at least half and usually the full or nearly full thickness of the ventricular wall in the distribution of the involved coronary artery. In contrast, a subendocardial (nontransmural non-Q wave) infarct constitutes an area of ischemic necrosis limited to the inner third to half of the ventricular wall. This process can be multifocal, often extending laterally beyond the perfusion territory of a single coronary artery. Subendocardial infarcts are commonly associated with diffuse stenosing coronary atherosclerosis without acute plaque rupture or superimposed thrombosis in the setting of episodic hypotension, global ischemia, or hypoxemia. A subendocardial infarct can also result from a coronary thrombus that is not completely occlusive or becomes

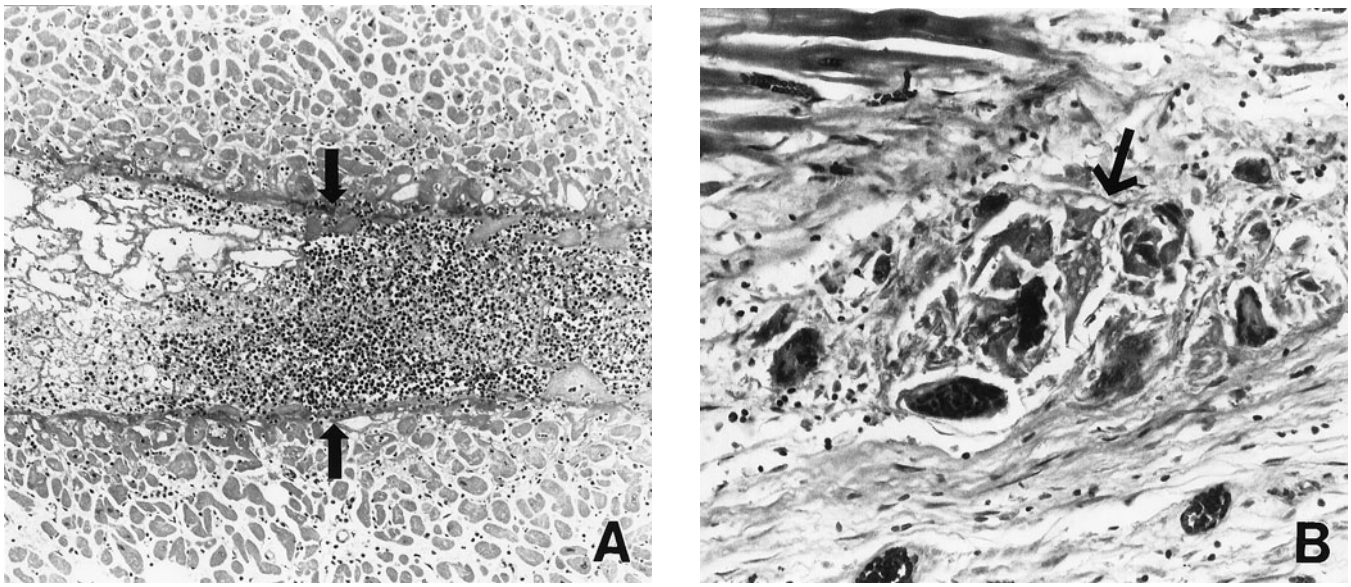


Figure 5-16. Myocardial changes following transmyocardial laser revascularization. (A) Transmyocardial channel (between arrows) filled with fibrin and inflammatory cells from the patient, who died 3 days following the procedure. (B) Transmyocardial channel filled with organizing fibrin (arrow) in a patient who died 18 days following the procedure. No patent channels were noted in either case. Hematoxylin and eosin 150x.

lysed before the progressive myocardial necrosis becomes transmural. In both transmural and subendocardial infarcts, a 1- to 2-mm rim of subendocardium may survive due to diffusion of oxygen and nutrients from the blood in the ventricular cavity.

The short-term mortality rate from AMI has declined from 30% in the 1960s to 7 to 10% or less today, especially for patients who receive aggressive reperfusion, revascularization, and pharmacologic therapy. However, half of all deaths from MI occur within the first hour after the onset of symptoms, often before the individual can reach the hospital. Poor prognostic factors include advanced age, female gender, diabetes mellitus, and a previous MI. The most important factors in long-term prognosis are LVF and the extent of obstructive lesions in vessels perfusing viable myocardium.

Important and frequent complications of MI include ventricular dysfunction, cardiogenic shock, arrhythmias, myocardial rupture, infarct extension and expansion, papillary muscle dysfunction, right ventricular involvement, ventricular aneurysm, pericarditis, and systemic arterial embolism. About one-half of patients with MI will experience one or more of these complications, with outcome dependent on infarct size, location, and transmurality. Patients with anterior infarcts are at greatest risk for regional dilation and mural thrombi and have a substantially worse clinical course than those with inferior-posterior infarcts. In contrast, inferior-posterior infarcts are more likely to have serious conduction blocks and right ventricular involvement. Mechanical complications are more frequent and significant in patients with transmural lesions.

Although many patients have cardiac rhythm abnormalities following MI, the conduction system is involved in only a minority, and heart block following MI usually is transient. These abnormalities require aggressive treatment when they impair hemodynamics, compromise myocardial viability by increasing oxygen requirements, or predispose to malignant ventricular tachycardia or fibrillation. Tachyarrhythmias usually originate in areas of severely ischemic or necrotic myocardium. The proposed mechanisms include the presence of electrically unstable ischemic myocardium, often at the edge of an infarct, causing a micro-reentry phenomenon, and the release of arrhythmogenic metabolites such as lactic acid and potassium from necrotic tissue. Autopsy studies of sudden death victims and clinical studies of resuscitated survivors show that only a minority of patients with ischemia-induced malignant ventricular arrhythmias develop a full-blown AMI. Thus, ischemia caused by severe chronic coronary arterial stenosis can lead directly to lethal arrhythmias owing to myocardial irritability. Tachyarrhythmias that develop long after infarction likely originate at the junction between scar tissue and viable myocardium.

Myocardial infarcts produce functional abnormalities approximately proportional to their size. Large infarcts have a higher probability of cardiogenic shock and congestive heart failure (CHF). Nonfunctional scar tissue resulting from previous infarcts and areas of stunned or hibernating myocardium may also contribute to overall ventricular dysfunction. Cardiogenic shock following MI is generally indicative of a large infarct (often >40% of the left ventricle). The high mortality of myocardial dysfunction and cardiogenic

shock has been alleviated somewhat in recent years by the use of intra-aortic balloon pumps (IABPs) and ventricular assist devices to bridge patients through phases of prolonged but reversible functional abnormalities after MI.

Frequently catastrophic, cardiac rupture syndromes comprise three entities: (1) rupture of the ventricular free wall (most common), usually with hemopericardium and cardiac tamponade; (2) rupture of the ventricular septum (less common), leading to an acquired ventricular septal defect (VSD) with a left-to-right shunt; and (3) papillary muscle rupture (least common), resulting in the acute onset of severe mitral regurgitation (MR). Cardiac rupture is the cause of death in 8 to 10% of patients with fatal acute transmural myocardial infarcts. Ruptures tend to occur relatively early following infarction (mean interval of 4 to 5 days; range, 1 to 10 days) with as many as 25% presenting within 24 hours of MI. Free-wall and septal ruptures almost always involve transmural infarcts. Although the lateral wall is the least common site for left ventricular infarction, it is the most common site for postinfarction free-wall rupture. Acute free-wall ruptures usually are rapidly fatal; repair is rarely possible.[130]

A fortuitously located pericardial adhesion that arrests the rapidly moving blood front and aborts a rupture may result in the formation of a false aneurysm, defined as a contained rupture with a hematoma communicating with the ventricular cavity.[131] False aneurysms contain no myocardial elements in their walls, consisting only of epicardium and adherent parietal pericardium and thrombus; one-half eventually rupture.

Acute VSDs secondary to postinfarction septal rupture complicate 1 to 2% of infarcts. Infarct-related septal defects are of two types: (1) single or multiple sharply localized, jagged, linear passageways that connect the ventricular chambers (simple type), usually involving the anteroapical aspect of the septum; and (2) defects that tunnel serpiginously through the septum to a somewhat distant opening on the right side (complex type), usually involving the basal inferoseptal wall.[132] In simple lesions, neither gross hemorrhage nor peripheral laceration is present. In complex lesions, the tract may extend into regions remote from the site of the infarct. Without surgery, the prognosis following infarct-related septal rupture is poor.

Mitral regurgitation secondary to papillary muscle rupture in either subendocardial or transmural MI reflects loss of the structural or functional integrity of the mitral valve apparatus. Mitral regurgitation in this setting has an acute onset, and its severity varies depending on the location and extent of papillary muscle disruption. If only part of a papillary muscle group is involved, the degree of regurgitation will be less severe than if the entire muscle group ruptures. Since chordae tendineae arise from the heads of the papillary muscles and provide continuity with each of the valve leaflets, interference with the structure or function of either papillary muscle can result in dysfunction of both mitral valve leaflets.

Papillary muscles are particularly vulnerable to ischemic injury. Since the collateral circulation of the posterior myocardium is not as extensive as it is in the anterolateral segments, the posterior medial papillary muscle is more susceptible to widespread necrosis and is more commonly (85%) the site of rupture. Papillary muscle rupture tends to occur later than other rupture syndromes (as late as 1 month after MI).

Other mechanisms can produce MR in the setting of chronic ischemic heart disease. These are discussed later in this chapter in the section on valvular heart disease.

Isolated right ventricular infarction is rare. However, involvement of the right ventricle by extension of an inferoseptal infarct occurs in approximately 10% of transmural infarcts and can have important functional consequences, including right ventricular failure with or without tricuspid regurgitation and arrhythmias.[133]

Infarct *extension* is characterized by new or recurrent necrosis in the same distribution as a completed recent infarct; this increases the amount of necrotic myocardium. Extension most often occurs between 2 and 10 days after the original infarction, forms along the lateral and subepicardial borders, and histologically appears younger than the necrotic myocardium of the original infarct.

In contrast, infarct *expansion* is a disproportionate thinning and dilation of the infarcted region occurring through a combination of (1) slippage between muscle bundles, reducing the number of myocytes across the infarct wall; (2) disruption of the normal myocardial cells; and (3) tissue loss within the necrotic zone.[134] This acute change in the architecture of the left ventricle does not in itself lead to additional necrotic myocardium. However, regional dilation contributes to a significant increase in ventricular volume, increasing the wall stress and workload of noninfarcted myocardium and predisposing to late aneurysm formation. In addition, expansion predisposes to intracardiac mural thrombus formation via myocardial contractility abnormalities, causing stasis and endocardial damage, which causes thrombogenicity. Patients with infarct expansion, which can be detected by echocardiography in 30% of transmural infarcts, have increased morbidity and mortality.

Healing myocardial infarcts have complex structure and mechanisms.[135] Following MI, structural changes occur both in the necrotic zone and in uninvolved areas of the heart (*ventricular remodeling*), which occur by a combination of left ventricular dilation, wall thinning by infarct expansion, compensatory hypertrophy of noninfarcted myocardium, and potentially late aneurysm formation.[136] Ventricular remodeling begins at the time of acute infarction and probably continues for months to years, until either a stable hemodynamic state is achieved or progressively severe cardiac decompensation occurs. Compensatory hypertrophy of noninfarcted myocardium is initially hemodynamically beneficial, but late decreases in ventricular performance with depression of regional and global contractile function may reflect degenerative

changes. Congestive heart failure secondary to CAD occurs when the overall function of nonscarred myocardium (outside the infarct zone) can no longer maintain an adequate cardiac output. Moreover, regions of hyperfunctioning residual myocardium are particularly vulnerable to additional ischemic episodes.

Ventricular aneurysms paradoxically bulge during ventricular systole and most commonly result from a large transmural infarct that undergoes expansion and heals as scar tissue.[137] Even though their walls are frequently as thin as 1 mm, true ventricular aneurysms rarely rupture because of their tough fibrous or fibrocalcific nature. Markedly hypertrophied myocardial remnants as well as necrotic but inadequately healed (i.e., mummified) myocardium often are present in aneurysm walls, indicating incomplete healing of an infarct. Although 50% of patients with chronic fibrous aneurysms have mural thrombus contained within the ventricle, systemic embolization occurs in only approximately 5% of cases. Some pharmacologic approaches to limiting infarct size, such as steroids and other anti-inflammatory agents, could exacerbate infarct expansion and aneurysm formation.

VALVULAR HEART DISEASE

Normal valve function requires structural integrity and coordinated interactions among multiple anatomic components. For the atrioventricular valves (mitral and tricuspid), these elements include leaflets, commissures, annulus, chordae tendineae (tendinous cords), papillary muscles, and the atrial and ventricular myocardium. For the semilunar valves (aortic and pulmonary), the key structures are the cusps, commissures, and their respective supporting structures in the aortic and pulmonary roots.

Structure-Function Correlations in Normal Valves

The anatomy of the mitral and aortic valves is illustrated in Fig. 5-17.

Mitral valve

Of the two leaflets of the mitral valve (see Fig. 5-17A), the anterior (also called septal, or aortic) leaflet is roughly triangular and deep, with the base inserting on approximately one-third of the annulus. The posterior (also called mural, or ventricular) leaflet, although more shallow, is attached to about two-thirds of the annulus and typically has a scalloped appearance. The mitral leaflets have a combined area approximately twice that of the annulus; they meet during systole with apposition to approximately 50% of the depth of the posterior leaflet and 30% that of the anterior leaflet. Each leaflet receives chordae tendineae from both anterior and posterior papillary muscles.

The mitral valve orifice is D-shaped, with the flat anteromedial portion comprising the attachment of the anterior mitral leaflet in the subaortic region. This part of the annulus is fibrous and noncontractile; the posterolateral portion of the annulus is muscular and contracts during systole to asymmetrically reduce the area of the orifice. The edges of the mitral leaflets are held in or below the plane of the orifice by the chordae tendineae, which themselves are pulled from below by the contracting papillary muscles during systole. This serves to draw the leaflets to closure and maintain competence. The orifice of the tricuspid valve is larger and less distinct than that of the mitral valve; its three leaflets (anterior, posterior, and septal) are larger and thinner than those of the mitral valve.

Aortic valve

The three aortic valve cusps (left, right, and noncoronary) attach to the aortic wall in a semilunar fashion, ascending to the commissures and descending to the base of each cusp (see Fig. 5-17B). Commissures are spaced approximately 120° apart and occupy the three points of the annular crown, representing the site of separation between adjacent cusps. Behind the valve cusps are dilated pockets of aortic root, called the sinuses of Valsalva. The right and left coronary arteries arise from individual orifices behind the right and left cusps, respectively. At the midpoint of the free edge of each cusp is a fibrous nodule called the nodule of Arantius. A thin, crescent-shaped portion of the cusp on either side of the nodule, termed the lunula, defines the surface of apposition of the cusps when the valve is closed (approximately 40% of the cuspal area). Fenestrations (holes) near the free edges commonly occur as a developmental or degenerative abnormality, are generally small (less than 2 mm in diameter), and have no functional significance, since the lunular tissue does not contribute to separating aortic from ventricular blood during diastole. In contrast, defects in the portion of the cusp below the lunula are associated with functional incompetence; such holes also suggest previous or active infection. When the aortic valve is closed during diastole, there is a back pressure on the cusps of approximately 80 mm Hg. The pulmonary valve cusps and surrounding tissues have architectural similarity to but are more delicate than those of the corresponding aortic components, and lack coronary arterial origins.

Valve histology

All cardiac valves essentially have the same microscopically inhomogeneous architecture, consisting of well-defined tissue layers covered by endothelium. Using the aortic valve as an example (see Fig. 5-17C), the *ventricularis* faces the left ventricular chamber, and is comprised predominantly of collagenous fibers with radially aligned elastic fibers. The rich elastin of the ventricularis enables the cusps to have minimal surface area when the valve is open, but stretch during diastole to form a large coaptation area. The *spongiosa* is centrally located and is composed of loosely arranged collagen and abundant proteoglycans. This layer has negligible structural strength, but accommodates relative movement

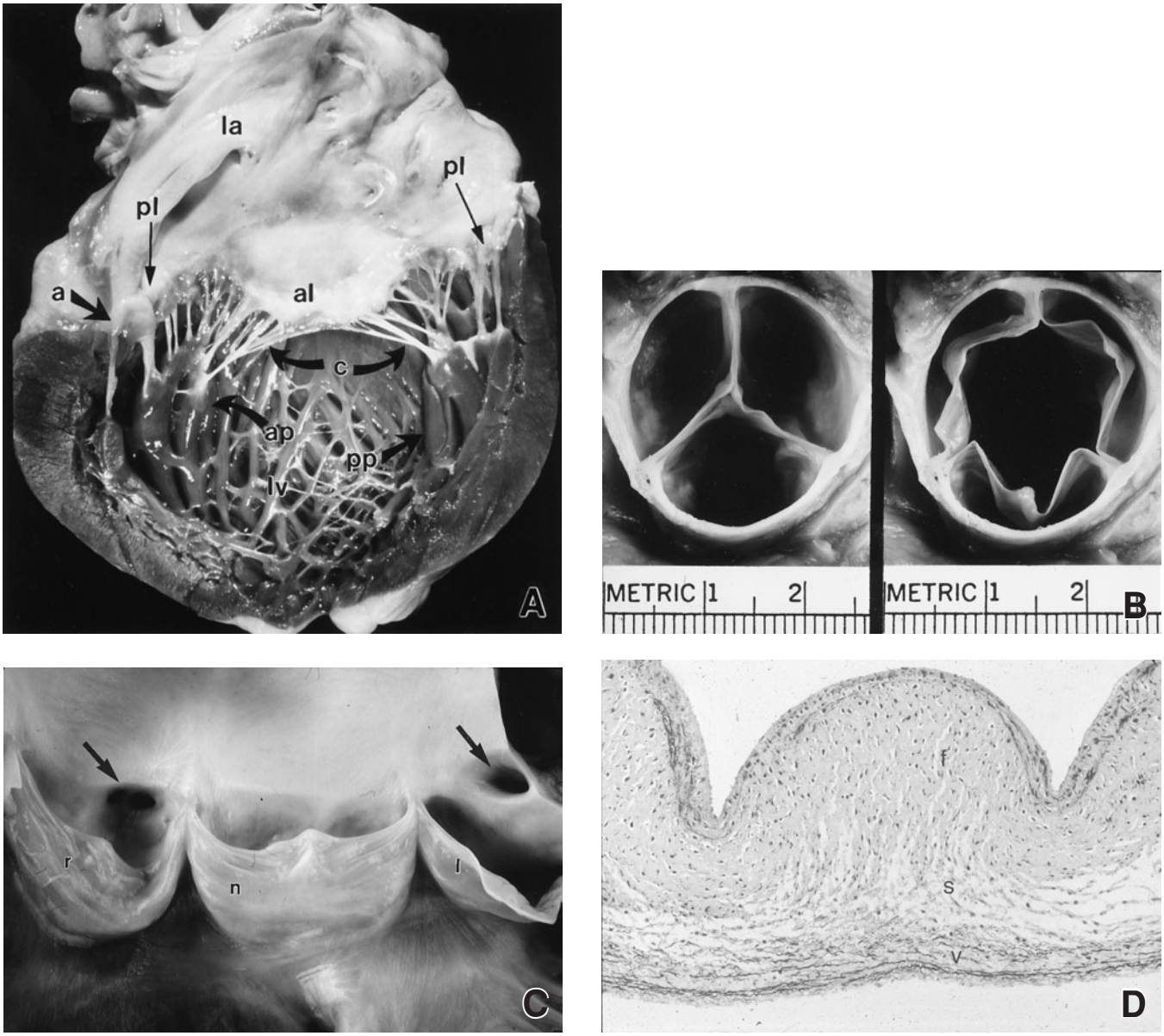


Figure 5-17. Normal mitral and aortic valves. (A) An opened left ventricle of the normal heart reveals the various components of the mitral apparatus. al = anterior leaflet; pl = posterior leaflet; a = annulus; c = chordae tendineae; ap = anterior papillary muscle; pp = posterior papillary muscle; la = left atrium; lv = left ventricle. (B) Aortic valve viewed from the distal aspect in closed (left) and open (right) phases. The closed cusps are closely opposed during ventricular diastole and open against the aortic wall during systole. (C) Aortic valve, opened anteriorly to reveal the relationships of the anterior mitral leaflet (lower right) to the aortic valve cusps (lrn = left/right/noncoronary cusps, respectively) and coronary arterial orifices (arrows). (D) Normal aortic valve histology, demonstrating layered structure, including the fibrosa (f), spongiosa (s), and ventricularis (v). The inflow surface is at bottom. Verhoeff van Giesen elastic tissue stain 150x. (*A: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989. B, C, and D: Reproduced with permission from Schoen and Edwards.*[185])

between layers during the cardiac cycle, and absorbs shock during closure. The *fibrosa* is a thick fibrous layer that provides structural integrity and mechanical stability and is composed predominantly of circumferentially aligned, densely packed collagen fibers, largely arranged parallel to the cuspal free edge. Normal human aortic and pulmonary valve cusps have few blood vessels; they are sufficiently thin to be perfused from the surrounding blood. In contrast, the mitral and tricuspid leaflets contain a few capillaries in their most basal thirds.

During diastole, adjacent cusps coapt with a substantial area of surface-to-surface contact. This involves,

for example, nearly one-third of the atrioventricular valve leaflets. Thus, normal cusp and leaflet areas are substantially greater than are needed to simply close the valve orifice.

The orientation of connective tissue and other architectural elements is nonrandom in the plane of the cusp, yielding greater compliance in the radial than circumferential direction (anisotropic behavior). With specializations that include crimp of collagen fibers along their length, bundles of collagen in the fibrous layer oriented toward commissures, and grossly visible corrugations, cusps are extremely soft and pliable when unloaded, but taut and stiff during the closed phase. Moreover, the fibrous network within the cusps effectively transfers the stresses of the closed phase to the annulus and aortic wall. This minimizes sagging of the cusp centers, preserves maximum coaptation, and prevents regurgitation. For the mitral valve, the subvalvular apparatus including tendinous cords and papillary muscles is the critical mechanism of valve competency.

Cell Biology of Cardiac Valves

Recent studies have enhanced our understanding of how valves form embryologically, mature in the fetus, and function, adapt, maintain homeostasis, and change throughout life. These essential relationships facilitate an understanding of valve pathology and mechanisms of disease, foster the development of improved tissue heart valve substitutes, and inform innovative approaches to heart valve repair and regeneration.[138,139]

During normal development of the heart, the heart tube undergoes looping, following which the valve cusps/leaflets originate from mesenchymal outgrowths known as endocardial cushions.[140,141] A subset of endothelial cells in the cushion-forming area, driven by signals from the underlying myocardium, change their phenotype to mesenchymal cells and migrate into the acellular extracellular matrix called cardiac jelly to form the endocardial cushions. Likely regulated by transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF), the activated endothelial cells lose cell-cell contacts and invade the cardiac jelly. This transformation of endocardial cells to mesenchymal cells and migration away from the endothelial layer is termed transdifferentiation or endothelial-to-mesenchymal transformation.

Two types of cells are present in the fully-formed aortic valve: endothelial cells located superficially and interstitial cells located deep to the surface. Aortic valve endothelial cells have a different phenotype than those in the aorta,[142,143] and different transcriptional profiles are expressed by the endothelium on the aortic side versus ventricular side of normal adult pig aortic valves.[144] The implications of these differences are not yet known.

The second cell type comprises the valvular interstitial cells (VICs). VICs have variable properties of fibroblasts, smooth muscle cells, and myofibroblasts. Valvular extracellular matrix (ECM) is produced and maintained by VICs, and its quality is the overwhelming determinant of valve durability. To maintain integrity and pliability throughout life, the aortic valve must undergo repetitive physiologic remodeling that entails synthesis, degradation, and reorganization of its ECM, which depends on matrix-degrading enzymes such as matrix metalloproteinases. Although interstitial cells are predominantly fibroblast-like in normal valves, VICs can become activated[145] when valves or their cells are exposed to environmental (i.e., mechanical and chemical) stimulation in vitro and in vivo.[146,147] Activated VICs assume a myofibroblast-like phenotype and mediate connective tissue remodeling. Aortic valves also seem to have contractile properties that are modulated by the VICs,[148] but the relevance of valve contraction to in vivo function is uncertain.

Subsequent to morphogenesis, embryonic fetal valves possess a dynamic structure composed of a nascent ECM and cells with characteristics of myofibroblasts.[149] These changes in cell phenotype and ECM remodeling continue throughout human fetal and postnatal development, and indeed, throughout life. Moreover, ongoing changes in valve cells and ECM lead to changes in properties and potentially function, as evidenced by increasing valve stiffness with increasing age.[150]

Etiology and Pathologic Anatomy of Valvular Heart Disease

Cardiac valve operations usually are undertaken for dysfunction caused by calcification, fibrosis, fusion, retraction, perforation, rupture, stretching, dilation, or congenital malformations of the valve leaflets/cusps or associated structures. Valvular stenosis, defined as inhibition of forward flow secondary to obstruction caused by failure of a valve to open completely, is almost always caused by a primary cuspal abnormality and a chronic disease process. In contrast, valvular insufficiency, defined as reverse flow caused by failure of a valve to close completely, may result from either intrinsic disease of the valve cusps or from damage to or distortion of the supporting structures (e.g., the aorta, mitral annulus, chordae tendineae, papillary muscles, and ventricular free wall) without primary cuspal pathology. Regurgitation may appear either acutely, as with rupture of cords, or chronically, as with leaflet scarring and retraction. Both stenosis and insufficiency can coexist in a single valve, usually with one process predominating. The most commonly encountered morphologies of valvular heart disease are illustrated in Figs. 5-18 and 5-19.

Changing disease patterns and an aging U.S. population have altered the relative frequency of the major causes of valve disease in the late twentieth century. Degenerative (senile) calcific aortic valve disease is the most common cause of aortic stenosis; calcification of congenitally bicuspid aortic valves comprises the second most common cause. Postinflammatory (rheumatic) disease has continued to decline as a cause of aortic valve

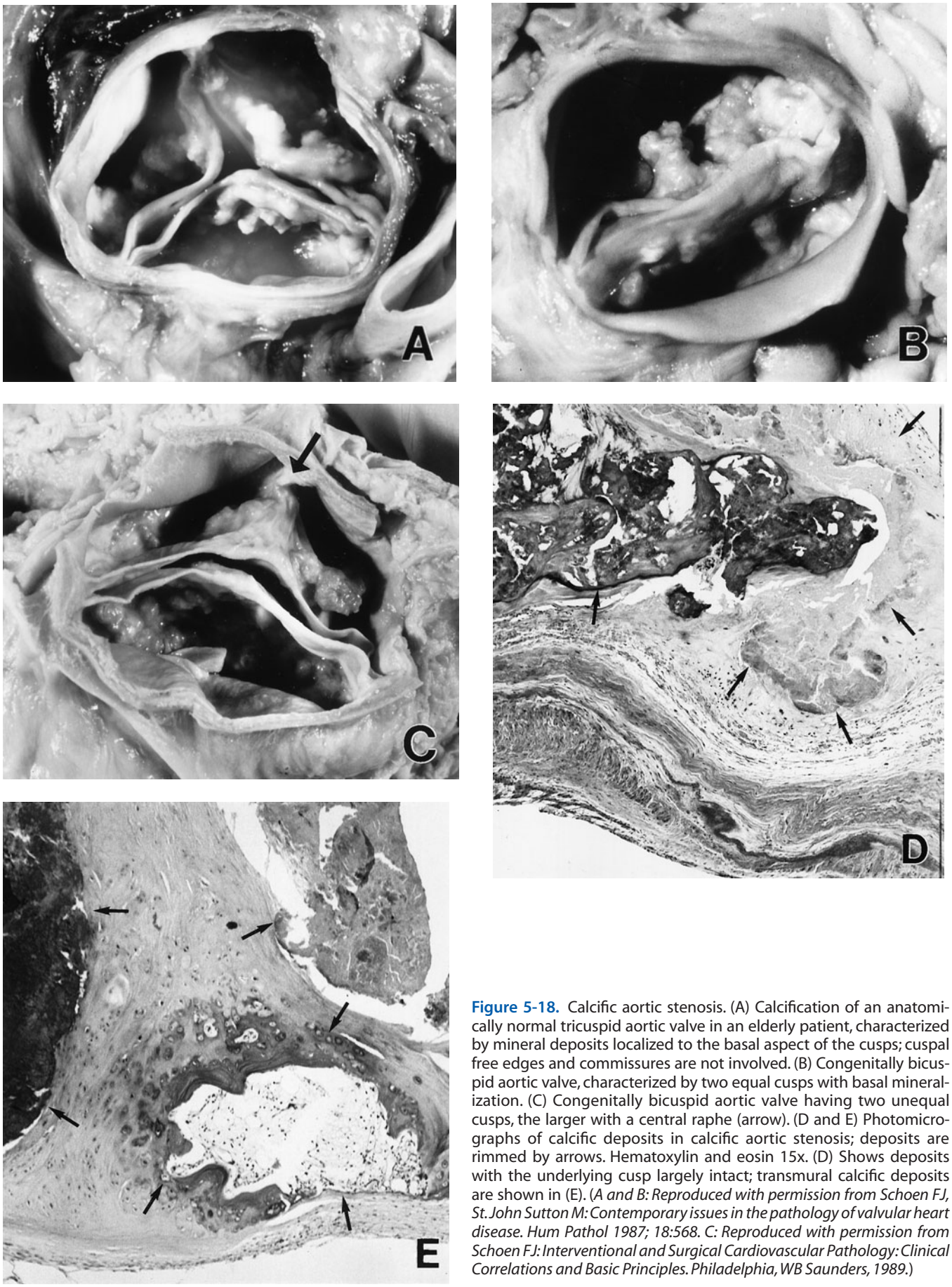


Figure 5-18. Calcific aortic stenosis. (A) Calcification of an anatomically normal tricuspid aortic valve in an elderly patient, characterized by mineral deposits localized to the basal aspect of the cusps; cuspal free edges and commissures are not involved. (B) Congenitally bicuspid aortic valve, characterized by two equal cusps with basal mineralization. (C) Congenitally bicuspid aortic valve having two unequal cusps, the larger with a central raphe (arrow). (D and E) Photomicrographs of calcific deposits in calcific aortic stenosis; deposits are rimmed by arrows. Hematoxylin and eosin 15x. (D) Shows deposits with the underlying cusp largely intact; transmural calcific deposits are shown in (E). (*A and B: Reproduced with permission from Schoen FJ, St. John Sutton M: Contemporary issues in the pathology of valvular heart disease. Hum Pathol 1987; 18:568. C: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

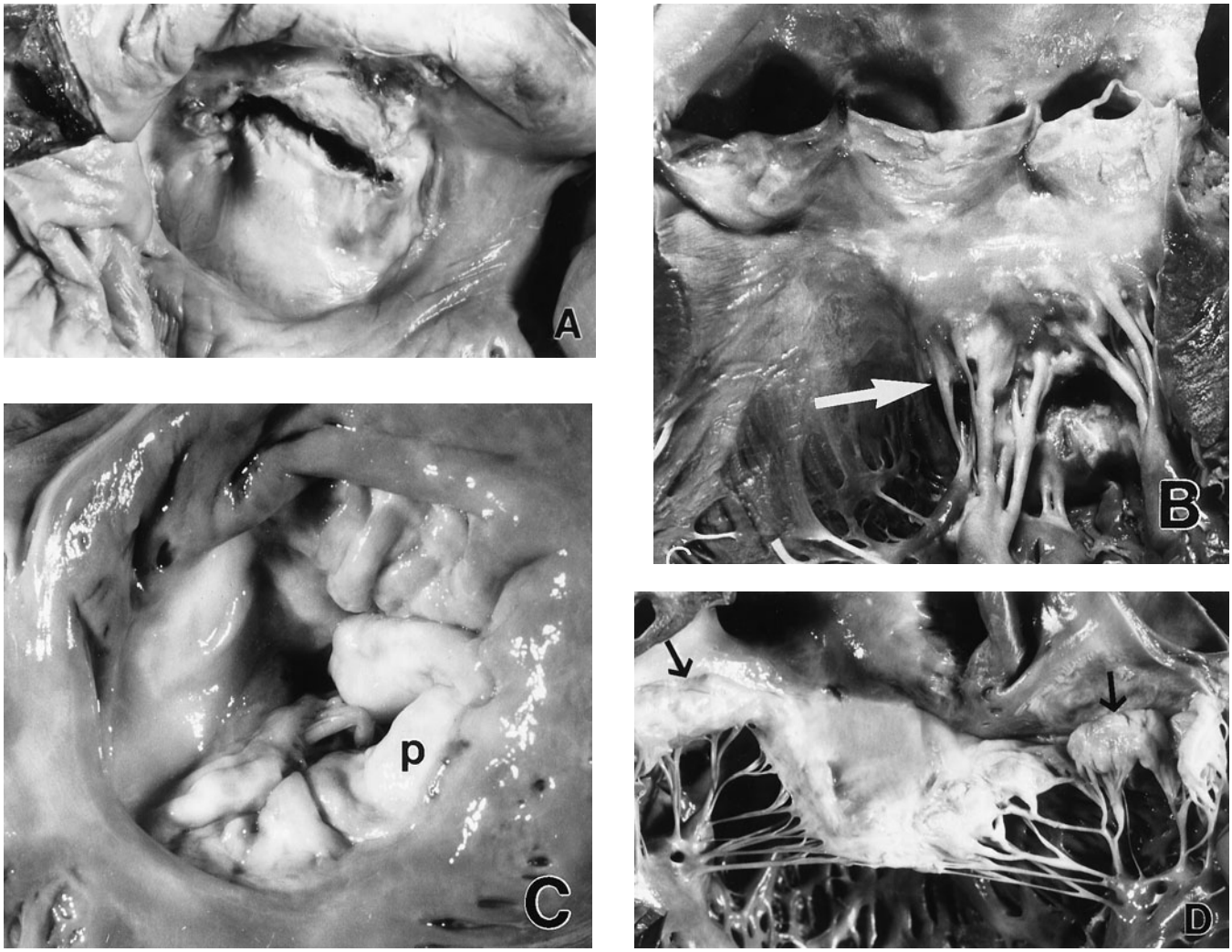


Figure 5-19. Major etiologies of mitral valvular disease. (A) Atrial view, and (B) subvalvular and aortic aspect of a valve from a patient with rheumatic mitral stenosis. There are severe valvular changes, including diffuse leaflet fibrosis and commissural fusion and ulceration of the free edges of the valve, as well as prominent subvalvular involvement with distortion (arrow in [B]). (C and D) Myxomatous degeneration of the mitral valve. In (C) (left atrial view), there is prolapse of a redundant posterior leaflet (p), whereas in (D) from another case, the opened annulus reveals a redundant posterior mitral leaflet (arrows), with thin elongated chordae tendineae. The patient with the valve shown in (D) had chronic mitral regurgitation with prolapse noted clinically, and Marfan syndrome. (*Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

dysfunction. Indeed, the leading cause of chronic aortic insufficiency is aortic root dilation, causing stretching and outward bowing of the commissures and a lack of cuspal coaptation. Over the age of 40, aortic root dilation is most often due to age-related aortic degeneration, or less commonly, aortitis. Under 40 years of age, root dilation occurs most frequently in association with Marfan syndrome, other connective tissue disorders, or operated congenital heart disease. Moreover, whereas postrheumatic deformity remains the leading cause of mitral stenosis, its incidence continues to decline. Moreover, myxomatous mitral valve disease and ischemic MR are the leading causes of pure mitral valve regurgitation; these pathologies are often amenable to and comprise the major indications for mitral valve repair.

Calcific aortic valve stenosis

The most frequent valvular abnormality requiring surgery, acquired aortic stenosis, usually is the consequence of age-related calcium phosphate deposition in either anatomically normal aortic valves or in congenitally bicuspid valves (see Fig. 5-18A).[151,152] With the rising average age of the population, the prevalence of aortic stenosis, estimated at 2%, is increasing. Stenotic, previously normal tricuspid valves come to clinical attention primarily in the eighth to ninth decades of life, while bicuspid valves with

superimposed age-related degenerative calcification generally become symptomatic earlier (usually in the sixth to seventh decades).[153]

Nonrheumatic, calcific aortic stenosis is characterized by heaped-up, calcified masses initiated in the cuspal fibrosa at the points of maximal cusp flexion (the margins of attachment); they protrude distally from the aortic aspect into the sinuses of Valsalva, inhibiting cuspal opening. The dystrophic calcification process generally does not involve the free cuspal edges. In contrast to rheumatic aortic stenosis, appreciable commissural fusion is absent in calcific aortic stenosis and the mitral valve generally is uninvolved. Aortic valve sclerosis comprises a common, earlier, and hemodynamically less significant stage of the calcification process. Nevertheless, aortic sclerosis is associated with an increase of approximately 50% in the risk of death from cardiovascular causes and the risk of MI, even in the absence of hemodynamically significant obstruction of left ventricular outflow.[154]

Aortic stenosis leads to a gradually increasing pressure gradient across the valve, which may reach 75 to 100 mm Hg in severe cases, necessitating a left ventricular pressure of 200 mm Hg or more. Cardiac output is maintained by the development of concentric LVH secondary to pressure overload. The onset of symptoms such as angina, syncope, or heart failure in aortic stenosis heralds the exhaustion of compensatory cardiac hyperfunction, and carries a poor prognosis if not treated by aortic valve replacement (AVR) (approximately 50% mortality within 3 to 5 years).[155] If cardiac output is low, as may occur in heart failure or in the elderly, then neither the gradient nor the resultant murmur may appear significant and aortic stenosis can be missed clinically. Other complications of calcific aortic stenosis include embolization that may occur spontaneously or during interventional procedures, hemolysis, and extension of the calcific deposits into the ventricular septum, causing conduction abnormalities.

The mechanisms of aortic valve calcification are traditionally believed to be degenerative, dystrophic, and passive accumulation of hydroxyapatite mineral in the setting of sclerosis.[156] However, recent studies suggest active regulation of calcification in aortic valves similar to that in the atherosclerotic process in arteries, with inflammation, lipid infiltration, and phenotypic modulation of VICs to an osteoblastic phenotype,[157] and risk factors in common with atherosclerosis. This has stimulated interest in the possibility that statin drugs may decrease the rate of aortic stenosis progression, but studies to date have not supported this contention.[158,159]

Bicuspid aortic valve

With a prevalence of approximately 1%, bicuspid aortic valve (BAV) is the most frequent congenital cardiovascular malformation in humans.[160] Men are affected three to four times more frequently than are women. The two cusps are typically of unequal size, with the larger (conjoined) cusp having a midline raphe, representing an incomplete separation or congenital fusion of two cusps. Less frequently, the cusps are of equal size (see Figs. 5-18B and 5-18C). When a raphe is present, the most commonly fused cusps are the right and left, accounting for about 75% of cases. Neither stenotic nor symptomatic at birth or throughout early life, bicuspid valves are predisposed to accelerated calcification, with about 85% becoming stenotic. About 15% of the time, they become purely incompetent, complicated by infective endocarditis, or associated with acute aortic dissection. Bicuspid aortic valves underlie over two-thirds of aortic stenosis in children and 50% of adults. Aortic abnormalities commonly accompany BAV, even when the valve is hemodynamically normal, and can cause dilation or dissection. Rarely, an uncomplicated bicuspid valve is encountered at autopsy.

Recent studies have confirmed previous reports of familial clustering of BAV and left ventricular outflow tract obstruction malformations, and their association with other cardiovascular malformations.[161,162] The high genetic determination suggests that these common valvular malformations are primary to defective valvulogenesis or secondary to other elements of cardiogenesis. Particularly interesting in this regard is the recent report that mutations in the signaling and transcriptional regulator NOTCH1 caused a spectrum of developmental aortic valve abnormalities and severe calcification in two families with nonsyndromic familial aortic valve disease.[163]

Mitral annular calcification

Degenerative calcific deposits also can develop in the ring (annulus) of the mitral valve of elderly individuals, especially women. Although generally asymptomatic, the calcific nodules may lead to regurgitation by interference with systolic contraction of the mitral valve ring, or very rarely stenosis, by impairing mobility of the mitral leaflets during opening. Occasionally, the calcium deposits may penetrate sufficiently deeply to impinge on the atrioventricular conduction system and produce arrhythmias (and rarely sudden death). Patients with mitral annular calcification have an increased risk of stroke, and the calcific nodules can be the nidus for thrombotic deposits or infective endocarditis.

Rheumatic heart disease

Rheumatic fever is an acute, often recurrent, inflammatory disease that generally follows a pharyngeal infection with group A beta-hemolytic streptococci, principally in children. In the past several decades, rheumatic fever and rheumatic heart disease have declined markedly but not disappeared in the United States and other developed countries. Evidence strongly suggests that rheumatic fever is the result of an immune response to streptococcal antigens, inciting either a cross-reaction to tissue antigens, or a streptococcal-induced autoimmune reaction to normal tissue antigens. The cardiac surgical implications of rheumatic fever primarily relate to chronic rheumatic heart

disease, characterized by chronic, progressive, deforming valvular disease (particularly mitral stenosis) that produces permanent dysfunction and severe, sometimes fatal, cardiac failure decades later.

Chronic rheumatic heart disease most frequently affects the mitral and to a lesser extent the aortic and/or the tricuspid valves. Chronic rheumatic valve disease is characterized by fibrous or fibrocalcific distortion of leaflets or cusps, valve commissures, and chordae tendineae, with or without annular or papillary muscle deformities (see Figs. 5-19A and 5-19B). Stenosis results from leaflet and chordal fibrous thickening and from commissural and chordal fusion, with or without secondary calcification. Regurgitation usually results from scarring-induced retraction of chordae and leaflets, and less commonly, fusion of a commissure in an opened position. Combinations of lesions may yield valves that are both stenotic and regurgitant. Although considered the pathognomonic inflammatory myocardial lesions in acute rheumatic fever, Aschoff nodules are found infrequently in myocardium sampled at autopsy or at valve replacement surgery, most likely reflecting the extended interval from acute disease to critical functional impairment.

Myxomatous degeneration of the mitral valve (mitral valve prolapse)

Myxomatous mitral valve disease (mitral valve prolapse) is the most frequent cause of chronic, pure, isolated mitral regurgitation.[164] Over the last decade, due to improved technology and large community studies, a prevalence of mitral valve prolapse (MVP) of 2.4% and a rate of the serious complications, namely heart failure, MR, infective endocarditis, stroke or other manifestations of thromboembolism, progressive CHF, sudden death, or atrial fibrillation of no more than 3% have been ascertained.[165] Mitral valve prolapse is the most common cause for surgical repair or replacement of the mitral valve. In MVP one or both mitral leaflets are enlarged, redundant, or floppy, and will prolapse, or balloon back into the left atrium during ventricular systole (see Fig. 5-19C). The three characteristic anatomic changes in MVP are: (1) interchordal ballooning (hooding) of the mitral leaflets or portions thereof (most frequently involving the posterior leaflet), sometimes accompanied by elongated, thinned, or ruptured cords (see Fig. 5-19D); (2) rubbery, diffuse leaflet thickening that hinders adequate coaptation and interdigitation of leaflet tissue during valve closure; and (3) substantial annular dilation, with diameters and circumferences that may exceed 3.5 and 11.0 cm, respectively.[166] Pathologic mitral annular enlargement is usually confined to the posterior leaflet, since the anterior leaflet is firmly anchored by the fibrous tissue at the aortic valve end and is far less distensible. The key microscopic changes in myxomatous degeneration are attenuation or focal disruption of the fibrous layer (with loss of collagen) of the valve, on which the structural integrity of the leaflet depends, and focal or diffuse thickening of the spongy layer by proteoglycan deposition (which gives the tissue an edematous, blue appearance on microscopy called "myxomatous" by pathologists).[167] These changes weaken the leaflet. Concomitant involvement of the tricuspid valve is present in 20 to 40% of cases, and the aortic and pulmonary valves also may be affected.

Secondary changes may occur, including: (1) focal pad-like fibrous thickening along both surfaces of the valve leaflets; (2) linear thickening of the subjacent mural endocardium of the left ventricle as a consequence of friction-induced injury by chordal hamstringing of the prolapsing leaflets; (3) thrombi on the atrial surfaces of the leaflets, particularly in the recesses behind the ballooned leaflet segments; (4) calcification along the base of the posterior mitral leaflet; and (5) chordal thickening and fusion with some features that resemble postrheumatic disease.

The pathogenesis of myxomatous degeneration is uncertain, but this valvular abnormality is a common feature of Marfan syndrome and occasionally occurs with other hereditary disorders of connective tissues such as Ehlers-Danlos syndrome, suggesting an analogous but localized connective tissue defect.[168] In these heritable disorders of connective tissue including Marfan syndrome, MVP is usually associated with mutations in fibrillin-1, and recent evidence has implicated abnormal TGF-β signaling (similar to the aortic abnormalities in the pathogenesis of Marfan syndrome and related disorders).[169,170] However, it is unlikely that more than 1 to 2% of patients with MVP have an identifiable connective tissue disorder. Nevertheless, studies utilizing genetic linkage analysis have mapped families with autosomal dominant MVP to the X chromosome, chromosomes 11p15.4, 16p11.2–p12.1 and 13q31.3–q32.1. The latter locus is particularly interesting in that there are at least 16 known genes in the region, several of which could be involved in valvular tissue remodeling.

Ischemic mitral regurgitation

There has been renewed interest in ischemic mitral regurgitation (IMR), also called functional mitral regurgitation. In IMR the leaflets are intrinsically normal while myocardial structure and function are altered by ischemia.[171,172] IMR is present in 10 to 20% of patients with CAD and worsens prognosis following MI, with reduced survival directly related to the severity of the regurgitation. These mechanisms include an ischemic papillary muscle that fails to tighten the chordae during systole, and a fibrotic, shortened papillary muscle that fixes the chordae deeply within the ventricle. Nevertheless, papillary muscle dysfunction alone is generally insufficient to produce IMR. The key causal factor is dilation and increasing spherical shape of the left ventricle, which pulls the papillary muscles down and away from the center of the chamber. Although there is substantial interest in developing surgical and/or percutaneous approaches to the repair of MR, none of the strategies developed so far have resulted in clearly improved patient outcomes.[173]

Drug-induced valve disease

Patients with the carcinoid syndrome often develop plaque-like intimal thickenings of the endocardium of the tricuspid valve, right ventricular outflow tract, and pulmonary valve superimposed on otherwise unaltered endocardium.[174] The left side of the heart is usually unaffected. These lesions are related to elaboration by carcinoid tumors of bioactive products, including serotonin, which cause valvular endothelial cell proliferation but are inactivated by passage through the lung.

Left-sided but similar valve lesions, usually causing regurgitation, have been reported to complicate the administration of fenfluramine and phentermine (fen-phen), appetite suppressants used for the treatment of obesity, which may affect systemic serotonin metabolism.[175] Typical diet drug–associated plaques have proliferation of myofibroblast-like cells in a myxoid stroma with variable vascular channels and lymphocytic and deep fibroelastic tissue. Similar left-sided plaques may be found in patients who receive methysergide or ergotamine therapy for migraine headaches; these serotonin analogs are metabolized to serotonin as they pass through the pulmonary vasculature. Moreover, drug-related valve disease has been reported in patients taking pergolide mesylate, an ergot-derived dopamine receptor agonist used to treat Parkinson disease and restless leg syndrome.[176]

Infective endocarditis

Infective endocarditis is characterized by colonization or invasion of the heart valves, mural endocardium, aorta, aneurysmal sacs, or other blood vessels by a microbiologic agent, leading to the formation of friable vegetations laden with organisms.[177] Virtually any type of microbiologic agent can cause infective endocarditis, but most cases are bacterial.

The so-called Duke criteria provide a standardized assessment of patients with suspected infective endocarditis that integrates factors predisposing patients to the development of infective endocarditis, blood-culture evidence of infection, echocardiographic findings, and clinical and laboratory information.[178] The previously important clinical findings of petechiae, subungual hemorrhages, Janeway lesions, Osler nodes, and Roth spots in the eyes (secondary to retinal microemboli) have now become uncommon owing to the shortened clinical course of the disease as a result of antibiotic therapy.

The clinical classification into acute and subacute forms is based on the range of severity of the disease and its tempo, on the virulence of the infecting microorganism, and on the presence of underlying cardiac disease. Acute endocarditis is a destructive infection, often involving a previously normal heart valve, with a highly virulent organism, and leads to death within days to weeks in over 50% of patients. In contrast, in a more indolent lesion often called subacute endocarditis, organisms of low virulence cause infection on previously deformed valves; the infection pursues a protracted course of weeks to months and may be undetected and untreated.

Vegetations in both acute and subacute endocarditis are composed of fibrin, inflammatory cells, and organisms. *Staphylococcus aureus* is the leading cause of acute endocarditis and produces necrotizing, ulcerative, invasive, and highly destructive valvular infections. The subacute form is usually caused by viridans streptococci. Cardiac abnormalities, such as rheumatic heart disease, congenital heart disease (particularly anomalies that have small shunts or tight stenoses creating high-velocity jet streams), myxomatous mitral valves, BAVs, and artificial valves and their sewing rings, predispose to endocarditis. In intravenous drug abusers, left-sided lesions predominate, but right-sided valves are commonly affected; the usual organism is *S. aureus.* In about 5 to 20% of all cases of endocarditis, no organism can be isolated from the blood (culture-negative endocarditis), often because of prior antibiotic therapy.

The complications of endocarditis include valvular insufficiency (or rarely stenosis), abscess of the valve annulus (ring abscess), suppurative pericarditis, and embolization. With appropriate antibiotic therapy, vegetations may undergo healing, with progressive sterilization, organization, fibrosis, and occasionally calcification. Regurgitation generally occurs on the basis of cusp or leaflet perforation, chordal rupture, or fistula formation from a ring abscess into an adjacent cardiac chamber or great vessel. Ring abscesses tend to be associated with virulent organisms, are technically difficult to deal with surgically, and are associated with a relatively high mortality rate.

Valve Reconstruction and Repair

Reconstructive procedures to eliminate mitral insufficiency of various etiologies and to minimize the severity of rheumatic mitral stenosis are now highly effective and commonplace. Reconstructive therapy of selected patients with aortic insufficiency and aortic dilation may also be done occasionally, but repair of aortic stenosis has been notably less successful. The major advantages of repair over replacement relate to the elimination of both prosthesis-related complications and the need for chronic anticoagulation. Other reported advantages include a lower hospital mortality, better long-term function owing to the ability to maintain the continuity of the mitral apparatus, and a lower rate of postoperative endocarditis. Figures 5-20 and 5-21 illustrate the pathologic anatomy of various mitral valve reconstruction procedures, and Fig. 5-22 illustrates aortic valve repairs for aortic stenosis.

Endovascular approaches to valvular heart disease include balloon valvuloplasty, percutaneous placement of a mitral annular constraint device in the coronary sinus, and double-orifice edge-to-edge mitral valve repair without cardiopulmonary bypass for the treatment of mitral regurgitation.[179,180] Percutaneous valve repair is most likely to be used in patients with severe disease deemed inoperable and in patients with early-stage regurgitant lesions in whom valve repair may

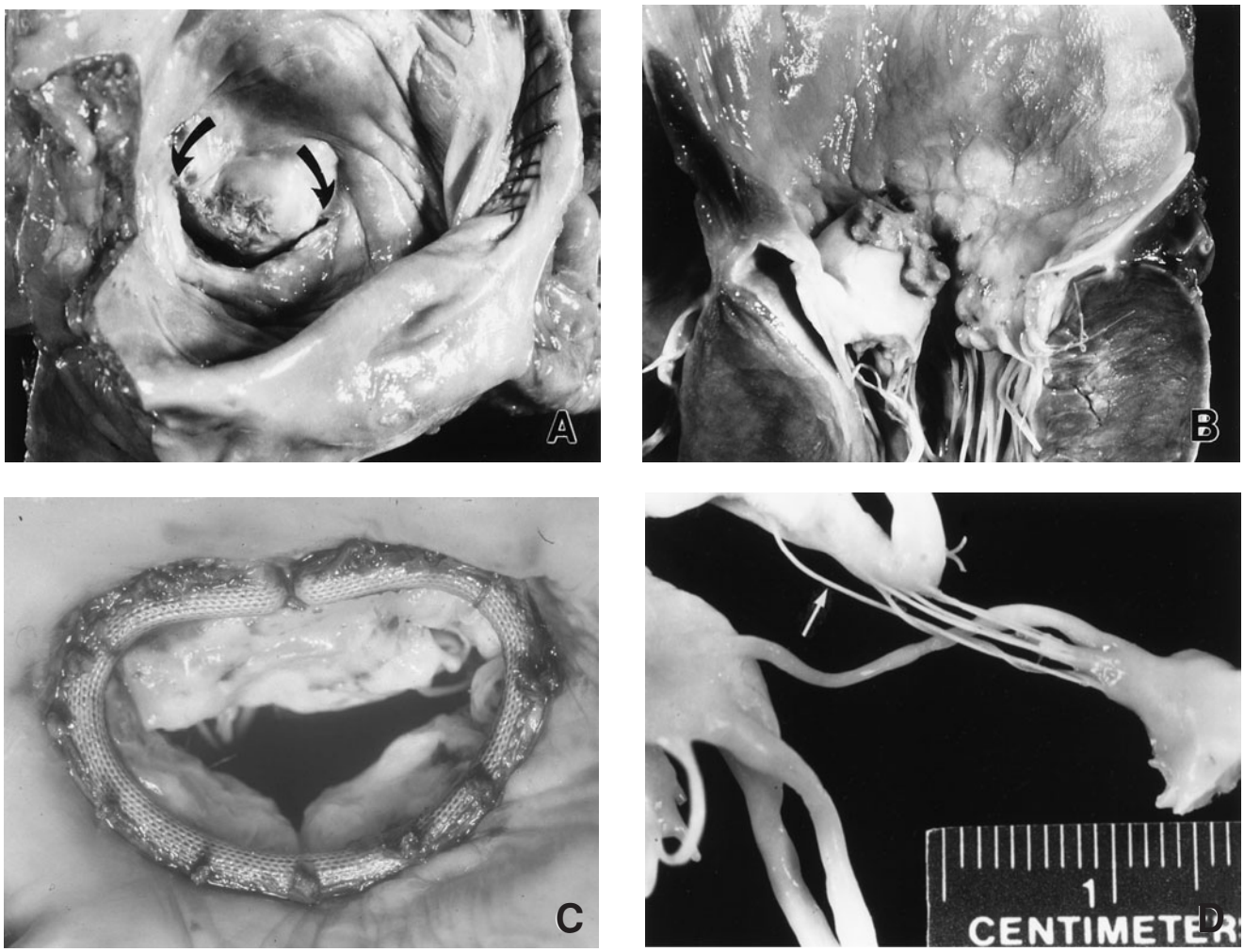


Figure 5-20. Surgical reconstructive procedures for mitral valve disease. (A) Open mitral commissurotomy for mitral stenosis. Incised commissures are indicated by arrows. (B) Mitral valve repair with partial leaflet excision. (C) Mitral valve repair with annuloplasty ring. (D) ePTFE suture replacement (arrow) of ruptured cord in myxomatous mitral valve. (*A: Reproduced with permission from Schoen FJ, St. John Sutton M: Contemporary issues in the pathology of valvular heart disease. Hum Pathol 1987; 18:568. D: Reproduced with permission from Schoen and Edwards.*[185] *D: Courtesy of William A. Muller, MD, PhD, Cornell Medical School, New York.*)

prevent progressive ventricular dilation. Percutaneous transluminal balloon dilation of stenotic valves has been used successfully to relieve some congenital and acquired stenoses of native pulmonary, aortic, and mitral valves, and stenotic right-sided porcine bioprosthetic valves.[181,182]

Mitral stenosis

Commissurotomy may be employed in the operative repair of some stenotic mitral valves in which fibrosis and shortening of both chordae and leaflets have markedly decreased leaflet mobility and area. Since the annular portions of the leaflet are normally devoid of chordal support, splitting them to a point 2 to 3 mm from the annulus may avoid the potential complication of a new or residual regurgitant jet. Anterior leaflet mobility often is sufficient to allow an acceptable mitral opening despite posterior leaflet immobility. Five factors compromise the late functional results of mitral commissurotomy: (1) left ventricular dysfunction; (2) pulmonary venous hypertension and right-sided cardiac factors, including right ventricular failure, tricuspid regurgitation, or a combination of these; (3) systemic embolization; (4) other coexistent cardiac disorders, such as coronary artery or aortic valve diseases; and (5) residual or progressive mitral valve disease, including valve restenosis, residual (unrelieved) stenosis, or regurgitation induced at operation. Progressive degrees of leaflet (especially commissural) calcification, subvalvular (predominantly chordal) fibrotic changes, and significant regurgitation owing to retraction may limit the ability to perform reconstructive surgical repair, and thereby necessitate valve replacement.

Percutaneous balloon mitral valvuloplasty has been used to treat mitral stenosis for over two decades, with

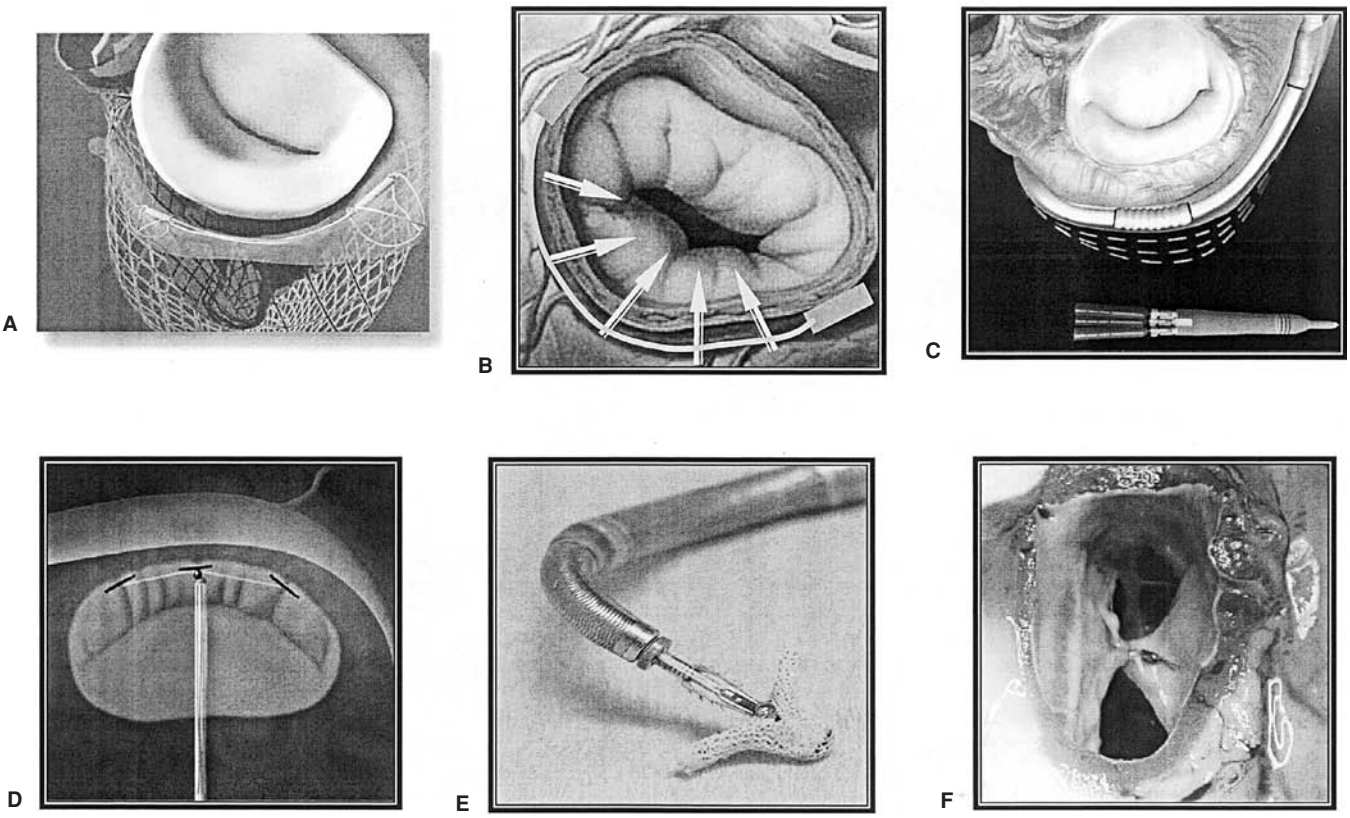


Figure 5-21. Percutaneous correction of mitral regurgitation. The Cardiac Dimensions Carillon (A), the Edwards Viking (B), and the Viacor device (C) all utilize the proximity of the coronary sinus to the posterior mitral annulus to effect a simulated annuloplasty. Other devices such as Mitralign (D) perform direct mitral annuloplasty using a percutaneous approach to the ventricular aspect of the annulus. Edge-to-edge approximation of the A2 and P2 portions of the mitral valve is achieved by either deployment of an eValve clip (E) or direct suture (Edwards Milano II, F). (*Reproduced with permission from Davidson and White.*[180])

excellent success in patients with suitable valvular and subvalvular morphology. However, since balloon valvuloplasty largely involves commissural separation, this procedure is unlikely to provide significant alteration in the subvalvular pathology of the chordae and papillary muscles of patients with rheumatic mitral stenosis.

Mitral regurgitation

Reconstructive techniques are widely used to repair mitral valves with nonrheumatic MR. Structural defects primarily responsible for MR include: (1) dilation of the mitral annulus; (2) leaflet redundancy and prolapse into the left atrium with or without elongation or rupture of chordae tendineae; (3) leaflet perforations or defects; (4) leaflet retraction; (5) chordal rupture or shortening; or (6) dilation of the left ventricle. The posterior leaflet is more delicate, has a shorter annulus-to-free-edge dimension than the anterior leaflet, and is therefore more prone to postinflammatory fibrous retraction.

Following surgical resection of excess anterior or posterior leaflet tissue in valves with redundancy, annuloplasty with or without a prosthetic ring is used to reduce the annulus dimension to correspond to the amount of leaflet tissue available. Edge-to-edge (Alfieri stitch) mitral valve repair has also been used.[183] Tissue substitutes such as glutaraldehyde-pretreated xenograft or autologous pericardium can be used to repair or enlarge leaflets. Ruptured or elongated chordae may be repaired by shortening or replacement with pericardial tissue or thick suture material.

Percutaneous approaches currently being evaluated for MR attempt to emulate one or more of the components of surgical mitral valve repair, including annular reduction and edge-to-edge mitral leaflet apposition (see Fig. 5-21). However, leaflet resection and chordal modification cannot be easily done via catheter. Percutaneous approaches in various stages of development and clinical evaluation include implantation of a device in the coronary sinus, left atrium (or both), or by device placement behind the posterolateral leaflet of the mitral valve, and at least three devices employing these concepts are in clinical trials. The goal is to plicate or straighten the posterior mitral annulus. A major challenge of coronary sinus approaches relates to anatomic variability of the coronary sinus.[184] Additional annuloplasty approaches presently in preclinical testing include a suture annuloplasty from the ventricular side of the mitral annulus,

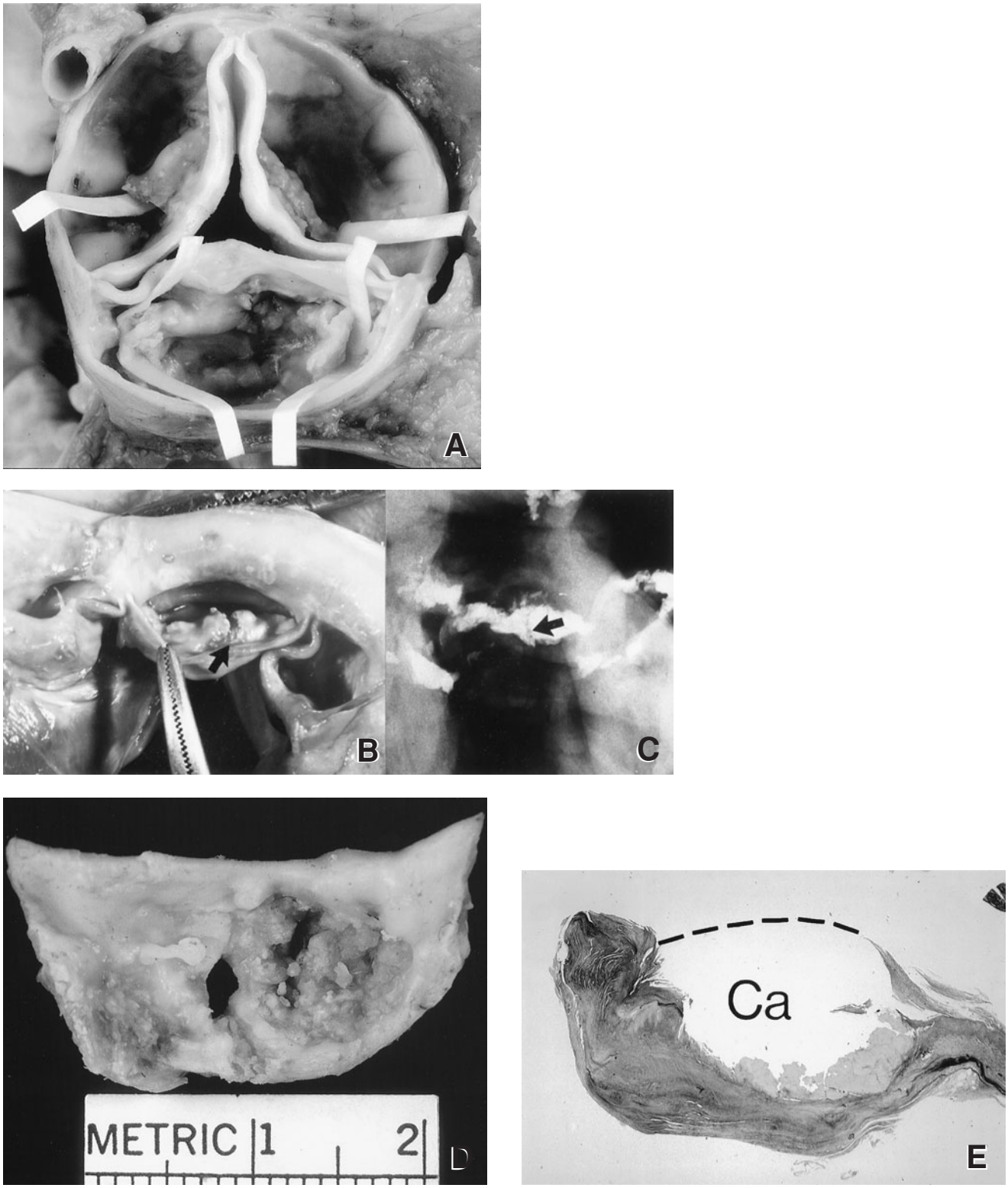


Figure 5-22. Reconstructive procedures for aortic stenosis. (A) Aortic valve balloon valvuloplasty for degenerative calcific aortic stenosis, demonstrating fractures of nodular deposits of calcifications highlighted by tapes. (B and C) Catheter balloon valvuloplasty–induced fracture of large calcific nodule of noncoronary cusp of aortic valve with calcific stenosis. This patient died during the procedure, owing to wide-open aortic insufficiency with inability of the cusp to close because of slight malposition of the edges of the calcific nodule with impingement of its fracture fascicles. (B) Gross photograph; (C) Specimen radiograph. Fracture site of nodular calcific deposit is demonstrated by arrows in (B) and (C). (D and E) Operative decalcification of the aortic valve. (D) Aortic valve after operative mechanical decalcification demonstrating perforated cusp. (E) Histologic cross section of aortic valve cusp after decalcification with lithotripter. Weigert elastic stain. Ca = calcium. (*A, D, and E: Reproduced with permission from Schoen and Edwards.*[185] *B and C: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

thermal modification of the annulus to obtain shrinkage, and a percutaneous ventricular restraint system that attempts to reshape the left ventricle. Another approach uses an edge-to-edge clip prosthesis emulating the edge-to-edge surgical (Alfieri stitch) repair in which the midportions of the anterior and posterior mitral leaflets are clipped together.

Aortic stenosis

Since valvular aortic stenosis in most patients over 60 years of age is characterized by calcific deposits superimposed upon a valve largely free of either congenital or rheumatic deformities, the leaflets are immobilized by extensive deposits of calcium. However, because the calcific deposits arise deep in the valve fibrous layer (see Fig. 5-18D and E), their removal by sharp dissection or ultrasonic débridement generally removes the fibrosa and may cause damage to the spongiosa and ventricularis, resulting in severe compromise of cuspal mechanical integrity (see Fig. 5-22D and E).[185]

In balloon dilation of acquired calcific aortic stenosis, individual functional responses vary considerably and data suggest a modest incremental benefit, high early mortality, and high restenosis rate.[186] The major complications of balloon valvuloplasty include cerebrovascular accident secondary to embolism, massive regurgitation owing to valve trauma, cardiac perforation with tamponade, and with mitral valvuloplasty, creation of an atrial septal defect owing to septal dilation.

Improvement following catheter balloon valvuloplasty of aortic stenosis derives from commissural separation, fracture of calcific deposits, and displacing and stretching of the valve cusps (see Fig. 5-22A). Fractured calcific nodules can themselves prove dangerous (see Fig. 5-22B and C).[187] In pediatric cases in which the cusps are generally pliable, cuspal stretching, tearing, or avulsion may also occur.

Valve Replacement

Severe symptomatic valvular heart disease other than pure mitral stenosis or incompetence is most frequently treated by excision of the diseased valve(s) and replacement by a functional substitute. Pathologic considerations in valve replacement have been reviewed.[188]

Five key factors determine the results of valve replacement in an individual patient: (1) technical aspects of the procedure; (2) intraoperative myocardial ischemic injury; (3) irreversible and chronic structural alterations in the heart and lungs secondary to the valvular abnormality; (4) coexistent obstructive CAD; and (5) valve prosthesis reliability and host-tissue interactions.

Valve types and prognostic considerations

Cardiac valvular substitutes are of two generic types, mechanical and biologic tissue (Fig. 5-23 and Table 5-2).[189] Prostheses function passively, responding to pressure and flow changes within the heart. Mechanical valves are usually composed of nonphysiologic biomaterials that employ a rigid, mobile occluder (composed of pyrolytic carbon in contemporary valves) in a metallic cage (cobalt-chrome or titanium alloy) as in the Bjork-Shiley, Hall-Medtronic, or OmniScience valves, or as two carbon hemidisks in a carbon housing (e.g., the St. Jude Medical and CarboMedics CPHV prostheses). Pyrolytic carbon has high strength and fatigue and wear resistance and good thromboresistance.[190] Tissue valves are more anatomically similar to natural valves, compared to mechanical prostheses, and their pseudoanatomic central flow and relative nonthrombogenicity usually obviate chronic anticoagulant therapy in the absence of another indication. Approximately one-half of all valves implanted in the present era are mechanical (mostly bileaflet tilting disk); the remainder are tissue, mostly bioprosthetic as xenografts fabricated from porcine aortic valve or bovine pericardium that have been preserved in a dilute glutaraldehyde solution, and a small percentage of cryopreserved allografts. In the past decade, innovations in tissue valve technologies and design have expanded indications for their use (Fig. 5-24).[191]

Early mortality after elective cardiac valve replacement now is generally in the range of 3 to 5%, with the majority of deaths owing to hemorrhage, pulmonary failure, low cardiac output, and sudden death with or without myocardial necrosis or documented arrhythmias. Early prosthetic valve–associated complications are unusual.[192] Potential complications related to valve insertion include hemorrhagic disruption and dissection of the atrioventricular groove, perforation or entrapment of the left circumflex coronary artery by a suture, and pseudoaneurysm or rupture of the left ventricular free wall.

Improvement in late outcome has derived predominantly from earlier referral of patients for valve replacement, decreased intraoperative myocardial damage, and improved surgical technique and cardiac valve prostheses. Following valve replacement with currently used devices, the probability of 5-year survival is about 80% and of 10-year survival about 70%, dependent on overall functional state, preoperative LVF, left ventricular and left atrial size, and extent and severity of CAD. Preservation of the subvalvular apparatus has also been an important advance in mitral valve replacement.[193]

Valve-related complications

Prosthetic valve–associated pathology becomes an important consideration beyond the early postoperative period. In the few randomized studies of mechanical prosthetic and bioprosthetic valves, approximately 60% or more patients had an important device-related complication within 10 years postoperatively.[194,195] Valve-related complications frequently necessitate reoperation, now accounting for approximately 15% of all valve procedures,

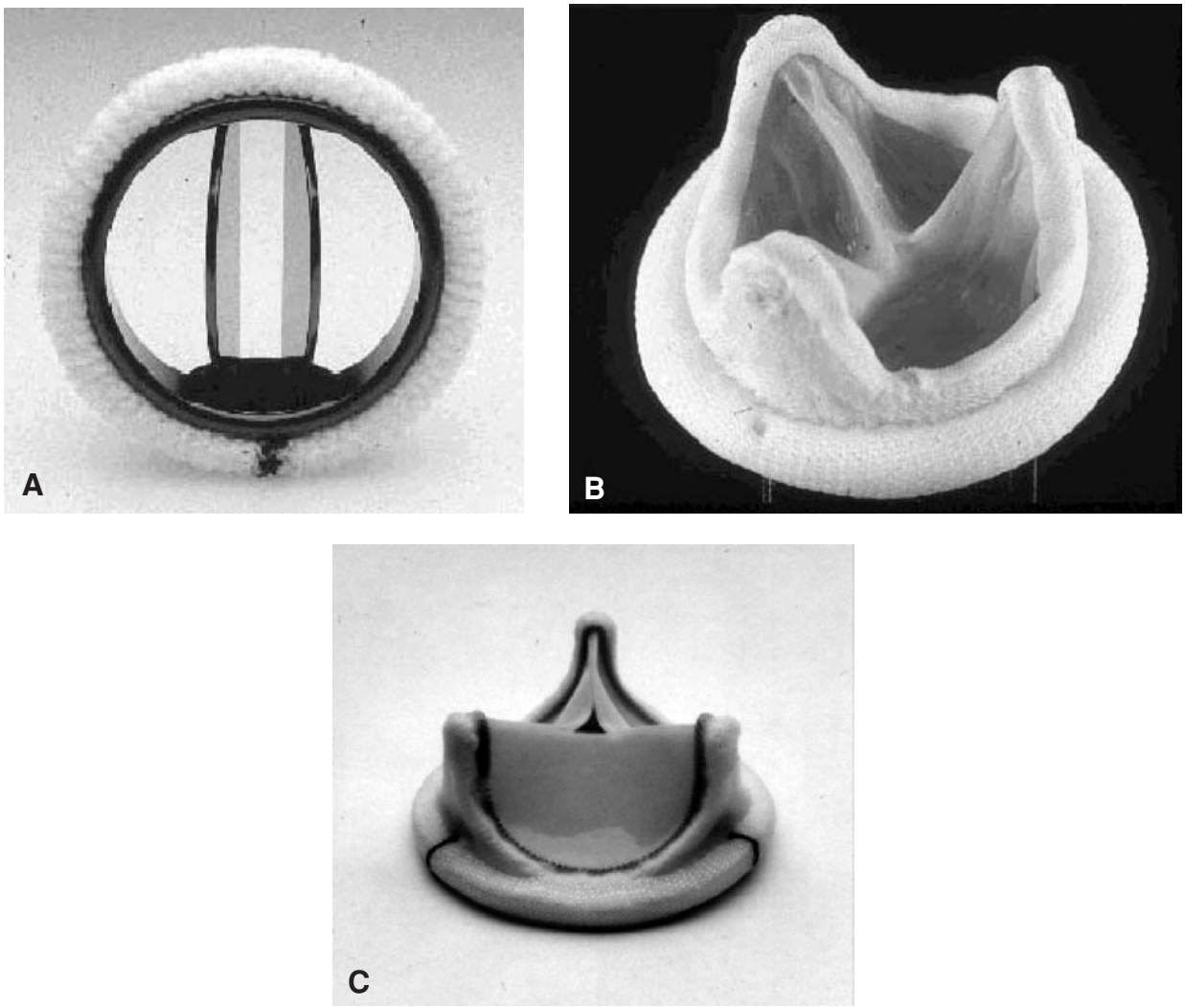


Figure 5-23. Photographs of the widely used generic types of valve substitutes. (A) Bileaflet tilting disk mechanical heart valve (St. Jude Medical, St. Jude Medical Inc., St. Paul, MN). (B) Porcine aortic valve bioprosthesis (Hancock, Medtronic Heart Valves, Santa Ana, CA). (C) Bovine pericardial bioprosthesis (Carpentier-Edwards, Edwards Life Sciences, Santa Ana, CA). (*A and B: Reproduced with permission from Schoen FJ: Approach to the analysis of cardiac valve prostheses as surgical pathology or autopsy specimens. Cardiovasc Pathol 1995; 4:241, and Schoen.*[188])

and they may cause death. Late death following valve replacement results predominantly from either cardiovascular pathology not related to the substitute valve or prosthesis-associated complications. In studies with prior generation valves late death was caused by a device-related complication in 25 to 61% of patients.[196] Autopsy studies generally reveal a higher rate of valve-related pathology than clinical investigations. One-fifth or more of valve recipients will ultimately die suddenly; in one autopsy study, 40% of valve recipients who died suddenly had a valve-related cause.[197]

Four categories of valve-related complications are most important: thromboembolism and related problems, infection, structural dysfunction (i.e., failure or degeneration of the biomaterials comprising a prosthesis), and nonstructural dysfunction (i.e., miscellaneous complications and modes of failure not encompassed by the other groups) (see Table 5-3).[198,199] The clinico-morphologic features of these problems have been widely described in the literature. The relative performance and risk of complications of various types of widely used substitute heart valve types are summarized in Table 5-3. The risk of some valve-related complications (particularly thromboembolism) is potentiated by preoperative or postoperative functional impairment.

THROMBOSIS AND THROMBOEMBOLISM: *Thromboembolic complications* are the major cause of mortality and morbidity after cardiac valve replacement with mechanical valves, and patients with them require chronic therapeutic anticoagulation with warfarin derivatives.[200] Thrombotic deposits can

Table 5–2.

Types and Characteristics of Commonly used Substitute Heart Valves*

Valve type	Model(s)	Hemodynamics	Freedom from thrombosis/ thromboembolism	Durability
Mechanical				
Caged ball	Starr-Edwards	+§	+	+++
Single tilting disk	Bjork-Shiley			
	Hall-Medtronic	++	++	+++†
	Omnicarbon			
Bileaflet tilting disk	St. Jude Medical	+++	+++	+++‡
	Carbomedics			
	Edwards-Duromedics			
Tissue				
Heterograft/xenograft bioprostheses	Carpentier-Edwards (porcine and bovine pericardial)	++	+++	++
	Hancock (porcine)			
	lonescu-Shiley (bovine pericardial)			
	Mitroflow (bovine pericardial)			
Homograft/allograft	Cryopreserved human aortic/pulmonic valve	++++	++++	++

*Presently or previously.
†Except Bjork-Shiley 60°/70° convexo-concave valve (see text).
‡Except Previous model of Edwards-Duromedics valve (see text).
§Performance criteria: + = least favorable to + + + + = most favorable.
Source: Data adapted from Vongpatanasin et al.[189]

immobilize the occluder or shed emboli (Fig. 5-25). Tissue valves are less thrombogenic than mechanical valves, with most patients not requiring long-term anticoagulation unless they have atrial fibrillation or another specific indication. Nevertheless, the rate of thromboembolism in patients with mechanical valves on anticoagulants is not widely different from that in patients with bioprosthetic valves without anticoagulation (2 to 4% per year). The thrombotic and thromboembolic problems that frequently complicate mechanical valves tend to occur earlier than the structural failures that complicate tissue valve prostheses.[201] Chronic oral anticoagulation also induces a risk of hemorrhage.

"Virchow's triad" of factors promoting thrombosis (surface thrombogenicity, hypercoagulability, and locally static blood flow) largely predicts the relative propensity toward and locations of thrombotic deposits. For example, with caged-ball prostheses, thrombi formed distal to the poppet at the cage apex. Tilting disk prostheses are particularly susceptible to total thrombotic occlusion or emboli from small thrombi, both generally initiated in a flow stagnation zone in the minor orifice of the outflow region of the prosthesis; bileaflet tilting disk valves are most vulnerable near the hinges where the leaflets insert into the housing. In contrast, late thrombosis of a bioprosthetic valve is marked by large thrombotic deposits in one or more of the prosthetic sinuses of Valsalva. Usually, no causal underlying cuspal pathology can be demonstrated by routine microscopic studies. Some valve thromboemboli, especially early postoperatively with any valve type, are initiated at the valve sewing cuff before it is incorporated by pannus, thus providing the rationale for early antithrombotic therapy regardless of the type of replacement valve. Noninvasive visualization of prosthetic valve thrombi is aided by transesophageal endocardiography.[202]

As with other devices in which nonphysiologic artificial surfaces are exposed to blood at high fluid shear stresses, platelet deposition dominates initial blood-surface interaction and prosthetic valve thromboembolism correlates strongly with altered platelet function. Nevertheless, although platelet-suppressive drugs largely normalize indices of platelet formation and partially reduce the frequency of thromboembolic complications in patients with mechanical prosthetic valves, antiplatelet therapy alone is generally considered insufficient to adequately prevent thromboembolism. The friability and susceptibility to embolization of thrombi that form on bioprosthetic or mechanical valves are prolonged because lack of adjacent

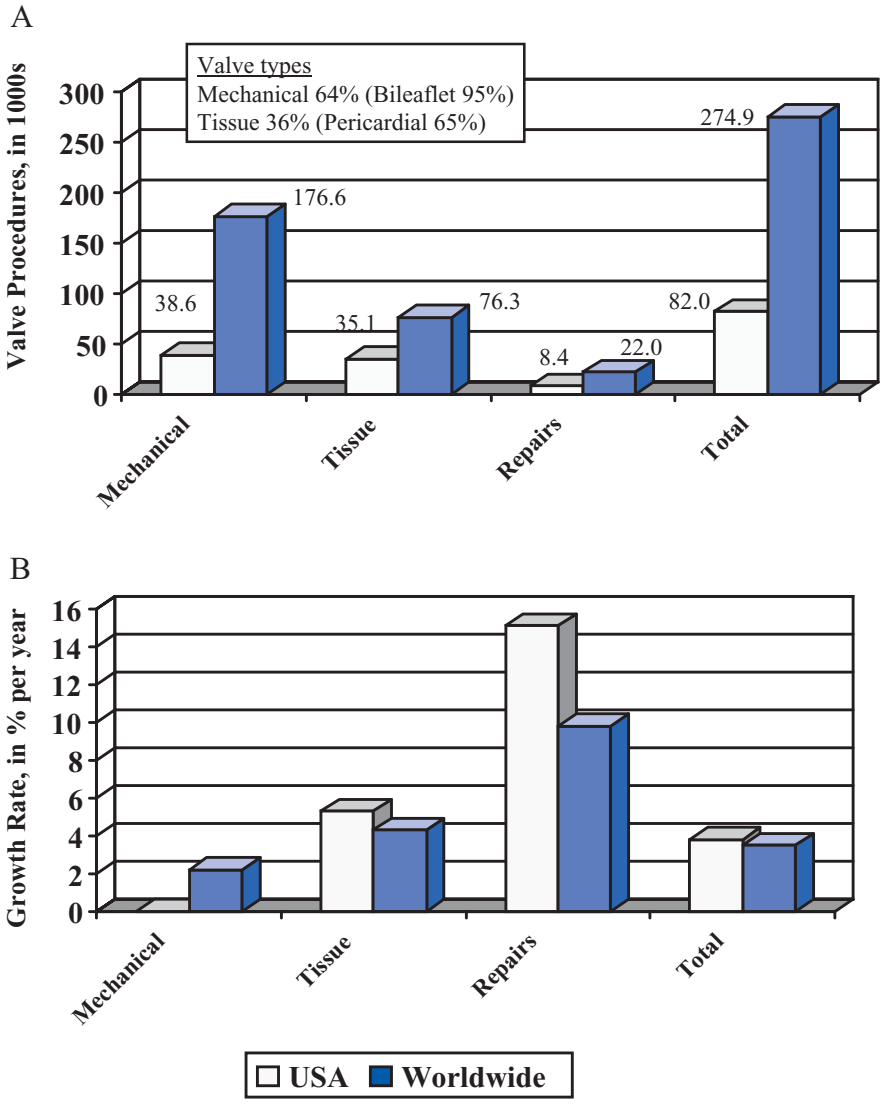


Figure 5-24. U.S. and worldwide use of substitute heart valves and heart valve repairs, estimated for the year 2000. (A) Usage. (B) Growth rate. While mechanical valves are implanted more frequently than tissue valves, the growth rate of tissue valves is approximately 4%, much more than that of mechanical valves. Ninety-five percent of mechanical valves are bilateral tilting disk valves; 65% of tissue valves are pericardial bioprostheses. The overall growth rate of repair operations is more than 10%. Approximately 7000 cryopreserved valves are implanted in the United States with a growth rate of approximately 5% per year (worldwide data not available). (*Data courtesy of St. Jude Medical, Inc., St. Paul, MN.*)

vascular tissue retards their histologic organization. Thus, in selected circumstances, thrombolytic therapy may be a practical nonsurgical option.[203,204] For similar reasons, the age of such thrombi is difficult to determine microscopically.

PROSTHETIC VALVE ENDOCARDITIS: *Prosthetic valve infective endocarditis* (Fig. 5-26) occurs in 3 to 6% of recipients of substitute valves.[205] Infection is generally categorized into early (usually less than 60 days postoperative) and late. The microbial etiology of early prosthetic valve endocarditis is dominated by the staphylococcal species *S. epidermidis* and *S. aureus,* even though prophylactic regimens used today are targeted against these microorganisms. The clinical course of early prosthetic valve endocarditis tends to be fulminant, with rapid deterioration of hemodynamic status due to valvular or annular destruction or persistent bacteremia. In late endocarditis, a probable source of infection can often be found, and the most frequent initiators are dental procedures, urologic infections and interventions, and indwelling catheters. The most common organisms in these late infections are *S. epidermidis, S. aureus,* viridans streptococci, and enterococci. Surgical reintervention usually is indicated for large highly mobile vegetations or cerebral thromboembolic episodes. Transesophageal echocardiography also enhances diagnosis of prosthetic valve endocarditis and its intracardiac complications.[206] Rates of infection of bioprostheses and mechanical valves are similar, and previous endocarditis on a natural or substitute valve markedly increases the risk.

Infections associated with mechanical prosthetic valves and some with bioprosthetic valves are localized to the prosthesis–tissue junction at the sewing ring, and accompanied by tissue destruction around the prosthesis (see Fig. 5-26A). This comprises a ring abscess, with potential paraprosthetic leak, dehiscence, fistula formation, or heart block caused by conduction system damage. Bioprosthetic valve infections may involve, and are occasionally

Table 5–3.

Complications of Substitute Heart Valves

Generic	Specific
Thrombotic limitations	Thrombosis Thromboembolism Anticoagulation-related hemorrhage
Infection	Prosthetic valve endocarditis
Structural dysfunction (intrinsic)	Wear Fracture Poppet escape Cuspal tear Calcification Commisural region dehiscence
Nonstructural dysfunction (most extrinsic)	Pannus (tissue overgrowth) Entrapment by suture or tissue Paravalvular leak Disproportion Hemolytic anemia Noise

Source: Modified with permission from Schoen FJ, Levy RJ, Piehler HR: Pathological considerations in replacement cardiac valves. Cardiovasc Pathol 1992; 1:29

limited to, the cuspal tissue, sometimes causing secondary cuspal tearing or perforation with valve incompetence or obstruction (see Fig. 5-26B). Cases without annular involvement have a better prognosis than those associated with an infected annulus. Embolization of vegetations and CHF secondary to obstruction or regurgitation may also occur.

STRUCTURAL VALVE DYSFUNCTION: *Prosthetic valve dysfunction* owing to materials degradation can necessitate reoperation or cause prosthesis-associated death (Fig. 5-27). Durability considerations vary widely for mechanical valves and bioprostheses, for specific types of each, for different models of a particular prosthesis (utilizing different materials or having different design features), and even for the same model prosthesis placed in the aortic rather than the mitral site. Mechanical valve structural failure is often catastrophic and may be life-threatening; in contrast bioprosthetic valve failure generally causes slowly progressive symptomatic deterioration.

Fractures of metallic or carbon valve components occur rarely. Of approximately 86,000 Bjork-Shiley 60- and 70-degree Convexo-Concave heart valves implanted, a cluster of over 500 cases have been reported in which the welded outlet strut fractured because of metal fatigue, leading to disk escape (see Fig. 5-27A).[207] Complete strut fracture is usually fatal. A cineangiographic imaging technique

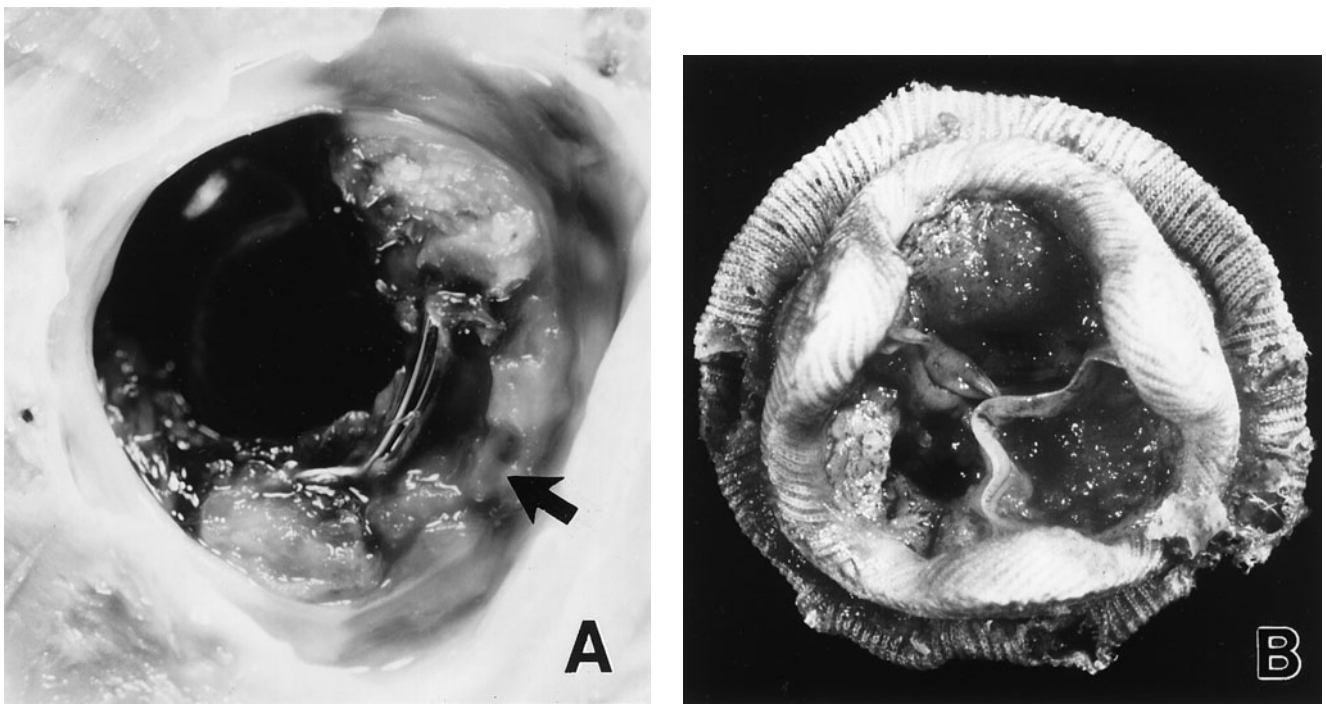


Figure 5-25. Thrombotic occlusion of substitute heart valves. (A) Tilting disk prosthesis. Thrombus was likely initiated in the region of stasis immediately distal to the smaller of the two orifices through which blood flows (arrow), causing near-total occluder immobility. (B) Porcine bioprosthesis, with thrombus filling the bioprosthetic sinuses of Valsalva. (*A: Reproduced with permission from Anderson and Schoen.*[54] *B: Reproduced with permission from Schoen and Hobson.*[199])

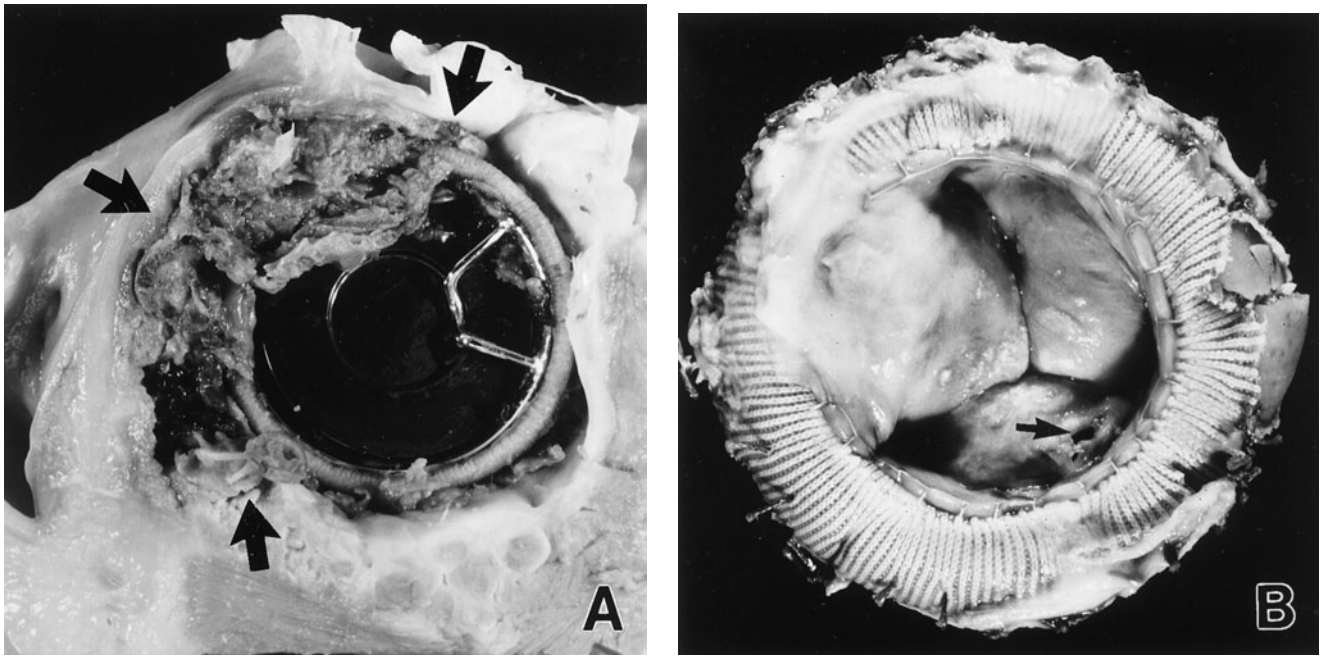


Figure 5-26. Prosthetic valve endocarditis. (A) Endocarditis with large ring abscess (arrows) observed from ventricular surface of aortic Bjork-Shiley tilting disk prosthesis in a patient who died suddenly. The ring abscess impinges on the proximal atrioventricular conduction system. (B) Bioprosthetic valve endocarditis with cuspal perforation by organism-induced necrosis (arrow). (*A: Reproduced with permission from Schoen FJ: Cardiac valve prostheses: pathological and bioengineering considerations. J Cardiac Surg 1987; 2:65. B: Reproduced with permission from Schoen FJ, et al: Long-term failure rate and morphologic correlations in porcine bioprosthetic heart valves. Am J Cardiol 1983; 51:957.*)

may facilitate detection of single leg strut fractures at a presymptomatic stage in some patients.[208] Fractures of carbon components (disks or housing) are unusual in most single leaflet or bileaflet tilting disk valves. However, a group of 37 fractures of an estimated 20,000 Edwards-Duramedics bileaflet tilting valves has occurred, possibly a combined result of carbon coating defects and cavitation bubbles impacting on the carbon surfaces during function.[209,210] Fracture of the St. Jude bileaflet tilting disk valve has been rare.[211]

In contrast, structural dysfunction of tissue valves is the major cause of failure of the most widely used bioprostheses (flexible-stent-mounted, glutaraldehyde-preserved porcine aortic valves, and bovine pericardial valves) (see Fig. 5-27B, C and D).[212] Within 15 years following implantation, 30 to 50% of porcine aortic valves implanted as either mitral or aortic valve replacements require replacement because of structural dysfunction manifested as primary tissue failure.[213] Cuspal mineralization is the major responsible pathologic process, with regurgitation through secondary tears the most frequent failure mode, particularly in porcine aortic bioprosthetic valves. Nevertheless, there is increasing recognition that noncalcific structural damage owing to collagen fiber disruption contributes to bioprosthetic heart valve failure.[214] Pure stenosis owing to calcific cuspal stiffening and noncalcific cuspal tears or perforations (reflecting direct mechanical destruction of collagen) occurs less frequently. Calcific deposits are usually localized to cuspal tissue (intrinsic calcification), but calcific deposits extrinsic to the cusps may occur in thrombi or endocarditic vegetations. Calcification is markedly accelerated in younger patients, with children and adolescents having an especially accelerated course. Bovine pericardial valves can also suffer tearing and calcification.[215,216] Abrasion of the pericardial tissue has been an important contributing factor.[217]

The morphology and determinants of calcification of bioprosthetic valve tissue have been widely studied in experimental models. The process is initiated primarily within residual membranes and organelles of the nonviable connective tissue cells that have been devitalized by glutaraldehyde pretreatment procedures. This dystrophic calcification mechanism involves reaction of calcium-containing extracellular fluid with membrane-associated phosphorus, causing calcification of the devitalized cells. Collagen calcification may occur later. The pathologic changes in bioprosthetic valves that occur following implantation are to a large extent rationalized on the basis of changes induced by the preservation and manufacture of a bioprosthesis, including: (1) denudation of endothelial cells, (2) loss of viability of the interstitial cells; and (3) locking of the cuspal microstructure in a static geometry.

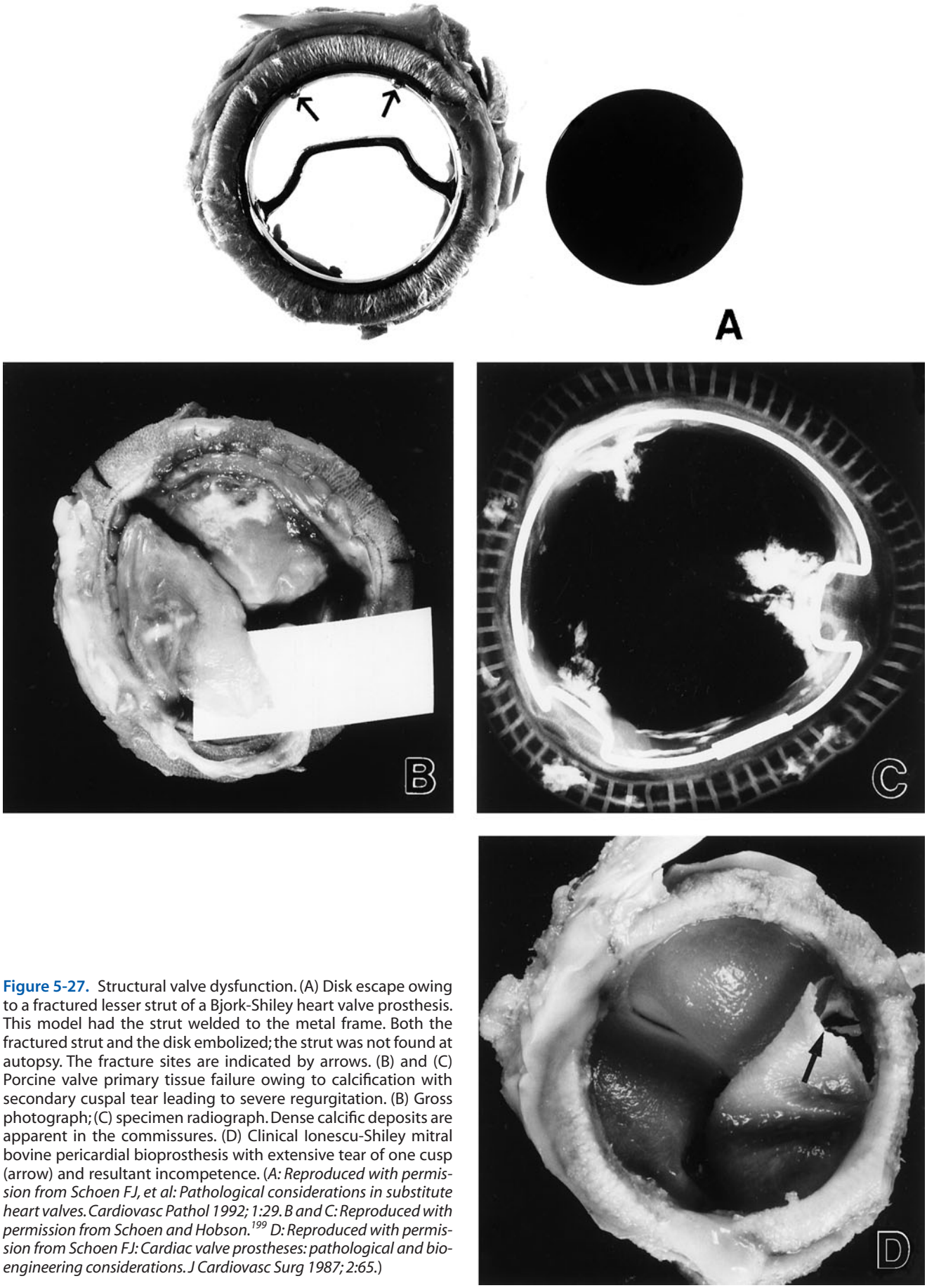


Figure 5-27. Structural valve dysfunction. (A) Disk escape owing to a fractured lesser strut of a Bjork-Shiley heart valve prosthesis. This model had the strut welded to the metal frame. Both the fractured strut and the disk embolized; the strut was not found at autopsy. The fracture sites are indicated by arrows. (B) and (C) Porcine valve primary tissue failure owing to calcification with secondary cuspal tear leading to severe regurgitation. (B) Gross photograph; (C) specimen radiograph. Dense calcific deposits are apparent in the commissures. (D) Clinical Ionescu-Shiley mitral bovine pericardial bioprosthesis with extensive tear of one cusp (arrow) and resultant incompetence. (*A: Reproduced with permission from Schoen FJ, et al: Pathological considerations in substitute heart valves. Cardiovasc Pathol 1992; 1:29. B and C: Reproduced with permission from Schoen and Hobson.*[199] *D: Reproduced with permission from Schoen FJ: Cardiac valve prostheses: pathological and bioengineering considerations. J Cardiovasc Surg 1987; 2:65.*)

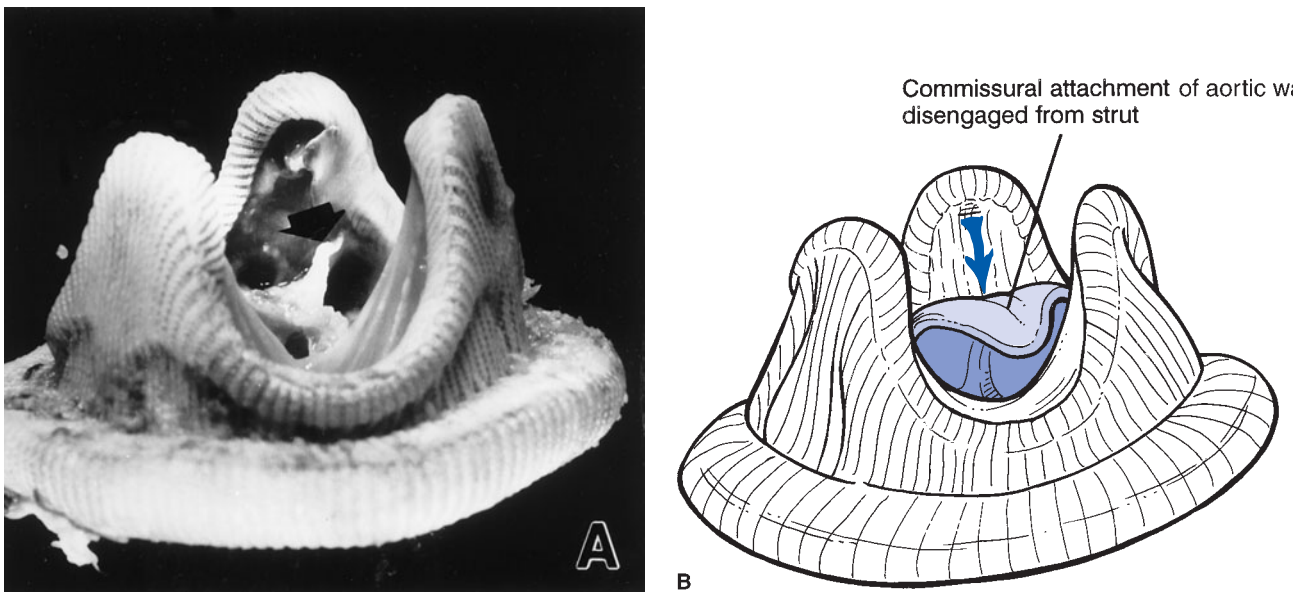


Figure 5-28. Dehiscence of commissural region of Hancock Standard porcine bioprosthetic valve. (A) Gross photograph. (B) Schematic diagram (arrow denotes loss of attachment of commissural support). Removed for regurgitation, this valve had prolapse of one cusp, minimal calcification, and no cuspal tears.

Commissural region dehiscence of the aortic wall tissue from the inside of porcine bioprosthetic valve stents causing insufficiency has also been described in several valve models (Fig. 5-28).

NONSTRUCTURAL DYSFUNCTION: *Extrinsic (nonstructural) complications* of substitute heart valves are illustrated in Fig. 5-29. The most common, paravalvular defects, may be clinically inconsequential or may aggravate hemolysis or cause heart failure through regurgitation. Early paravalvular leaks may be related to suture knot failure, inadequate suture placement, or separation of sutures from a pathologic annulus in endocarditis with ring abscess, myxomatous valvular degeneration, or calcified valvular annulus as in calcific aortic stenosis or mitral annular calcification. Late small paravalvular leaks usually are caused by anomalous tissue retraction from the sewing ring between sutures during healing. They tend to be small and difficult to locate by surgical or pathologic examination (see Fig. 5-29A).

The St. Jude Medical bileaflet tilting disk valve with a silver coating (Silzone) was introduced to prevent bacterial colonization of the valves and consequent prosthetic valve endocarditis. This valve has a conventional polyethylene terephthalate polyester sewing ring coated with metallic silver by an ion beam vapor deposition process. Some studies have suggested that this modification yields a higher-than-expected rate of paravalvular leak and thromboembolism,[218–220] hypothesized to be a result of inhibition of normal fibroblast response and incorporation of the fabric of the sewing cuff into host tissues in some patients.

Hemolysis owing to turbulent flow and blood–material surface interactions has resulted in renal tubular hemosiderosis or cholelithiasis in many patients with earlier model heart valve prostheses. Severe hemolytic anemia is unusual with properly functioning contemporary valves; paravalvular leaks or dysfunction owing to materials degeneration may induce hemolysis.

Extrinsic factors can mediate late prosthetic valve stenosis or regurgitation, including a large mitral annular calcific nodule, septal hypertrophy, exuberant overgrowth of fibrous tissue (see Fig. 5-29B), interference by retained valve remnants (such as a retained posterior mitral leaflet or components of the submitral apparatus; see Fig. 5-29C), or unraveled, long, or looped sutures or knots (see Fig. 5-29D, E, and F). With bioprosthetic valves, cuspal motion can be restricted by sutures looped around stents, and suture ends cut too long may erode into or perforate a bioprosthetic valve cusp.

Valvular allografts/homografts

Aortic or pulmonary valves (with or without associated vascular conduits) transplanted from one individual to another have exceptionally good hemodynamic profiles, a low incidence of thromboembolic complications without chronic anticoagulation, and a low reinfection rate following valve replacement for endocarditis.[221,222] Early valvular allografts sterilized and/or preserved with chemicals (using propiolactone or ethylene oxide) or irradiation suffered a high rate of leaflet fibrosis, calcification, and rupture, resulting in failure rates of nearly 50% at 10 to 12 years and 50 to 90% at 15 to 20 years.[223] Subsequent

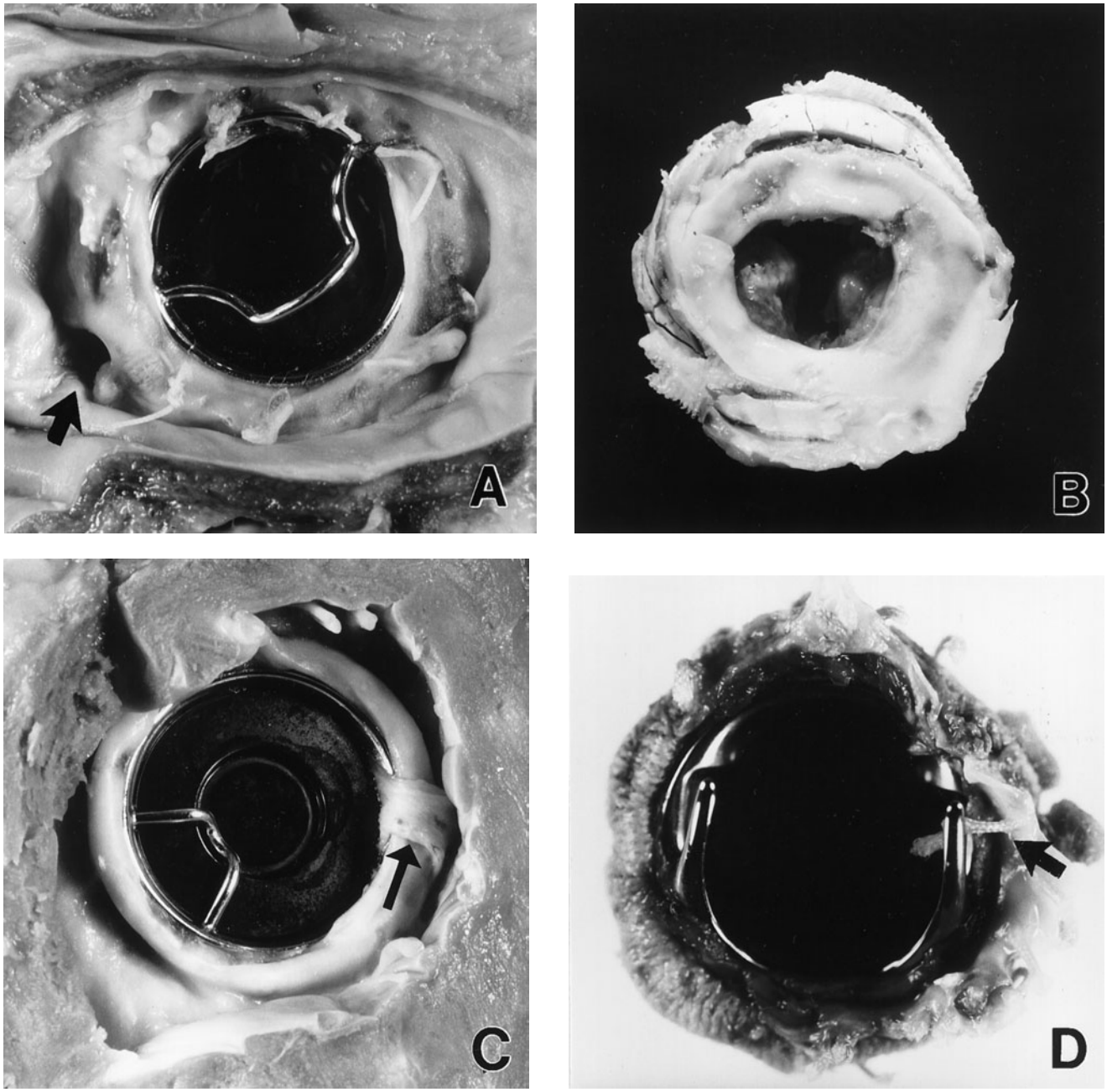


Figure 5-29. Nonstructural dysfunction of prosthetic heart valves. (A) Late paravalvular leak adjacent to mitral valve prosthesis (arrow). (B) Tissue overgrowth compromising inflow orifice of porcine bioprosthesis. (C) Immobility of tilting disk leaflet by impingement of retained component of submitral apparatus (arrow) that had moved through the orifice late following mitral valve replacement surgery. (D) Suture with long end inhibiting free disk movement (arrow) of Lillehei-Kaster tilting disk valve. (*A and C: Reproduced with permission from Schoen FJ: Histologic considerations in replacement heart valves and other cardiovascular prosthetic devices, in Schoen FJ, Gimbrone MA [eds]: Cardiovascular Pathology: Clinicopathologic Correlations and Pathogenetic Mechanisms. Philadelphia, Williams & Wilkins, 1995; p 194. B: Reproduced with permission from Schoen FJ, et al: Pathologic considerations in substitute heart valves. Cardiovasc Pathol 1992; 1:29. D: Reproduced with permission from Schoen FJ: Pathology of cardiac valve replacement, in Morse D, Steiner RM, Fernandez J [eds]: Guide to Prosthetic Cardiac Valves. New York, Springer-Verlag, 1985; p 209.)*

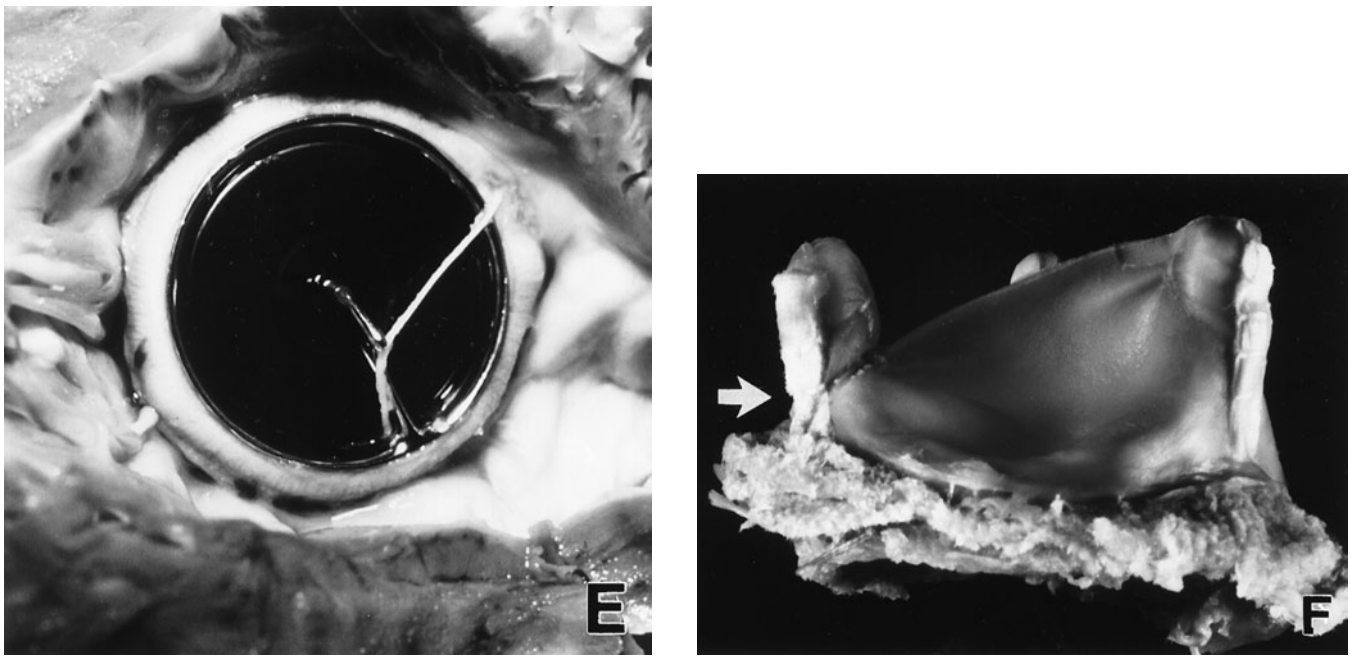


Figure 5-29. (*Continued*) Nonstructural dysfunction of prosthetic heart valves. (E) Suture looped around central strut of a Hall-Medtronic tilting disk valve causing disk immobility. (F) Suture looped around stent post of bovine pericardial bioprosthesis causing stenosis (arrow). (*E: Photo courtesy of Office of the Chief Medical Examiner, New York City. F: Reproduced with permission from Schoen FJ: Cardiac valve prostheses: pathologic and bioengineering considerations. J Cardiac Surg 1987; 2:65.*)

technical developments have led to cryopreserved allografts, in which freezing is performed with protection from crystallization by dimethylsulfoxide; storage until valve use is done at –196°C in liquid nitrogen. Contemporary allograft valves are free from degeneration and have durability equal to or better than those of conventional porcine bioprosthetic valves (approximately 50 to 90% valve survival at 10 to 15 years, compared with 40 to 60% for bioprostheses).

We studied 33 explanted left- and right-sided cryopreserved human allograft heart valves/conduits in place several hours to 9 years in children and adults.[224] Cryopreserved human allograft heart valves/conduits implanted more than 1 day had progressively severe loss of normal structural demarcations. Long-term explants were generally devoid of both surface endothelium and deep connective tissue cells, and had hyalinized collagen, laminated elastin, and minimal inflammatory cellularity (Fig. 5-30). Our studies and most others have demonstrated that the function of cryopreserved allograft heart valves/conduits is primarily related to the largely preserved collagen network, rather than cellular viability.

Pulmonary valvular autografts

Often called the Ross operation in recognition of its originator (Sir Donald Ross), pulmonary autograft replacement of the aortic valve is technically difficult but yields excellent hemodynamic performance, avoids anticoagulation, and carries a low risk of thromboembolism.[225,226]

We studied the structural features, cell viability, and ECM remodeling of pulmonary autograft valves in place for 15 days to 6 years.[227] Throughout the postoperative period pulmonary autograft cusps showed (1) near-normal trilaminar structure, (2) near-normal collagen architecture, (3) viable endothelium and interstitial cells, (4) usual outflow surface corrugations, (5) sparse inflammatory cells, and (6) absence of calcification and thrombus. Most valves also had an irregular layer of intimal thickening (up to 1 mm), particularly on the ventricular aspect, and they maintained remarkably preserved semilunar valve morphology, cell viability, and collagen microstructure up to 6 years. The arterial walls showed considerable transmural damage (probably perioperative ischemic injury caused by disruption of the vasa vasorum) with scarring and loss of medial smooth muscle cells and elastin. The early necrosis and healing with probable resultant loss of strength and elasticity of the aortic wall may potentiate late dilation.

Stentless porcine aortic valve bioprostheses

Nonstented (stentless) porcine aortic valve bioprostheses comprise glutaraldehyde-pretreated pig aortic root and valve cusps that have no supporting stent.[228] Three such models approved by the FDA are the St. Jude Medical Toronto SPV (St. Jude Medical Inc., St. Paul, MN), Medtronic Freestyle (Medtronic Heart Valves, Santa Ana, CA) and

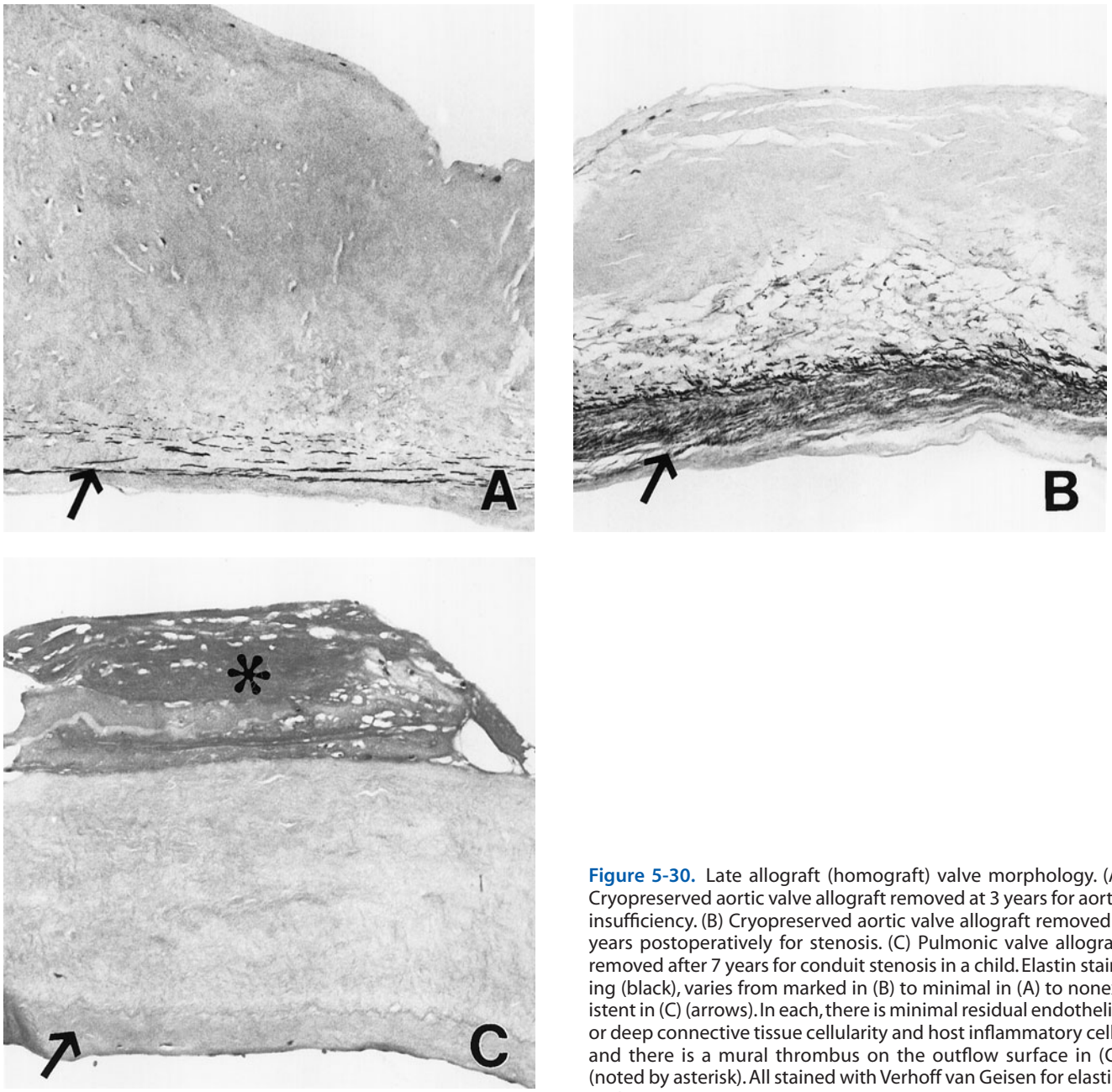


Figure 5-30. Late allograft (homograft) valve morphology. (A) Cryopreserved aortic valve allograft removed at 3 years for aortic insufficiency. (B) Cryopreserved aortic valve allograft removed 5 years postoperatively for stenosis. (C) Pulmonic valve allograft removed after 7 years for conduit stenosis in a child. Elastin staining (black), varies from marked in (B) to minimal in (A) to nonexistent in (C) (arrows). In each, there is minimal residual endothelial or deep connective tissue cellularity and host inflammatory cells, and there is a mural thrombus on the outflow surface in (C); (noted by asterisk). All stained with Verhoff van Geisen for elastin, each 100x.

the Edwards Prima stentless porcine bioprostheses (Fig. 5-31).[229,230] They differ slightly in overall configuration (particularly the amount of aortic wall included), details of glutaraldehyde pretreatment conditions, and overall fabrication, and whether anticalcification technology is used (the Freestyle valve is treated with 2-amino-oleic acid). The principal advantage of a stentless porcine aortic valve is that it generally allows for the implantation of a larger bioprosthesis (than a stented valve) in any given aortic root, which may enhance hemodynamics and thereby regression of hypertrophy and patient survival.[231–233] However, at least one study that compared stented (bovine pericardial) valves implanted in the supra-annular position and stentless valves implanted in the subcoronary position found no difference in hemodynamic function or clinical events between the two groups.[234]

The available evidence suggests that the durability of stentless bioprostheses is comparable to that of contemporary stented bioprostheses; however, similarly to the results for stented bioprostheses, younger recipients have a higher vulnerability to structural valve deterioration. The potential and observed complications with nonstented bioprostheses are comparable to those of stented valves. However, nonstented porcine aortic valves have greater portions of aortic wall

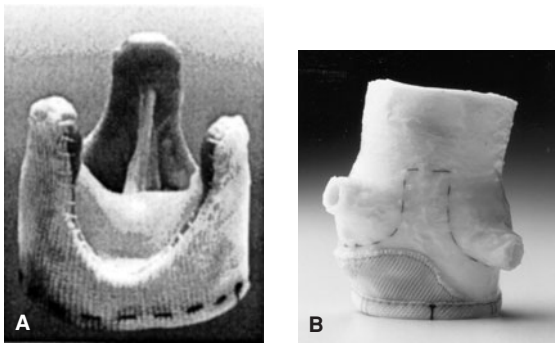


Figure 5-31. Stentless porcine bioprosthetic heart valves. (A) Toronto SPV. (B) Edwards Prima.

exposed to blood than in currently used stented valves, and calcification of the aortic wall and inflammation at the junction of aortic wall with the recipient's tissue may develop, owing to the large area of this interface and may potentially be deleterious. Calcification of the wall portion of a stentless valve could stiffen the root, altering hemodynamic efficiency; may cause nodular calcific obstruction or wall rupture; or provide a nidus for emboli. Pathologic analyses of nonstented valves shows pannus and tissue degeneration, manifest as tears and cuspal calcification, but not substantial aortic wall calcification.[235,236]

Percutaneous valve replacement

New catheter techniques for inserting foldable prosthetic valves within stenotic aortic and pulmonary valves, and for emulating surgical repair of regurgitant mitral valves, are in various stages of preclinical development and clinical testing.[237–239] Percutaneous implantation of a heart valve that can be mounted on an expandable stent, delivered percutaneously through standard catheter-based techniques, and implanted within a diseased valve annulus has been demonstrated to be feasible. Percutaneous valve replacement is most likely to be used in patients with severe aortic stenosis deemed otherwise inoperable, and in congenital heart disease, in which percutaneous pulmonary valve replacement may find a distinct niche to obviate the morbidity of reoperation to replace malfunctioning pulmonary conduits.

Percutaneous valve replacement uses (1) an outer stent-like structure, which (2) contains leaflets; these two components together constitute a functioning valvular prosthesis. Representative designs under development are illustrated in Fig. 5-32. The stent holds open a valve annulus or segment of a prosthetic conduit and resists the tendency of a vessel, valve annulus, and diseased native leaflets to recoil following balloon dilation, supports the valve leaflets, and provides the means for seating the prosthesis in the annulus or vessel. In patients with repaired congenital heart disease, complications of a right ventricle-to-pulmonary artery conduit are frequent, and the opportunity for palliation to delay or prevent surgery is attractive in many cases. For aortic valve disease, the excellent clinical success with surgical AVR restricts the use of balloon valvuloplasty/percutaneous valve replacement to nonsurgical candidates, or as a bridge to valve replacement in patients in whom surgery needs to be delayed.

Several valve designs for endovascular implantation are under development and testing. Valve assemblies composed of either a shape-memory nitinol alloy stent (which is self-expandable) housing a valve constructed of porcine pericardial leaflets, a platinum-iridium alloy stent with a bovine jugular vein valve, and a stainless steel cage (which is balloon-expandable) with equine pericardial leaflets have had the most extensive clinical application, comprising more than 100 patients.[240,241] This early clinical experience demonstrates the feasibility of percutaneous valve replacement in both aortic and pulmonary locations, and the potential and challenges of transcatheter valve replacement. Given the overall clinical success of this approach to date, as well as the morbidity associated with reoperative surgery in repaired congenital heart disease, percutaneous pulmonary valve replacement is the most likely of all the catheter-based valve technologies to achieve near-term broad clinical application.

Key challenges are associated with the use of stent-mounted prosthetic valves. Valved stents are significantly larger than most existing percutaneous cardiac catheters and devices, and presently are on the order of 22 to 24F. In the aortic position, there is the potential to impede coronary flow, or interfere with anterior mitral leaflet mobility, the conduction system, or the diseased native leaflets. Stent architecture may also preclude future catheter access to the coronaries for possible interventions. Secure seating within the aortic annulus or a pulmonary conduit and long-term durability of both the stent and the valve tissue are also major considerations.

MYOCARDIAL DISEASE

A new classification for the cardiomyopathies[242] updates the 1995 World Health Organization/International Society and Federation of Cardiology schema.[243] The proposed system distinguishes broadly between "primary cardiomyopathies" (solely or predominantly confined to heart muscle) and "secondary cardiomyopathies" (myocardial involvement as part of generalized systemic or multisystem disorders). Primary cardiomyopathies are subdivided into genetic, mixed, and acquired categories, underscoring the role of recently elucidated molecular and genetic factors that may lead to cardiomyopathy (Fig. 5-33).[244] Genetic causes of primary cardiomyopathy include hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, left ventricular noncompaction, and the ion channel disorders (e.g., long QT syndrome and Brugada syndrome). The mixed category of primary cardiomyopathies represents diseases that are often acquired, but also have important genetic contributions, and include both dilated and restrictive patterns. Acquired causes of primary cardiomyopathy include

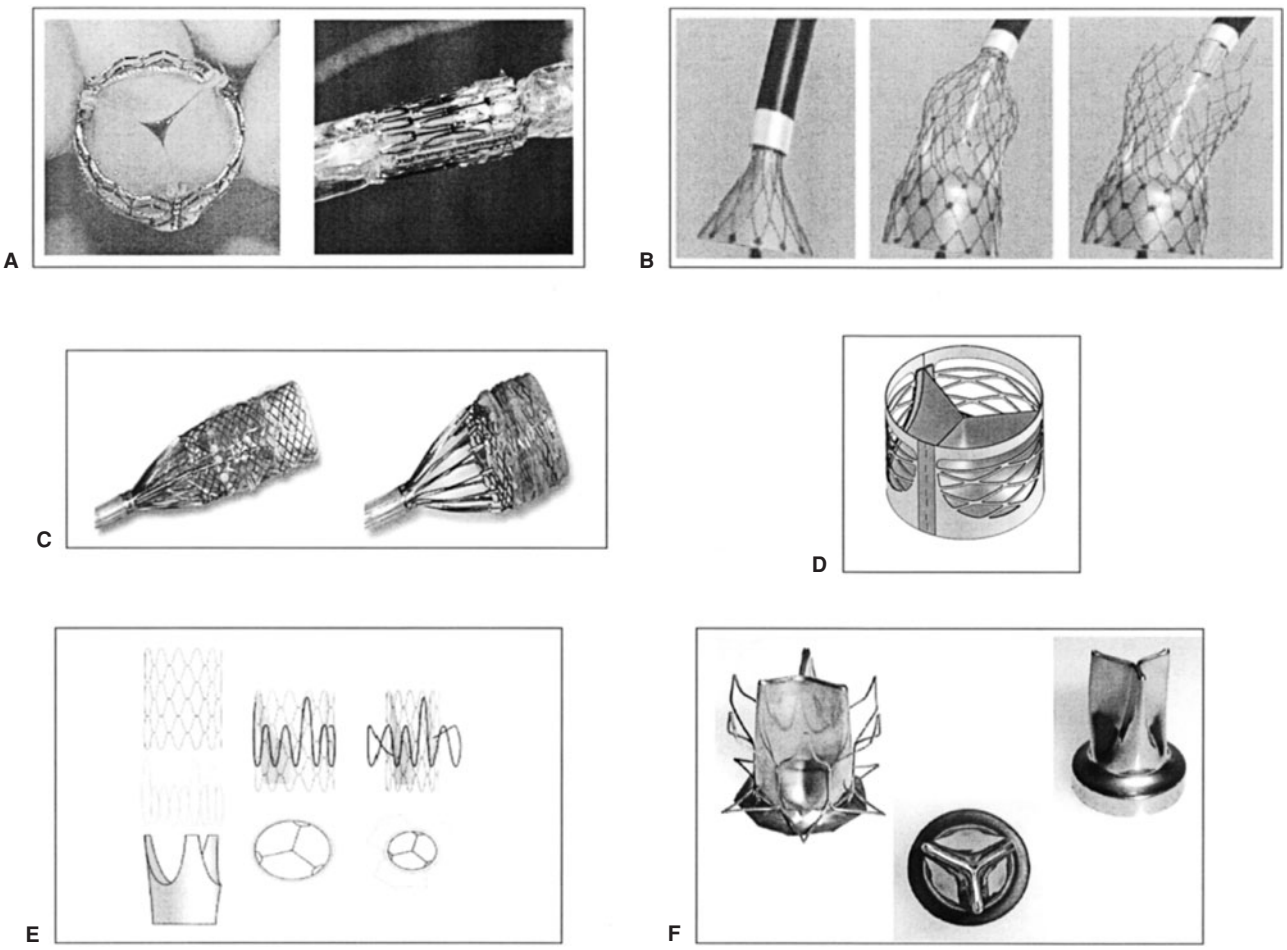


Figure 5-32. Percutaneous valve devices and concepts. (A) The Cribier-Edwards valve consists of three equine pericardial leaflets fixed to a balloon-expandable steel stent. It is hand-crimped over a delivery balloon prior to deployment. (B) The Corevalve system is a self-expanding nitinol cage housing three porcine pericardial leaflets. Devices in preclinical development include (C) the Sadra self-expanding Lotus valve (D), the Aortx valve (E), the Bonhoeffer valve (F), and the eNitinol thin membrane PercValve. (*Reproduced with permission from Davidson et al.*[180])

myocarditis ("inflammatory cardiomyopathy"), stress-provoked ("tako-tsubo"), and tachycardia-induced and peripartum cardiomyopathy. The secondary cardiomyopathies consist of systemic diseases that may have myocardial involvement leading to dysfunction, such as amyloidosis and other infiltrative diseases, hemochromatosis and other storage diseases, drug and other toxic reactions, sarcoidosis, autoimmune/collagen vascular diseases, and neuromuscular/neurologic diseases (e.g., Duchenne-Becker muscular dystrophy). The terms "ischemic cardiomyopathy," "valvular cardiomyopathy," and "hypertensive cardiomyopathy" have been eliminated from the classification. The heart disease seen in these conditions more likely reflects compensatory and remodeling changes, rather then a cardiomyopathy as currently defined, so the terms "ischemic heart disease," "valvular heart disease," and "hypertensive heart disease" are preferred.

The cause of a cardiomyopathy is often revealed by light and/or electron microscopic examination. Myocarditis, sarcoidosis, amyloidosis, hemochromatosis, and many other diseases may be apparent on evaluation of endomyocardial biopsy, and other conditions such as arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy have characteristic gross and microscopic morphologies upon evaluation of the heart at the time of transplantation or autopsy. However, microscopic features are generally nonspecifically abnormal in dilated cardiomyopathy, and the severity of the morphologic changes does not necessarily correlate with the severity of dysfunction or the patient's prognosis. The understanding and potential treatment of myocardial disease have advanced substantially over the last decade as a result of genetic studies and their correlations with clinical features.[245–248]

Endomyocardial biopsy is used in the diagnosis and management of patients with myocardial disease and in the ongoing surveillance of cardiac transplant recipients.[249] The bioptome, inserted into the right internal jugular or

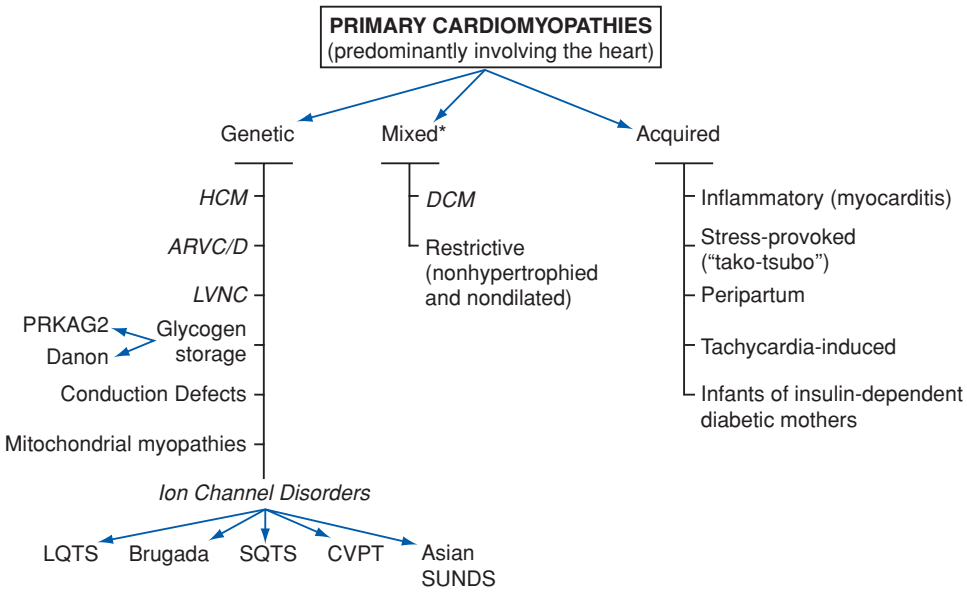


Figure 5-33. Primary cardiomyopathies in which the clinically relevant disease processes solely or predominantly involve the myocardium. The conditions have been segregated according to their genetic or nongenetic etiologies. * = predominantly nongenetic; familial disease with a genetic origin has been reported in a minority of cases; ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; CVPT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LQTS = long-QT syndrome; LVNC = left ventricular nonconpaction; SQTS = short-QT syndrome; SUNDS = sudden unexplained nocturnal death syndrome. (*Reproduced with permission from Marron et al.*[242])

femoral vein and advanced under fluoroscopic or echocardiographic guidance through the tricuspid valve, obtains 1- to 3-mm fragments of endomyocardium, most frequently from the apical half of the right side of the ventricular septum. Since most myocardial diseases affect both ventricles, correlation between right- and left-sided findings generally is good.

Cardiomyopathies

The most common variants of primary cardiomyopathy are the dilated and hypertrophic types. Both are illustrated in Fig. 5-34, as is right ventricular cardiomyopathy.

Dilated cardiomyopathy

Dilated cardiomyopathy is characterized by hypertrophy, dilation, and systolic ventricular dysfunction. Dilated cardiomyopathy has a familial basis in approximately 30 to 50% of cases, with autosomal dominant (most common), autosomal recessive, X-linked, and mitochondrial inheritance all described. Mutations in several different genes can cause autosomal dominant dilated cardiomyopathy, including the cytoskeletal protein-encoding genes δ-sarcoglycan, desmin, and lamin A/C, as well as the sarcomeric protein-encoding genes actin, β-myosin heavy chain, cardiac troponin T, and α-tropomyosin. X-linked disease is most often the result of mutations in dystrophin, and mutations in cardiac troponin I have shown autosomal recessive inheritance patterns. Secondary cardiomyopathies such as alcoholic cardiomyopathy and myocarditis manifest as cardiac dilation. Pregnancy-associated nutritional deficiency or immunologic reaction is another possible contributory factor.

The primary functional abnormality in dilated cardiomyopathy is impairment of left ventricular systolic function, as measured by the ejection fraction (<25% in end-stage and normal in approximately 50 to 65%). Pathologic findings include cardiomegaly with heart weight two to three times normal and four-chamber dilation (see Fig. 5-34A). Cardiac mural thrombi, a potential source of thromboemboli, are sometimes present and predominate in the left ventricle, but may occur in any chamber. The histologic changes include myocyte hypertrophy and interstitial and endocardial fibrosis of variable degrees; the myocardial histology in dilated cardiomyopathy is indistinguishable from that in myocardial failure secondary to ischemic or valvular heart disease (see Fig. 5-34B).

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is characterized by massive myocardial hypertrophy without dilation (see Fig. 5-34C).[250] The classic pattern has disproportionate thickening of the ventricular septum relative to the free wall of the left ventricle (ratio >1.5), termed asymmetric septal hypertrophy, and is usually localized to the subaortic region. When the basal septum is markedly thickened at the level of the mitral valve, the outflow of the left ventricle may be narrowed during systole. Endocardial thickening in the left ventricular outflow tract and thickening of the anterior mitral leaflet result from

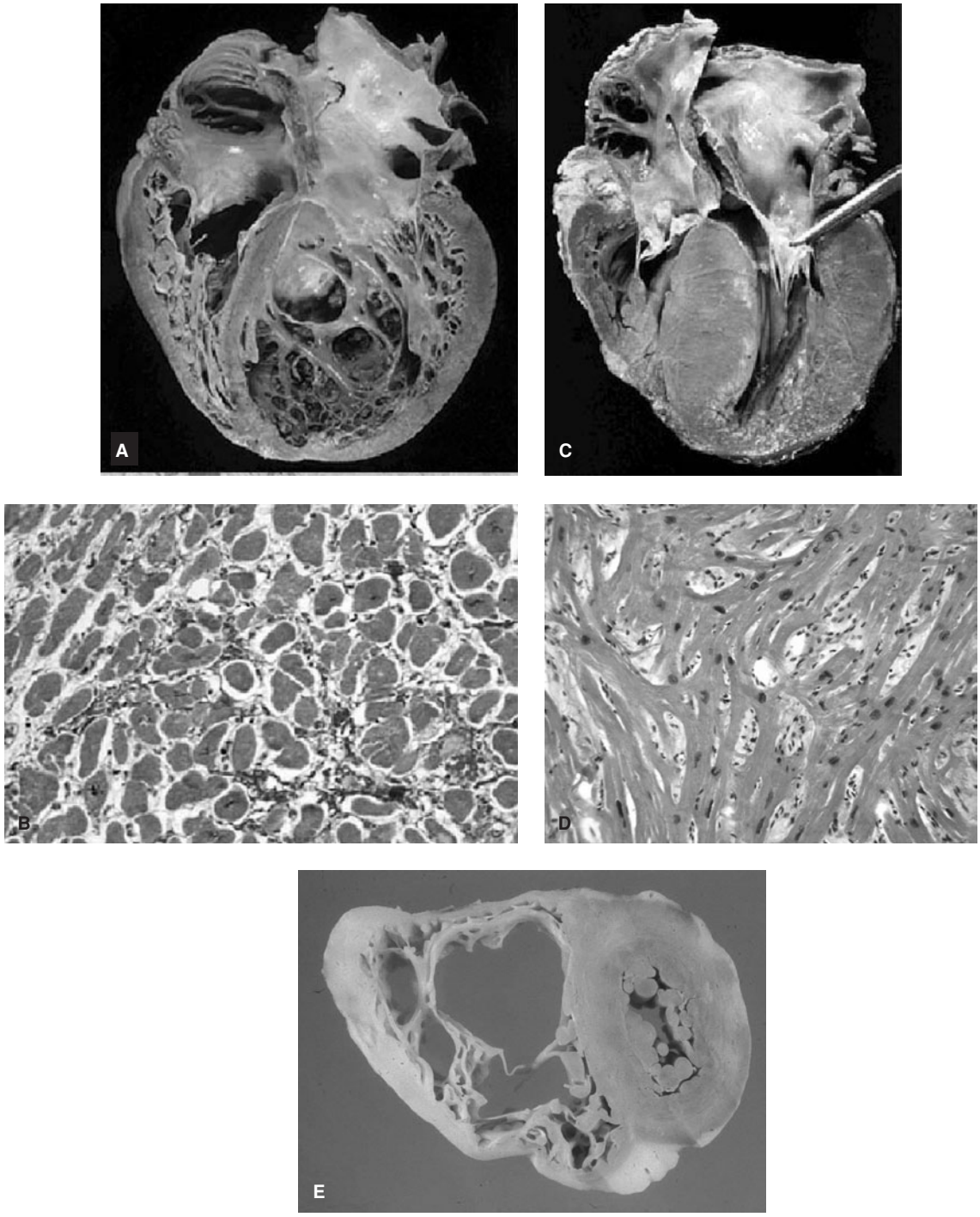


Figure 5-34. Cardiomyopathy. (A) and (B) Dilated cardiomyopathy. (A) Gross photo showing four-chamber dilation and hypertrophy. There is granular mural thrombus at the apex of the left ventricle (on the right in this apical four-chamber view). The coronary arteries were unobstructed. (B) Histology demonstrating irregular hypertrophy and interstitial fibrosis. (C and D) Hypertrophic cardiomyopathy with asymmetric septal hypertrophy. (C) Gross photo. The septal muscle bulges into the left ventricular outflow tract, and the left atrium is enlarged. The anterior mitral leaflet has been moved away from the septum to reveal a fibrous endocardial plaque (see text). (D) Histologic appearance demonstrating disarray, extreme hypertrophy, peculiar branching of myocytes, and interstitial fibrosis characteristic of hypertrophic cardiomyopathy. (E) Right ventricular cardiomyopathy, gross photograph, showing right ventricular dilation and wall thinning, with replacement of the right ventricular wall by fibrosis and fat. (*Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989, and Schoen FJ: The heart, in Kumar V, Fausto N, Abbas A [eds]: Robbins & Cotran Pathologic Basis of Disease, 7th ed. Philadelphia, WB Saunders, 2004; p 555.*)

contact between the two during ventricular systole (observed by echocardiography as systolic anterior motion of the mitral valve), correlating with systolic left ventricular outflow tract obstruction. In about 10% of cases, LVH is symmetric, and in other cases disproportionate hypertrophy involves the mid-ventricular or apical septum, extends onto the left ventricular free wall anteriorly or inferiorly, or causes right ventricular outflow tract obstruction.

The most important microscopic features in hypertrophic cardiomyopathy include: (1) disarray of myocytes and contractile elements within cells (myofiber disarray) typically involving 10 to 50% of the septum; (2) extreme myocyte hypertrophy, with transverse myocyte diameters frequently more than 40 μm (normal approximately 15 to 20 μm); and (3) interstitial and replacement fibrosis (see Fig. 5-34D).

Hypertrophic cardiomyopathy has an extremely variable course, with potential complications including atrial fibrillation with mural thrombus formation and embolization, infective endocarditis of the mitral valve, intractable cardiac failure, and sudden death. Sudden death occurs in approximately 2 to 3% of adults and 4 to 6% of children per year, is the most common cause of death from hypertrophic cardiomyopathy, and is particularly common in young males with familial hypertrophic cardiomyopathy or a family history of sudden death. The risk is related to the degree of hypertrophy.[251,252] Cardiac failure from hypertrophic cardiomyopathy results from reduced stroke volume due to decreased diastolic filling of the massively hypertrophied left ventricle. Although symptoms are not solely a result of ventricular septal thickening, some patients benefit from thinning of the septum by surgical myotomy/myectomy.[253,254] More recently, the technique of chemical septal ablation appears to be a safe and effective procedure, with hemodynamic and functional improvement.[255–257] End-stage heart failure can be accompanied by dilation, for which cardiac transplantation may be recommended.

Hypertrophic cardiomyopathy has a genetic basis in almost all cases. In approximately one-half or more of patients the disease is familial, and the pattern of transmission is autosomal dominant with variable expression; remaining cases appear to be sporadic. Hundreds of mutations have been identified in 11 genes in patients with hypertrophic cardiomyopathy; all are genes for sarcomeric proteins including β-myosin heavy chain, troponin T and I, α-tropomyosin, and titin. Different responsible gene mutations carry vastly differing prognoses, and certain genetic defects indicate a relatively high likelihood of sudden death.

The mechanism by which defective sarcomeric proteins produce the phenotype of hypertrophic cardiomyopathy is incompletely defined.

Restrictive cardiomyopathy

Restrictive cardiomyopathy is characterized by impeded diastolic relaxation and left ventricular filling, with systolic function often unaffected (*diastolic dysfunction*). Any disorder that interferes with ventricular filling can cause restrictive cardiomyopathy (including eosinophilic endomyocardial disease, amyloidosis, hemochromatosis, or postirradiation fibrosis) or mimic it (constrictive pericarditis or hypertrophic cardiomyopathy). The ventricles are of approximately normal size or slightly enlarged, but the cavities are not dilated and the myocardium is firm. Biatrial dilation is commonly observed. Distinct morphologic patterns indicative of specific heart muscle disease may be revealed by light or electron microscopy of endomyocardial biopsy specimens, including deposition of amyloid or of products of an inborn error of metabolism such as trihexosylceramide in Fabry disease.[258]

Arrhythmogenic right ventricular cardiomyopathy

A recently described variant of dilated cardiomyopathy is arrhythmogenic right ventricular cardiomyopathy, characterized by a dilated right ventricular chamber and severely thinned right ventricular wall, with extensive fatty infiltration, loss of myocytes with compensatory myocyte hypertrophy, and interstitial fibrosis (see Fig. 5-34E).[259,260] Clinical features of right ventricular cardiomyopathy include right-sided heart failure and arrhythmias. The arrhythmias are often brought on by exertion, explaining the association of this condition with sudden death in athletes.[261,262] Mutational analysis of patients with right ventricular cardiomyopathy has identified several genes involved in desmosomal cell adhesion, including plakoglobin, desmoplakin, plakophilin-2, and desmoglein-2. Recent studies have shown the high prevalence of plakophilin-2 mutations in this condition (particularly in the familial form of the disease), and the earlier onset of symptoms and arrhythmias when mutations in this gene are present.[263,264]

CARDIAC ASSIST AND REPLACEMENT

Cardiac Transplantation

Cardiac transplantation provides long-term survival and rehabilitation for many individuals with end-stage cardiac failure.[265] Overall predicted 1-year survival is presently approximately 86% and 5-year survival is about 70%.[266] The most common indications for cardiac transplantation, accounting for 90% of the patients, are idiopathic cardiomyopathy and end-stage ischemic heart disease; other recipients have congenital, other myocardial, or valvular heart disease.[267]

Hearts explanted at the time of transplantation typically have the expected pathologic features of the underlying diseases. However, previously undiagnosed conditions and unexpected findings may be encountered. Most frequent is eosinophilic or hypersensitivity myocarditis, seen in from 7 to 20% of explants and characterized by a focal or diffuse mixed inflammatory infiltrate, rich in eosinophils, and generally associated with minimal associated myocyte necrosis.[268,269] In virtually all cases, the myocarditis represents hypersensitivity to one or more of the many drugs taken by

transplant candidates, including dobutamine, and is unrelated to but superimposed on the original disease necessitating transplantation. Several diseases responsible for the original cardiac failure can recur in and cause dysfunction of the allograft, including amyloidosis, sarcoidosis, giant-cell myocarditis, acute rheumatic carditis, and Chagas disease.

Recipients of heart transplants undergo surveillance endomyocardial biopsies on an institution-specific schedule, which typically evolves from weekly during the early postoperative period, to twice weekly until 3 to 6 months, and then approximately one to four times annually, or at any time when there is a change in clinical state. Histologic findings of rejection frequently precede clinical signs and symptoms of acute rejection. Optimal biopsy interpretation requires four or more pieces of myocardial tissue; descriptions of technical details and potential tissue artifacts are available.[270]

The major sources of mortality and morbidity following cardiac transplantation are perioperative ischemic injury, infection, allograft rejection, lymphoproliferative disease, and obstructive graft vasculopathy.

Early ischemic injury

Ischemic injury can originate in the ischemia that accompanies procurement and implantation of the donor heart. Several time intervals are potentially important: (1) the donor interval between brain death and heart removal, perhaps partially related to terminal administration of pressor agents or the release of norepinephrine and cytokines associated with brain death; (2) the interval from warm ischemia between donor cardiectomy to cold storage; (3) the interval during cold transport; and (4) the interval during warming, trimming, and reimplantation. Hypertrophy and coronary obstructions tend to enhance injury, whereas decreased tissue temperature and cardioplegic arrest slow chemical reactions and thereby protect myocytes from progressive ischemic damage. As in other situations of transient myocardial ischemia, frank necrosis or prolonged ischemic dysfunction of viable myocardium or both may be present. Myocardial injury can cause low cardiac output in the perioperative period.

Perioperative myocardial ischemic injury may be detectable in endomyocardial biopsies early after heart transplantation.[271] Because of the anti-inflammatory effects of immunosuppressive therapy, the histologic progression of healing of myocardial necrosis in transplanted hearts may be delayed (Fig. 5-35). Therefore, the repair phase of perioperative myocardial necrosis frequently confounds the diagnosis of rejection in the first postoperative month, and in some cases for as long as 6 weeks. In contrast, ischemic necrosis noted after 3 to 6 months postoperatively is usually secondary to occlusive graft vasculopathy. There is evidence that early ischemic injury may accelerate the progression of graft vasculopathy.[272]

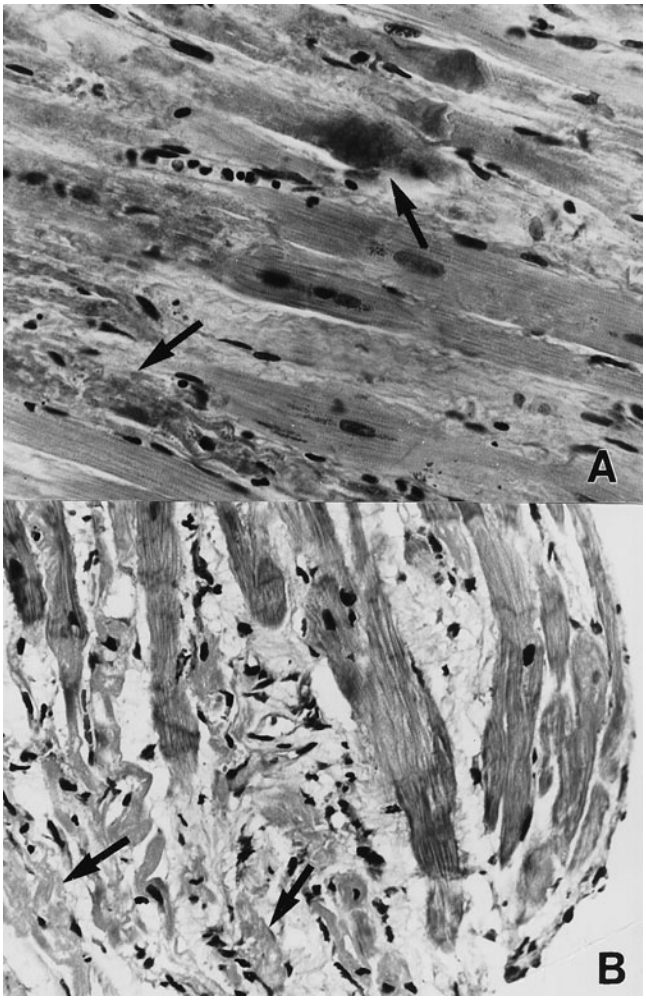


Figure 5-35. Perioperative ischemic myocardial injury demonstrated on endomyocardial biopsy. (A) Coagulative myocyte necrosis (arrows). (B) Healing perioperative ischemic injury with predominantly interstitial inflammatory response (arrows), not encroaching on and clearly separated from adjacent viable myocytes. The infiltrate consists of a mixture of polymorphonuclear leukocytes, macrophages, lymphocytes, and plasma cells. Hematoxylin and eosin 200x. (*Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

Rejection

Improved immunosuppressive regimens in heart transplant patients have substantially decreased the incidence of serious rejection episodes. Nonetheless, rejection phenomena still cause cardiac failure or serious arrhythmias in some patients. Hyperacute rejection occurs rarely, most often when a major blood group incompatibility exists between donor and recipient, and acute rejection is unusual earlier than 2 to 4 weeks postoperatively. Acute rejection episodes occur largely but not exclusively in the first several months after transplantation; rejection can occur years postoperatively, validating the practice of many transplant centers to continue late surveillance biopsies at widely spaced intervals.[273]

Acute cellular rejection is characterized histologically by an inflammatory cell infiltrate, with or without damage to cardiac myocytes; in late stages, vascular injury may become prominent (Fig. 5-36). Until recently, the International Society for Heart and Lung Transplantation (ISHLT) working

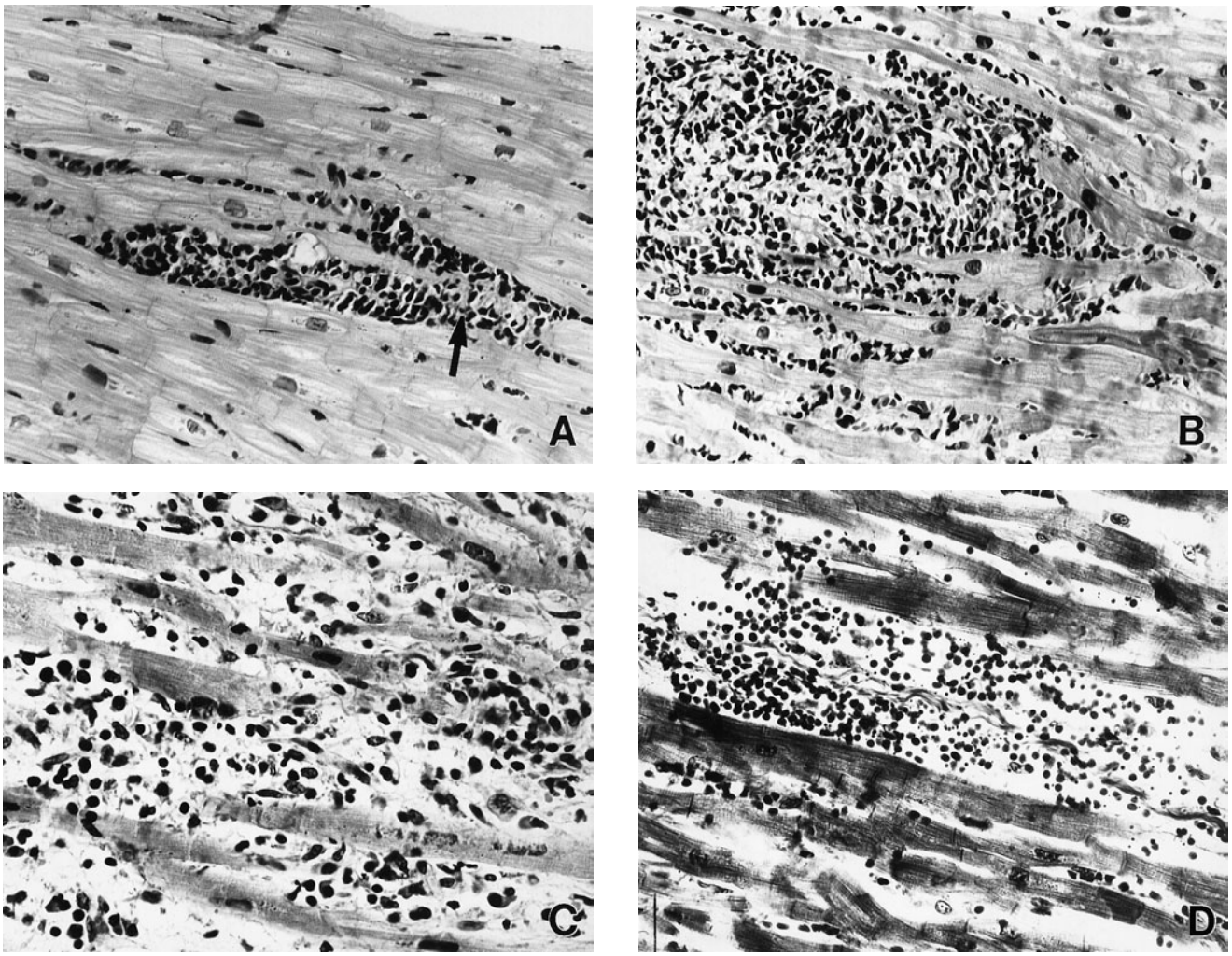


Figure 5-36. Histologic features of rejection. (A) Focal moderate rejection with necrosis. The area of myocyte necrosis is indicated by an arrow. (B) More intense focus of inflammatory infiltrate, with large focus of myocyte necrosis. (C) Fatal rejection with extensive infiltrate and myocyte necrosis. (D) Fatal rejection with widespread myocardial hemorrhage, and necrosis edema. Hematoxylin and eosin 375x. (*Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

formulation from 1990 was the most widely accepted and was used to guide immunosuppressive therapy in heart transplant recipients.[274,275] In this grading system, grade 0 represents no evidence of acute cellular rejection. Mild acute cellular rejection (grades 1A and 1B) is characterized by a focal or diffuse, respectively, mild perivascular or interstitial lymphocytic infiltrate without myocyte damage. Lymphocytic inflammatory infiltrates with associated myocyte encroachment or damage, generally called moderate rejection, can be limited to a single focus (grade 2), present in a multifocal pattern (grade 3A), or be distributed diffusely (grade 3B). In severe rejection (grade 4), myocyte necrosis is more evident, there is often patchy interstitial hemorrhage due to vascular damage, and vasculitis (usually arteriolitis) may be prominent. The increased inflammatory infiltrate often also includes neutrophils or eosinophils, presumably in response to myocyte necrosis or vascular damage. In 2004, the grading system was revised as follows (with the "R" reflecting the revised system): grade 0R—no rejection (no change from 1990); grade 1R—mild rejection (1990 grades 1A, 1B, and 2); grade 2R—moderate rejection (1990 grade 3A); and grade 3R—severe rejection (1990 grades 3B and 4). The 1990 and 2004 formulations are compared in Table 5-4.

Acute antibody-mediated rejection, also called humoral rejection, is recognized as a clinical entity in the transplanted heart, but remains problematic, as no clear consensus has been reached on its recognition or diagnosis either histopathologically or immunologically. If there is suspicion of antibody-mediated rejection, either clinically or by proposed histologic criteria, biopsies may be analyzed by immunofluorescence or immunohistochemistry for (1) immunoglobulin (IgG, IgM, and/or IgA) plus complement deposition (C3d, C4d, and/or C1q) in capillaries, (2) CD68 staining of macrophages within capillaries, and/or (3) C4d staining of capillaries. Treatment of

Table 5–4.

ISHLT Standardized Cardiac Biopsy Grading of Acute Cellular Rejection: Clinicopathologic Comparison of 1990 and 2004 Formulations

Rejection level	Histologic findings	Rejection grade 1990	Rejection grade 2004	Clinical response
None	Normal	0	0	No change
Mild	Lymphocytic inflammation ± one focus of myocyte damage	1A, 1B, 2	1R	No/minimal change to chronic immunosuppressive regimen
Moderate	Lymphocytic inflammation + multiple foci of myocyte damage	3A	2R	Steroid bolus ± change in chronic immunosuppressive regimen
Severe	Lymphocytic inflammation + diffuse myocyte damage ± vascular injury	3B, 4	3R	Aggressive therapy (e.g., steroids ± monoclonal antibodies [OKT3])

ISHLT = International Society for Heart and Lung Transplantation.

patients with antibody-mediated rejection typically requires the presence of hemodynamic compromise and the presence of circulating human leukocyte antigen antibodies in addition to positive biopsy findings.

Immunosuppressive protocols and the threshold for treatment of histologic rejection vary greatly among heart transplant centers; in particular, the clinical significance of mild to moderate rejection is controversial.[276,277] ISHLT grades 1A, 1B, and 2 (from the 1990 system) have been shown to resolve without specific change in management in over 80% of cases, and therefore these levels of rejection remain untreated in many (but not all) heart transplant centers (and they were merged into a single category in the 2004 grading system). Progression of lower rejection grades to advanced rejection on subsequent biopsies becomes less likely with increasing postoperative interval, and is especially unusual beyond 2 years.

Other important findings in surveillance endomyocardial biopsies that must be distinguished from rejection include lymphoid infiltrates, either confined to the endocardium or extending into the underlying myocardium and often accompanied by myocyte damage (so-called Quilty lesions, which have no known clinical significance), old biopsy sites, and healing ischemic injury either in the perioperative period or resulting from the development of graft vasculopathy. Lymphoproliferative disorders and infections may also be seen in biopsies. Apoptosis of myocytes occurs during rejection, with its prevalence paralleling the severity of rejection.[278]

Infection

The immunosuppressive therapy required in all heart transplant recipients confers an increased risk of infection with bacterial, fungal, protozoan, and viral pathogens, with cytomegalovirus and *Toxoplasma gondii* remaining the most common opportunistic infections. Prophylaxis in the form of oral ganciclovir is typically given to patients at high risk of primary cytomegalovirus infection (donor seropositive, recipient seronegative). Viral and parasitic infections can present a challenge in endomyocardial biopsies, as the multifocal lymphocytic infiltrates with occasional necrosis seen with these infections can mimic rejection.

Graft vasculopathy (graft coronary arteriosclerosis)

Graft vasculopathy is the major limitation to long-term graft and recipient survival following heart transplantation.[279] Up to 50% of recipients have angiographically evident disease 5 years after transplantation, while intravascular ultrasound identifies graft vasculopathy in 75% of patients at 3 years posttransplant.[280,281] However, graft vasculopathy may become significant at any time and can progress at variable rates. We have encountered numerous instances of graft coronary disease within 6 to 12 months postoperatively at the Brigham and Women's Hospital.

Graft vasculopathy (Fig. 5-37) occurs diffusely within small distal vessels and ultimately involves both intramyocardial and epicardial allograft vessels, potentially leading to MI, arrhythmias, CHF, or sudden death.[282] Although this process has been called accelerated atherosclerosis, the morphology of the obstructive lesion of graft vasculopathy is distinctive in comparison to typical atherosclerosis (Table 5-5).

The vessels involved have concentric occlusions characterized by marked intimal proliferation of myofibroblasts and smooth muscle cells with deposition of collagen, ground substance, and lipid. Lymphocytic infiltration varies from almost none to quite prominent, with the lymphocytes often noted in a subendothelial location. The internal elastic lamina often is almost completely intact, with only focal fragmentation. The resulting myocardial pathology includes subendocardial myocyte vacuolization (indicative of sublethal

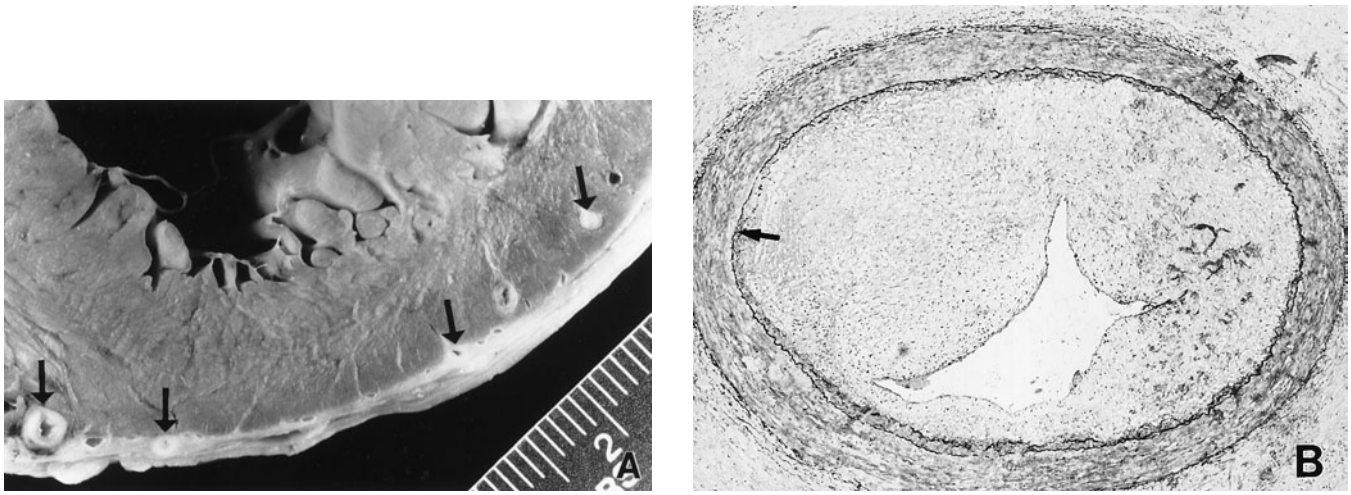


Figure 5-37. Gross and microscopic features of graft coronary disease. (A) Gross photograph of transverse cross-section of heart from a patient who died of graft arteriosclerosis. Severe concentric stenosis of epicardial and large intramural coronaries is apparent (arrows). (B) Histologic appearance of graft arteriosclerosis in low-power photomicrograph of vessel cross-section, demonstrating severe, near-complete, and predominantly concentric intimal proliferation with nearly intact internal elastic lamina (arrow). Verhoeff-van Gieson stain (for elastin) 60x. (*A: Reproduced with permission from Schoen FJ, Libby P: Cardiac transplant graft arteriosclerosis. Trends Cardiovasc Med 1991; 1:216. B: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

ischemic injury) and myocardial coagulation necrosis (indicative of infarction).

Although the precise mechanisms of graft vasculopathy are not definitely established, there is mounting evidence that graft vasculopathy is caused by both chronic allogenic immune response to the transplant and nonimmunologic factors that contribute to vascular injury. Endothelial injury, both cell-mediated and humoral, is likely the initiating event; endothelial cell dysfunction precedes the angiographic manifestations of graft vasculopathy. Alloreactive T cells, activated by major histocompatibility complex class II molecules on donor endothelium, secrete cytokines that amplify the immune response and result in upregulation of endothelial cell adhesion molecules, leading to accumulation of macrophages in the vessel wall and a localized, sustained inflammatory response. Activated macrophages, foam cells that have taken up oxidized low-density lipoprotein cholesterol, and lymphocytes express cytokines and growth factors such as platelet-derived growth factor, fibroblast growth factor, and transforming growth factor-β, that promote proliferation of smooth muscle cells and myofibroblasts and extracellular matrix synthesis. Hyperlipidemia, specifically high levels of oxidized low-density lipoprotein cholesterol, can predict the development of graft vasculopathy. Advanced donor age, cytomegalovirus infection, perioperative graft ischemia, diabetes, and hyperhomocysteinemia have been associated with graft vasculopathy, but their roles in the evolution of the disease remain uncertain. There is no apparent difference in the frequency with which graft vasculopathy develops in patients who were transplanted for end-stage CAD and those operated for idiopathic cardiomyopathy. Recent studies suggest that the intimal cells present in the intima in graft arteriosclerosis may be at least partially derived from the bone marrow of the recipient.[283]

Early diagnosis of graft vasculopathy is limited by the lack of clinical symptoms of ischemia in the denervated allograft, by the relative insensitivity of coronary angiography, which frequently underestimates the extent and severity of this diffuse disease, and by the exclusive or predominant involvement of small intramyocardial vessels. Histologic changes of chronic ischemia such as subendothelial myocyte vacuolization can be seen on surveillance biopsies and may suggest graft vasculopathy (Fig. 5-38). Although not usually amenable to angioplasty, endarterectomy, or CABG because of their diffuse distribution, stenoses may be alleviated by these procedures in occasional cases. For most cases, however, retransplantation is the only effective therapy for established graft atherosclerosis.

Posttransplant lymphoproliferative disorders

Posttransplant lymphoproliferative disorders (PTLDs) are a well-recognized complication of the high-intensity long-term immunosuppressive therapy required to prevent rejection in cardiac allografts. Several factors increase the risk of developing PTLD, including pretransplant Epstein-Barr virus (EBV) seronegativity (10- to 75-fold increase), young recipient age, and cytomegalovirus infection or mismatching (donor-positive, recipient-negative).[284,285] The incidence of PTLD in cardiac transplant recipients is approximately 3%, and the mortality can be as high as 55% at 1 year following the diagnosis of PTLD.[286]

PTLDs can present as an infectious mononucleosis-like illness or with localized solid tumor masses, especially in extranodal sites (e.g., heart, lungs, and gastrointestinal tract). The vast majority (>90%) of PTLDs derive from the B-cell lineage and are associated with EBV infection, although T- or NK-cell origin and late-arising EBV-negative lymphoid

Table 5–5.

Characteristics of Graft Arteriosclerosis versus Typical Atherosclerosis

Graft arteriosclerosis	Typical atherosclerosis
Rapid onset (months to years)	Slow onset (many years)
Risk factors uncertain	Hypertension, lipids, smoking, etc.
Usually silent/congestive heart failure, sudden death	Chest pain, etc.
Diffuse	Focal
Epicardial/intramural	Epicardial
Concentric	Eccentric
Lesions rarely complicated	Lesions often complicated
Smooth muscle cells, macrophages, lymphocytes	Smooth muscle cells, macrophages, foam cells
Primary immunologic mechanism(s)	Complicated stimuli
Difficult to treat; retransplant usually only option	Revascularization by angioplasty, stents, aortocoronary bypass

Source: Reproduced with permission from Schoen FJ, Libby P: Cardiac transplant graft arteriosclerosis. Trends Cardiovasc Med 1991; 1:216.

malignancies have been described. There is strong evidence that the lesions progress from polyclonal B-cell hyperplasias ("early lesions") to lymphomas ("monomorphic PTLDs") in a short period of time, in association with the appearance of cytogenetic abnormalities. Therapy centers on a stepwise approach of antiviral treatment and reduction of immunosuppression, and then progression to lymphoma chemotherapy. Monoclonal antibodies (rituximab) against the B-cell marker CD20 have yielded impressive initial results and may become an important component of PTLD therapy.[287] As the understanding of the risk factors and pathogenesis of PTLDs has expanded, pre-emptive or prophylactic therapies may help prevent this complication of transplantation.

Cardiac Assist Devices and Total Artificial Hearts

Continuing and increasing discrepancy between the number of available donor hearts and therefore transplants performed (less than 2300 annually in the United States, and declining)[288] and the number of patients in the terminal phase of heart failure and refractory to medical management (estimated 250,000 to 500,000 in the United States, and rising)[289] has prompted efforts in the development of ventricular assist devices (VADs), total artificial hearts, and cardiomyoplasty techniques.[290–292] These areas are briefly reviewed in the following sections, from the perspective of cardiac pathology.

Mechanical cardiac assist devices and artificial hearts have traditionally been used in two settings: for ventricular augmentation sufficient to permit a patient to survive postcardiotomy or postinfarction cardiogenic shock while ventricular recovery is occurring, and as a bridge to transplantation when ventricular recovery is not expected and the

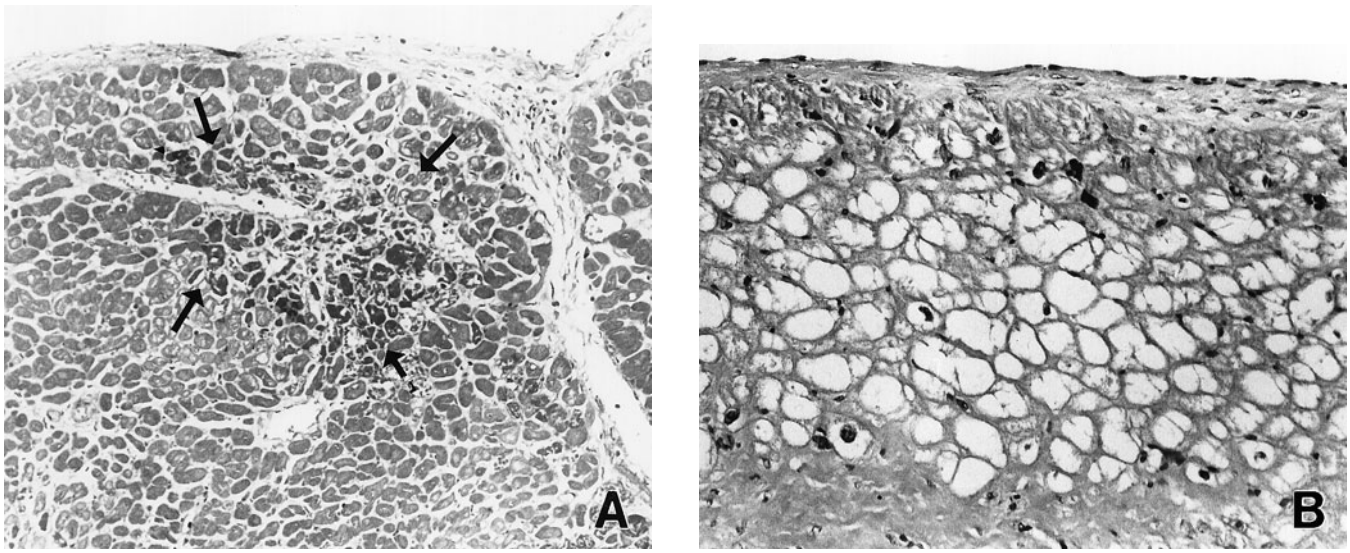


Figure 5-38. Graft arteriosclerosis–induced myocardial pathology in heart transplant recipients. (A) Myocardial microinfarct indicative of disease of small intramural arteries (outlined by arrows) and (B) subendocardial myocyte vacuolization indicative of severe chronic ischemia. Hematoxylin and eosin, 375x.

goal is hemodynamic support until a suitable donor organ is located.[293,294] More recently, LVADs have been shown to provide long-term cardiac support with survival and quality-of-life improvement over optimal medical therapy in patients with end-stage CHF who are not candidates for transplantation.[295,296] LVADs are also being investigated as a bridge to recovery in patients with CHF to induce reverse ventricular remodeling leading to an improvement in cardiac function that would eventually allow device removal.[297] Many types of pumps are currently under development or in clinical use as VADs.[298] Mechanical devices that entirely replace the native heart are currently in use or under development as a bridge to transplant (e.g., CardioWest Total Artificial Heart)[299] or as destination therapy (e.g., AbioCor).[300,301]

The major complications of cardiac assist devices are hemorrhage, thrombosis/thromboembolism, and infection (Fig. 5-39).[302–305] Hemorrhage continues to be a problem in device recipients, although the risk of major hemorrhage has been decreasing with improved therapies and methods. Many factors predispose to perioperative hemorrhage including: (1) coagulopathy secondary to hepatic dysfunction, poor nutritional status, and antibiotic therapy; (2) platelet dysfunction and thrombocytopenia secondary to cardiopulmonary bypass; and (3) the extensive nature of the required surgery.

Nonthrombogenic blood-contacting surfaces are essential for a clinically useful cardiac assist device or artificial heart. Indeed, thromboembolism occurred in most patients having long-term implantation of the Jarvik-7 artificial heart and is a major design consideration for current devices. Thrombi form primarily in association with crevices and voids, especially in areas of disturbed blood flow such as near connections of conduits, valves and other components to each other and to the natural heart (see Fig. 5-39A and B). Most pumps have used smooth polymeric pumping bladders; these are frequently associated with thromboembolic complications. One approach (HeartMate, Thoratec, Pleasanton, CA) to the design of the blood pump is the use of textured polyurethane and titanium surfaces, which accumulate a limited platelet/fibrin pseudointimal membrane that is resistant to thrombosis, allowing only antiplatelet therapy for anticoagulation in most device recipients.[306,307]

Infectious complications have been a major limiting factor in the prolonged use of cardiac assist devices. Infection can occur within the device (see Fig. 5-39C), but may also be associated with percutaneous drive lines. Susceptibility to infection is not only potentiated by the usual prosthesis-associated factors, but also by the multisystem organ damage from the underlying disease, the periprosthetic culture medium provided by postoperative hemorrhage, and by prolonged hospitalization with the associated risk of nosocomial infections. Accounting for significant morbidity and mortality following device use, these infections are often resistant to antibiotic therapy and host defenses. However, infection is not an absolute contraindication to subsequent cardiac transplantation.[308] In the REMATCH trial, sepsis accounted for 21 of the 57 deaths among the patients receiving LVADs. Novel device designs, including alternative sites for driveline placement[309] and the elimination of the driveline altogether with transcutaneous energy transmission technology[310] may play a role in further decreasing this devastating complication.

Other complications include hemolysis, pannus formation around anastomotic sites, calcification (see Fig. 5-39D and E), and device malfunction.[311] Device failure can occur secondary to fracture or tear of one of the prosthetic valves within the device conduits, as this application provides a particularly severe test of valve durability (see Fig. 5-39F). Device failure can also occur secondary to damage or dehiscence of the pumping bladder (see Fig. 5-39G). There is evidence that patients on VADs are more likely to develop allosensitization, which can pose a significant risk to post-transplantation outcome in the bridge-to-transplant patients.[312] These complications not only have significant morbidity and can be fatal in themselves, but they may make a patient ineligible for future transplantation.

To what extent recovery of myocardial function can occur during VAD implantation is uncertain. Many pathophysiologic changes occur during the progression to end-stage heart failure, ranging from the subcellular (e.g., abnormal mitochondrial function and calcium metabolism) to the organ and system level (e.g., ventricular dilation, decreased ejection fraction, and neurohormonal changes), leading to the signs and symptoms of congestive failure. Implantation of an LVAD can reverse many of these changes ("reverse remodeling"), leading to increased cardiac output, decreased ventricular end-diastolic volume, and normalization of neurohormonal status such that a small fraction of patients can be weaned from the device without the need for subsequent cardiac transplantation. Current research focuses on the mechanisms of cardiac recovery, identification of patients who could achieve recovery, and specifics such as the timing and duration of therapy.[313–315]

Skeletal Muscle Augmentation of Cardiac Function

Autologous skeletal muscle has been used to provide active cardiac assist in the form of both cardiomyoplasty and skeletal muscle ventricles for patients with heart failure.[316] In cardiomyoplasty, the latissimus dorsi is wrapped around the ventricles, and this has been shown to stabilize left ventricular size and prevent further dilation. Skeletal muscle can adapt its physiologic, biochemical, and structural characteristics to overcome fatigue and adjust to a more demanding pattern of use by increases in capillary density, activity of oxidative enzymes, and increased mitochondrial volume. While these procedures had some promising experimental and clinical results,[317] interest in their application has waned due to several factors, including the improvement in medical therapy for CHF, the development of the mechanical cardiac assist devices discussed above, and the hesitancy of clinicians to refer patients for this procedure given the alternative therapies. Recent investigations have shown improvement in

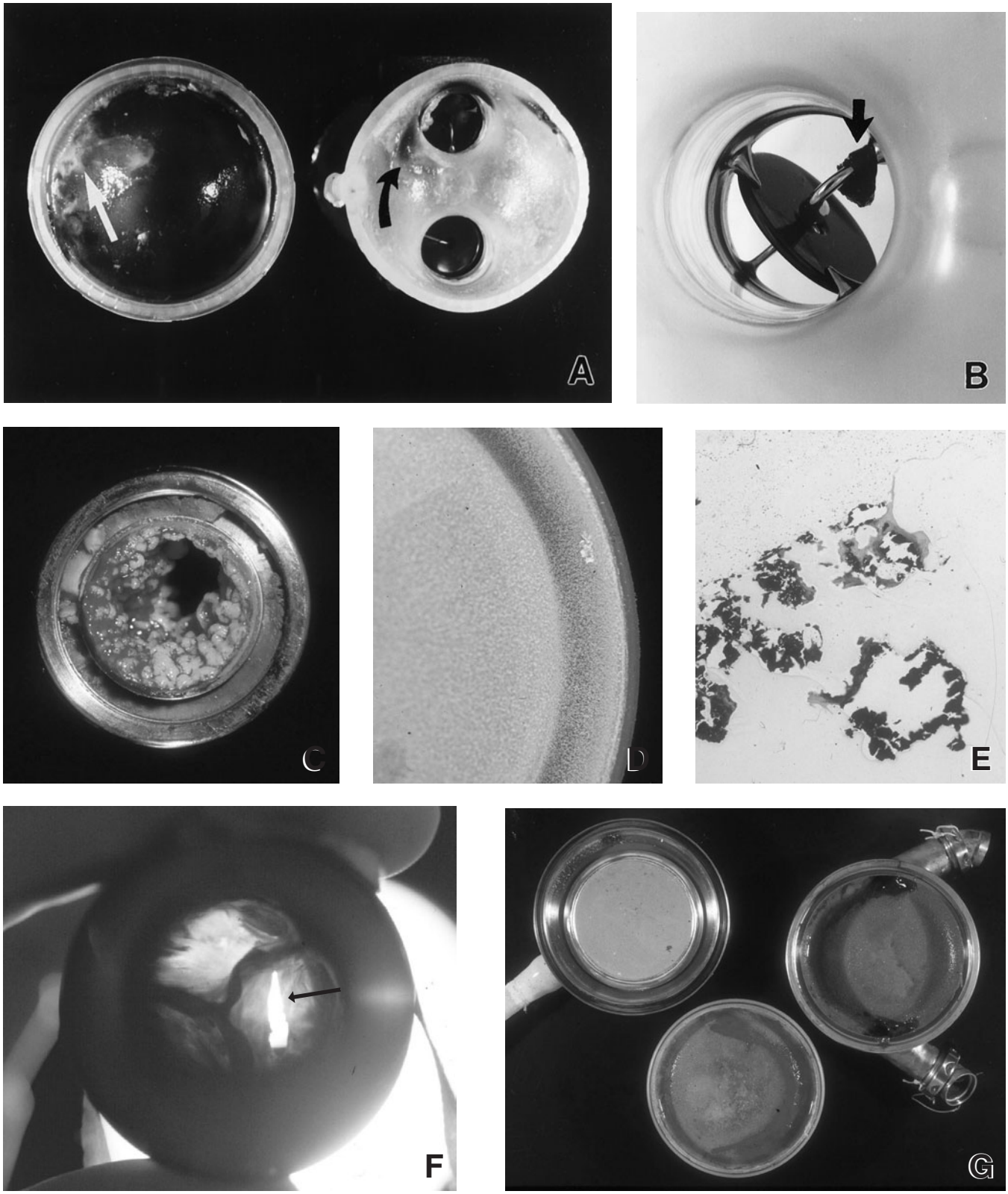


Figure 5-39. Complications of left ventricular assist devices (LVADs). (A and B) Thrombotic deposits at the pump outflow and bladder/housing junction, respectively. (C) Fungal infection in LVAD outflow graft. (D and E) Focal calcification of clinical LVAD. (D) A gross photograph. (E) Histologic section demonstrating calcification (black) (von Kossa stain). (F) Cuspal tear in inflow valve of LVAD. This patient was not a transplant candidate and had been on the LVAD as destination therapy for about 12 months before the tear occurred, causing regurgitation. The valve was replaced without incident. (G) Dehiscence of the bladder of an LVAD. (*A and B: Reproduced with permission from Fyfe and Schoen.*[302] *C, D, E, and G: Reproduced with permission from Schoen and Edwards.*[4])

long-term muscle function using stimulation protocols in which the skeletal muscle is not stimulated with every heartbeat, or is given rest during periods of low demand such as during sleep.[318,319] In addition, this procedure is an alternative in regions without access to cardiac transplantation and mechanical assist,[320] especially given the improvements with new stimulation protocols.

ARRHYTHMIAS

Arrhythmias generally occur as a result of disorders of electrical impulse formation, disorders of electrical impulse conduction, or a combination of the two. The underlying anatomic substrates for arrhythmogenesis are many. Many of the primary cardiomyopathies can present with arrhythmias, including the genetic (e.g., hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and the ion channelopathies), mixed (e.g., dilated cardiomyopathy) and acquired (e.g., myocarditis) groups. Many secondary cardiomyopathies also may have arrhythmias as a predominant feature (e.g., sarcoidosis). A common cause of arrhythmias and sudden death (especially in the older adult population) is ischemic heart disease, both in patients with and without a prior MI. Myocardial hypertrophy and fibrosis of any etiology (e.g., secondary to valvular heart disease, hypertension, or a remote infarction) also can provide the anatomic and functional substrate for the development of an arrhythmia. These underlying processes and pathologic anatomy increase the risk of spontaneous lethal arrhythmias in the setting of acute initiating events such as acute ischemia, neurohormonal activation, changes in electrolytes, and other metabolic stressors.[321]

Treatments for arrhythmias and their complications include pharmacologic therapy, device therapy[322] (pacemakers and implantable defibrillators), and ablation therapy.

Pacemakers and Implantable Cardioverter-Defibrillators

Modern cardiac pacing (Fig. 5-40) is achieved by a system of interconnected components consisting of (1) a pulse generator that includes a power source and electric circuitry to initiate the electric stimulus and to sense normal activity; (2) one or

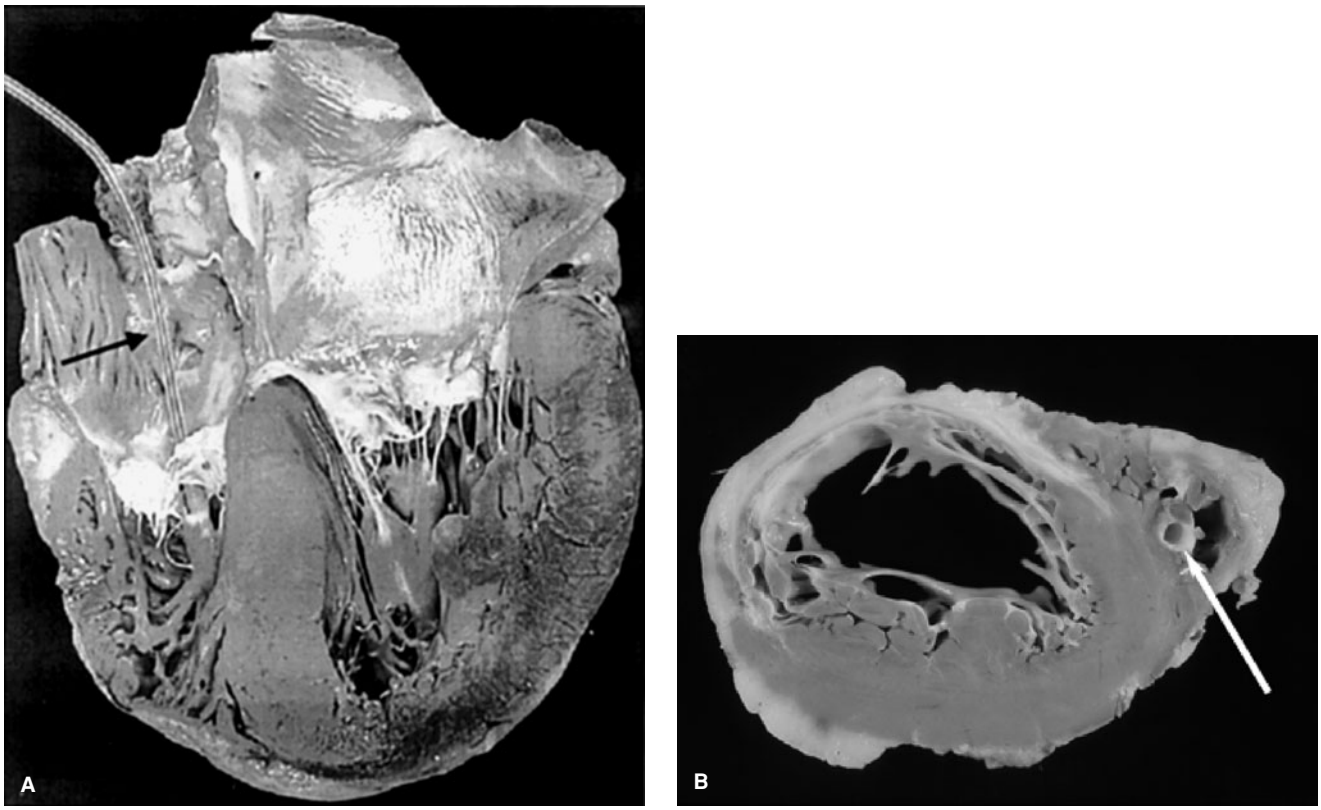


Figure 5-40. Cardiac pacemaker leads in the heart. (A) Pacemaker coursing through right atrium (arrow) and tricuspid valve, ending in right ventricle of heart of patient with hypertensive concentric thickening of the left ventricular wall. (B) Low ventricular section demonstrating fibrosis (arrow) around a pacemaker lead (removed) in the right ventricle of the heart of a patient with an anterior/septal scar (remote transmural myocardial infarction). (A) Reproduced by permission from Schoen FJ: The heart, In: Robbins/Cotran Pathologic Basis of Disease, 7th ed., Kumar V, Fausto N, Abbas A [eds.] Philadelphia, WB Saunders, 2004. pp.555–618.

more electrically insulated conductors leading from the pulse generator to the heart, with a bipolar electrode at the distal end of each; and (3) a tissue, or blood and tissue, interface between the electrode and adjacent stimulatable myocardial cells, which is of critical importance in the proper functioning of the pacemaker. Typically, a layer of nonexcitable fibrous tissue forms around the tip of the electrode (see Fig. 40-B). This fibrosis may be induced by the electrode itself or may be due to myocardial scarring from some other cause, most commonly a healed MI. The thickness of this nonexcitable tissue between the electrode and excitable tissue determines the stimulus threshold, or the strength of the pacing stimulus required to initiate myocyte depolarization, and thus the amount of energy required from the pacemaker. Attempts to reduce the thickness of this layer (thereby extending battery life) include improved lead designs[323] with active fixation, and the use of slow, local release of corticosteroids from the lead tip.[324] Implantable cardioverter-defibrillators (ICDs) are used in the treatment of patients who have life-threatening ventricular arrhythmias that are refractory to medical management and unsuitable for other surgical or ablative therapy. They have similar components to the pacemaker described above. These devices sense arrhythmias that can lead to sudden death and deliver therapy in the form of rapid ventricular pacing and/or a defibrillation current to terminate the dysrhythmic episode. ICDs also must overcome the barrier posed by the interfacial fibrosis at the electrode tip.

Complications from the use of pacemakers include lead displacement; vascular or cardiac perforation leading to hemothorax, pneumothorax, or tamponade; lead entrapment; infection; erosion of the device into adjacent tissues due to pressure necrosis; rotation of the device within the pocket; thrombosis and/or thromboembolism; and lead fracture, in addition to malfunctions of the device itself. If the lead needs to be extracted for chronic infection or device-related defects, damage to the myocardium and/or tricuspid valve may occur secondary to encasement of the lead in fibrous tissue. Similar complications affect ICDs, with additional considerations being the consequences of repeated defibrillations on the myocardium and vascular structures including myocardial necrosis, and the risk of oversensing (with resultant unnecessary shocks) or undersensing (with resultant sudden death). Increased attention has been paid of late to malfunctioning ICDs because of electrical flaws in a specific model that resulted in failure to terminate fatal arrhythmias.[325] It should be noted that it was through the performance of an autopsy on a patient with hypertrophic cardiomyopathy and sudden death (finding no other cause of sudden death) and the subsequent evaluation of the device by the manufacturer that the flaw in this device was brought to light. As a result, there have been many discussions on the topics of postmarket surveillance, device reliability, and the responsibilities of industry, physicians, and regulators. Diligent postmarket surveillance is especially important for ICDs in particular, as the majority of patients who die suddenly are unfortunately not autopsied and it is unknown how many of these deaths may be device related.

Ablation

Ablation involves the directed destruction of arrhythmogenic myocardium, accessory pathways, or conduction system structures to control or cure a variety of arrhythmias, including atrial flutter and fibrillation, ventricular tachycardias and paroxysmal supraventricular tachycardias, that are refractory to medical management.[326–328] Ablation can be carried out as part of a surgical procedure or via percutaneous catheter. Electrophysiologic studies can be used to (1) provide information on the type of rhythm disturbance, (2) terminate a tachycardia by electrical stimulation, (3) evaluate the effects of therapy, (4) ablate myocardium involved in the tachycardia, and (5) identify patients at risk for sudden cardiac death.

Radiofrequency ablation acutely produces coagulation necrosis within the myocardium directly underneath the source tip, eliminating the source or pathway of the arrhythmia (Fig. 5-41). The characteristic histologic changes include loss of myocyte striations, loss or pyknosis of nuclei, hypereosinophilia, and contraction bands. The edge of the fresh lesion is often hemorrhagic with interstitial edema and inflammation. The area undergoes the usual progression of healing similar to that in an infarct, with an early neutrophilic infiltrate, followed by macrophages to handle the necrotic debris, followed by granulation tissue formation and eventual scarring. Through the use of irrigated, cooled catheters, the lesions can penetrate deeply into the myocardium. Techniques using other forms of energy, including cryoablation, microwave, and lasers have been used to create lesions in the myocardium for the treatment of arrhythmias.

NEOPLASTIC HEART DISEASE

Although metastatic tumors to the heart are present in 1 to 3% of patients dying of cancer, primary tumors of the heart are unusual.[329–331] The most common tumors, in descending order of frequency, are: myxomas, lipomas, papillary fibroelastomas, angiomas, fibromas, and rhabdomyomas, all benign and accounting for approximately 80% of primary

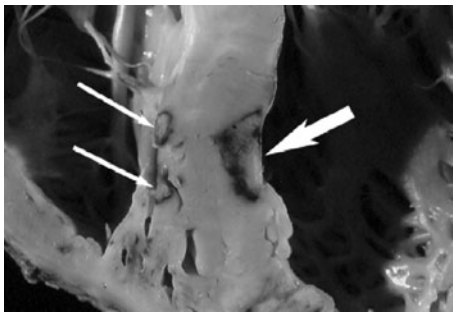


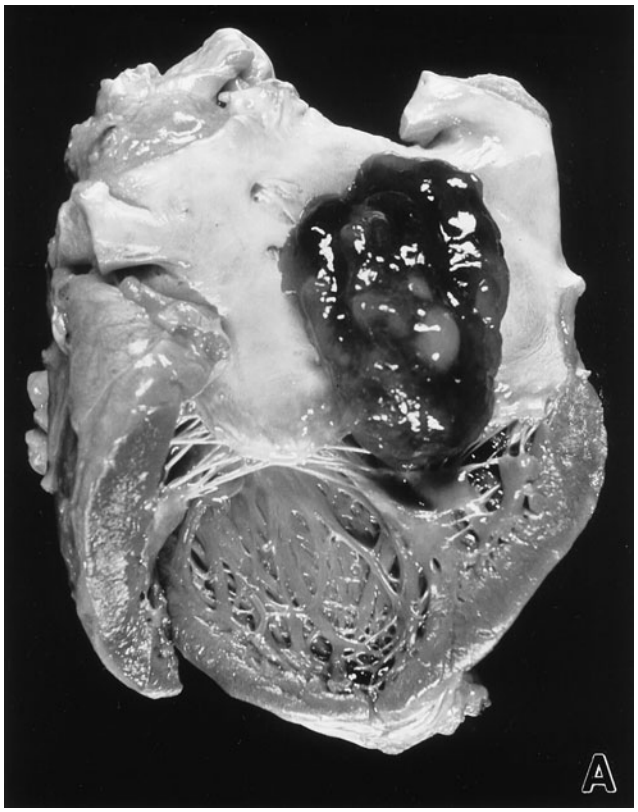
Figure 5-41. Ablation of arrhythmogenic foci by radiofrequency ablation. Recent endocardial ablation site on right (2 small arrows) and left (single arrow) ventricular sides of interventricular septum.

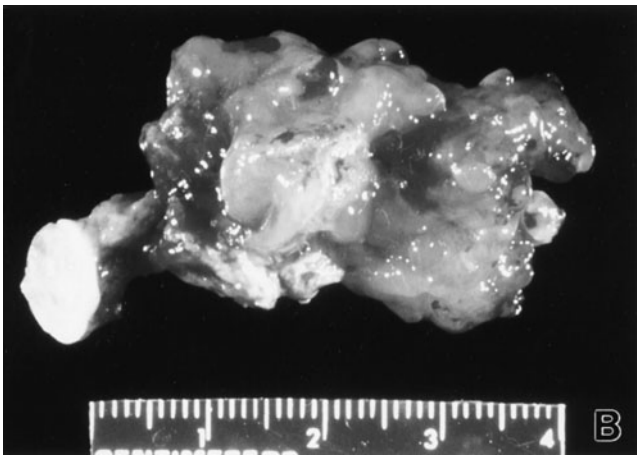
tumors of the adult heart. The remaining 20% are malignant tumors, including angiosarcomas, other sarcomas and lymphomas. Many cardiac tumors have a genetic basis.[332]

Myxoma

Myxomas are the most common primary tumor of the heart in adults, accounting for about 50% of all benign cardiac tumors.[333] They typically arise in the left atrium (80%) along the interatrial septum near the fossa ovalis. Occasionally, myxomas arise in the right atrium (15%), the ventricles (3 to 4%), or valves. These tumors arise more frequently in women and usually present between the ages of 50 and 70 years. Sporadic cases of myxoma are almost always single, while familial cases can be multiple and present at an earlier age.

Myxomas range from small (<1 cm) to large (up to 10 cm) and form sessile or pedunculated masses that vary from globular and hard lesions mottled with hemorrhage to soft, translucent, papillary, or villous lesions having a myxoid and friable appearance (Fig. 5-42). The pedunculated form frequently is sufficiently mobile to move into or sometimes through the ipsilateral atrioventricular valve annulus during





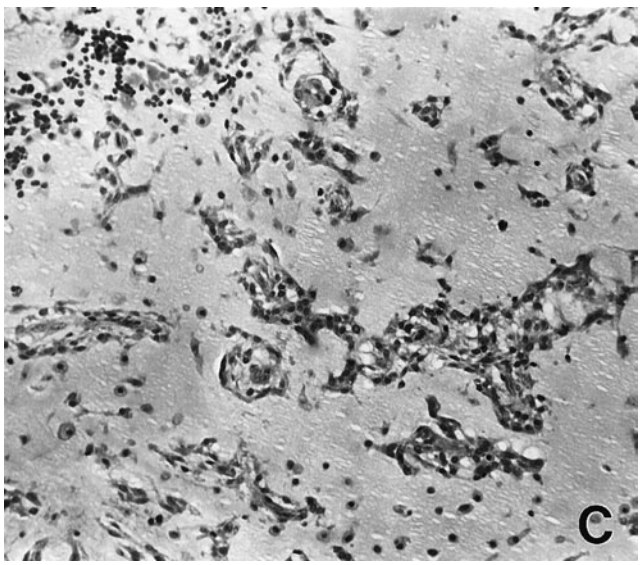


Figure 5-42. Gross and histologic features of cardiac myxomas. (A) Smooth, round, hemorrhagic left atrial myxoma, noted at autopsy. The tumor mass nearly fills the left atrium and extends into the mitral valve orifice. (B) Irregular polypoid, gelatinous friable myxoma mass that was surgically removed. The resection margin that surrounds the proximal portion of the stalk is at left. (C) Characteristic histologic features of myxoma, including individual tumor cells and clusters and islands scattered throughout the characteristic granular extracellular matrix. Hematoxylin and eosin 50x. (*A: Reproduced with permission from Schoen FJ: The heart, in Cotran RS, Kumar V, Collins T [eds]: Pathologic Basis of Disease, 6th ed. Philadelphia, WB Saunders, 1994; p 543. B: Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

ventricular diastole, causing intermittent and often position-dependent obstruction. Sometimes such mobility exerts a wrecking ball effect, causing damage to and secondary fibrotic thickening of the valve leaflets.

Clinical manifestations are most often determined by tumor size and location; some myxomas are incidentally detected in patients undergoing echocardiography for other indications, while others may present with sudden death. Symptoms are generally a consequence of valvular obstruction, obstruction of pulmonary or systemic venous return, embolization, or a syndrome of constitutional symptoms. Intracardiac obstruction may mimic the presentation of mitral or tricuspid stenosis with dyspnea, pulmonary edema, and right-sided heart failure. Fragmentation of a left-sided tumor with embolization may mimic the presentation of infective endocarditis with transient ischemic attacks, strokes, and cutaneous lesions; emboli from right-sided lesions may present as pulmonary hypertension. Constitutional symptoms such as fever, erythematous rash, weight loss, and arthralgias may be due to the release of the acute phase reactant interleukin-6 from the tumor, leading to these inflammatory and autoimmune manifestations. Echocardiography, including transesophageal echocardiography, provides a means to noninvasively identify the masses and their location, attachment, and mobility. Surgical removal usually is curative with excellent short- and long-term prognosis. Rarely, the neoplasm recurs months to years later, usually secondary to incomplete removal of the stalk.

The Carney complex, as it is now known, is a multiple neoplasia syndrome featuring cardiac and cutaneous myxomas, endocrine and neural tumors, as well as pigmented skin and mucosal lesions. Previously described cardiac myxoma syndromes such as LAMB (*l*entigines, *a*trial myxoma, *m*ucocutaneous myxomas, and *b*lue nevi) and NAME (*n*evi, *a*trial myxomas, *m*ucinosis of the skin, and *e*ndocrine overactivity) are now encompassed by the Carney complex. The Carney complex is inherited as an autosomal dominant trait, and is associated with mutations in the *PRKAR1α* gene encoding the R1α regulatory subunit of cyclic adenosine monophosphate–dependent protein kinase A.[334–338] A careful history and physical examination in patients with cardiac myxoma is therefore important to identify other signs of the Carney complex, as this diagnosis carries implications for family members of the patient.

Histologically, myxomas are composed of stellate or globular cells ("myxoma cells"), often in formed structures that variably resemble poorly formed glands or vessels, endothelial cells, macrophages, mature or immature smooth muscle cells, and a variety of intermediate forms embedded within an abundant acid mucopolysaccharide matrix and covered by endothelium. Although it had long been questioned whether cardiac myxomas were neoplasms, hamartomas, or organized thrombi, it is now widely believed that they represent benign neoplasia. These tumors are thought to arise from remnants of subendocardial vasoformative reserve cells or multipotential primitive mesenchymal cells that can differentiate along multiple lineages, giving rise to the mixture of cells present within these tumors.

Other Cardiac Tumors and Tumor-Like Conditions

Cardiac lipomas are discrete masses that are typically epicardial, but may occur anywhere within the myocardium or pericardium. Most are clinically silent, but some may cause symptoms secondary to arrhythmias, pericardial effusion, intracardiac obstruction, or compression of coronary arteries. Magnetic resonance imaging is useful in the diagnosis of adipocytic lesions due to its ability to identify fatty tissues. Histologically, these tumors are comprised of mature adipocytes, identical to lipomas elsewhere. A separate, non-neoplastic condition called lipomatous hypertrophy of the interatrial septum is characterized by accumulation of unencapsulated adipose tissue in the interatrial septum that can lead to arrhythmias. Histologically, this tissue is composed of a mixture of adipose tissue and cardiac myocytes, in contrast to the pure adipose tissue of a proper lipoma.

Papillary fibroelastomas[339,340] are usually solitary and located on the valves, particularly the ventricular surfaces of semilunar valves and the atrial surfaces of atrioventricular valves. The most common site is the aortic valve, followed by the mitral valve. They constitute a distinctive "sea anemone" cluster of hair-like projections up to 1 cm or more in length, and can mimic valvular vegetations echocardiographically (Fig. 5-43).[341] Histologically they are composed of a dense core of irregular elastic fibers coated with myxoid connective tissue and lined by endothelium. They may contain focal platelet-fibrin thrombus and serve as a source for embolization, commonly to cerebral or coronary arteries. Surgical excision is recommended to eliminate these embolic events. Although classified with neoplasms, fibroelastomas may represent organized thrombi, similar to the much smaller, usually trivial, whisker-like Lambl's excrescences that are frequently found on the aortic valves of older individuals.

Rhabdomyomas comprise the most frequent primary tumor of the heart in infants and children.[342] They are usually multiple and involve the ventricular myocardium on either side of the heart. They consist of gray-white myocardial masses up to several centimeters in diameter that may protrude into the ventricular or atrial chambers, causing functional obstruction. These tumors tend to spontaneously regress, so surgery is usually reserved for patients with severe hemodynamic disturbances or arrhythmias refractory to medical management. Most cardiac rhabdomyomas occur in patients with tuberous sclerosis, the clinical features of which also include infantile spasms, skin lesions (hypopigmentation, shagreen patches, and subcutaneous nodules), retinal lesions, and angiomyolipomas. In its familial form, this disease exhibits autosomal dominant inheritance, but about one-half of cases are sporadic, owing to new mutations. Histologically, rhabdomyomas contain characteristic "spider cells," which are large, myofibril-containing rounded or polygonal cells with numerous glycogen-laden vacuoles separated by strands of cytoplasm running from the plasma membrane to the centrally located nucleus.

Figure 5-43. Papillary fibroelastoma. Gross photograph demonstrating resemblance of this lesion to a sea anemone, with papillary fronds arising from the chordae tendineae and near the mitral leaflet (large arrow). In this case multiple lesions were present, all associated with the mitral valve apparatus (small arrowheads). (*Reproduced with permission from Sabatine M, Colucci WS, Schoen FJ: Primary tumors of the heart, in Braunwald E, Libby P, Zipes DP [eds]: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, WB Saunders, 2005; p 1741.*)

Cardiac fibromas, while also occurring predominantly in children and presenting with heart failure or arrhythmias, or incidentally, differ from rhabdomyomas in being solitary lesions that may show calcification on a routine chest radiograph.[343] Fibromas are white, whorled masses that are typically ventricular. There is an increased risk of cardiac fibromas in patients with Gorlin syndrome (nevoid basal cell carcinoma syndrome),[344] an autosomal dominant disorder characterized by skin lesions, odontogenic keratocysts of the jaw, and skeletal abnormalities. Gorlin syndrome is a result of germline mutations in the *PTC* gene on chromosome 9; the role of this gene product in myocardial growth and development is unknown. Histologically, fibromas consist of fibroblasts showing minimal atypia and collagen with the degree of cellularity decreasing with increasing age of the patient at presentation. While they are grossly well circumscribed, there is usually an infiltrating margin histologically. Calcifications and elastin fibers are not uncommon in these lesions.

Sarcomas, with angiosarcomas, undifferentiated sarcomas, and rhabdomyosarcomas being the most common, are not distinctive from their counterparts in other locations. They tend to involve the right side of the heart, especially the right atrioventricular groove (Fig. 5-44). The clinical course

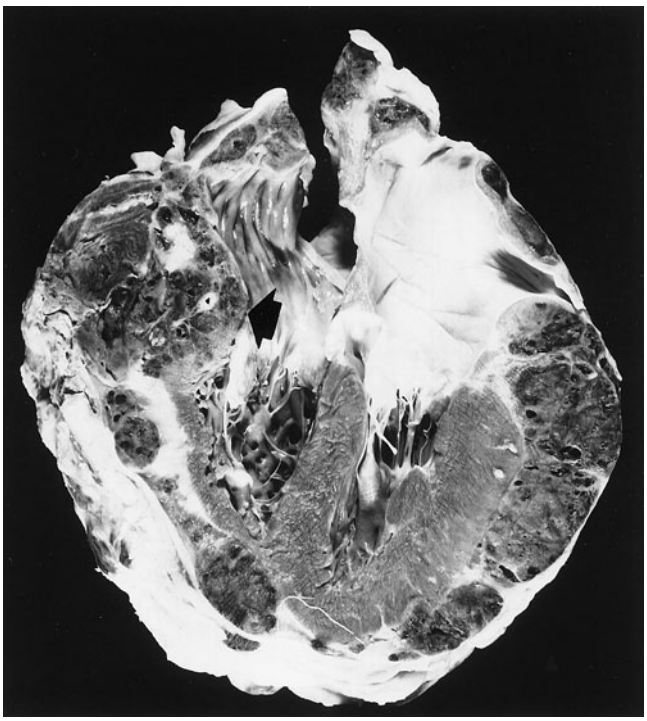


Figure 5-44. Massive pericardial angiosarcoma with deep myocardial invasion at multiple sites, particularly at the right atrium (arrow). (*Reproduced with permission from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, WB Saunders, 1989.*)

is rapidly progressive as a result of local infiltration with intracavity obstruction and early metastatic events.

Recently described, and of importance only insofar as they need to be distinguished from primary cardiac tumors or metastatic carcinoma, are peculiar microscopic-sized cellular cardiac lesions that have been noted incidentally as part of endomyocardial biopsy, surgically removed tissue specimens, or at cardiac surgery, and are free-floating or loosely attached to a valvular or endocardial mass.[345] Termed mesothelial/monocytic incidental cardiac excrescences, they appear histologically largely as clusters and ribbons of mesothelial cells and entrapped erythrocytes and leukocytes, embedded within a fibrin mesh. Some represent reactive mesothelial and/or monocytic (histiocytic) hyperplasia, whereas others are now considered to be artifacts formed by compaction of mesothelial strips (likely from the pericardium) or other tissue debris and fibrin, which are transported via catheters or around an operative site on a cardiotomy suction tip.

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CHAPTER 6

Cardiac Surgical Imaging

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Over the last decade, advances in computed tomography (CT) technology have revolutionized the diagnosis of cardiovascular disease. As illustrated in this chapter, CT has reduced dramatically and, for some clinical indications, eliminated the need for diagnostic arterial catheterization. In the process, CT has become invaluable in cardiac diagnosis and surgical planning.

CT is based on a source of x-rays and a system to detect those x-rays that pass though a patient. The x-ray source and detector are mounted on the CT gantry that rotates around the patient. Two major technological advances have enabled CT to image the beating heart. The first is the speed at which the CT gantry rotates. The second is the incorporation of an increasing number of detectors that can resolve small anatomic detail. One of the great promises of modern CT is the ability to exclude coronary artery disease noninvasively in less than 1 minute with a single CT acquisition (Fig. 6-1). However, the role of CT extends far beyond the coronary arteries alone. Using the same CT acquisition, native coronary imaging can be extended to coronary bypass grafts, the beating myocardium, valve motion, ventricular outflow tracks, and cardiac lesions.

In order to understand the clinical contribution of CT and to avoid pitfalls in image interpretation, it is essential for the surgeon to appreciate the basic principles of CT used in cardiac imaging. This chapter is divided into two parts. The first part describes the technical considerations for cardiac CT. By understanding each component, the surgeon will be better able to distinguish image artifacts from pathology. The second part reviews the CT examinations that are performed most frequently in the Cardiovascular Imaging Section at Brigham and Women's Hospital (BWH), detailing the strengths and limitations of each examination.

CARDIAC CT PROTOCOLS

Most advances in cardiac CT, e.g., in coronary artery CT angiography (CTA), have focused on the development of protocols consistent with the rapid incremental improvements in the technology. One of the major technological advances has been the incorporation of multiple elements into the CT detector system, called *multidetector CT* (MDCT). MDCT is synonymous with *multislice CT*. Data from each of the detectors are used to reconstruct an axial slice perpendicular to the long axis, or *z* axis, of the patient. The width of the detectors determines the width of the slices and thus the ability of the scanner to resolve small anatomic detail (spatial resolution). Thinner slices yield superior spatial resolution; however, comparing two scanners that produce the same number of slices, the scanner with thinner slices will have less *z*-axis coverage per gantry rotation and thus will have a longer scan time.

Temporal Resolution

Successful cardiac imaging by any modality relies on the ability of the hardware to produce motion-free images or, in other words, to image faster than the heart beats. Because it requires that the gantry be rotated around the patient, CT is inherently slower than digital subtraction angiography (DSA), in which each frame corresponds to a single projection image. As described below, CT recently has become much faster, and thus cardiac CT now can be performed routinely.

Temporal resolution is the metric that measures imaging speed. For a CT scanner with a single photon source, the temporal resolution is one-half the CT gantry rotation time. This is so because image reconstruction requires CT data acquired from one half (180 degrees) of a complete gantry rotation. All manufacturers have gantry rotation times of less than 500 ms; at the time of publication, the minimum (or fastest) gantry rotation time is 330 ms (Siemens Sensation 64 Cardiac, Siemens Medical Solutions, Forchheim, Germany). With this gantry rotation, an electrocardiogram (ECG)–gated cardiac image can be reconstructed (using

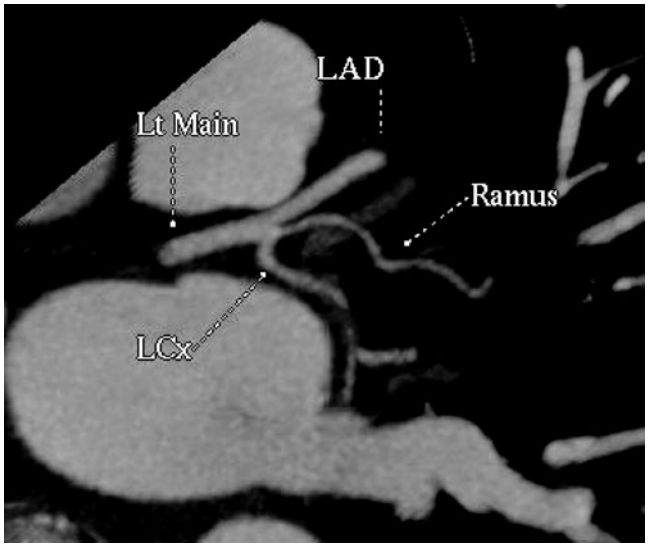

Figure 6-1. Selected coronary computed tomography angiography (CTA) image of the proximal left coronary arterial system in a patient scheduled for isolated mitral valve surgery. Using the protocol detailed in this chapter, CT demonstrated normal coronary arteries in this patient, eliminating the need for arterial catheterization.

single-segment reconstruction, described below) with CT data acquired over 165 ms of the cardiac cycle. Thus the reconstructed images inherently display the average of the cardiac motion over the 165 ms during which the data were acquired. This is how ECG gating enables cardiac CT. Without gating, cardiac images are nondiagnostic because the reconstruction "averages" the motion over the entire RR interval, e.g., over 1000 ms for a patient with a heart rate of 60 bpm.

There are two main strategies to improve temporal resolution. The more recent uses two independent sources and two independent (64-slice) detector systems built into the CT gantry (Siemens Definition, Siemens Medical Solutions, Forchheim, Germany). The second x-ray source is positioned 90 degrees from the first x-ray source, and the second detection system is positioned 90 degrees from the first detection system. With respect to temporal resolution, the practical consequence of this CT configuration is that 180 degrees of gantry rotation can be achieved in half the time (e.g., 82.5 ms as opposed to 165 ms). This halves the temporal resolution (to 82.5 ms), and thus, for this "dual-source" CT configuration, motion is averaged over only 82.5 ms.

For single-source scanners, temporal resolution can be improved by adopting a so-called multisegment image reconstruction. The difference between single-segment and multisegment reconstruction is that in the former, 180 degrees of data are acquired from a single heartbeat, whereas multisegment reconstruction uses several heartbeats to obtain the one-half gantry CT data. For example, in a two-segment reconstruction, two heartbeats are used to generate a single axial slice, and thus the temporal resolution is halved. Similarly, if four heat beats are used (four-segment reconstruction), only 45 degrees of data are used from each heartbeat. This yields a fourfold reduction in the effective temporal resolution, making it theoretically possible to perform high-spatial-resolution cardiac CT in patients with a rapid (e.g., >70 bpm) heart rate. However, since multiple heartbeats are used to fill the 180 degrees of gantry rotation necessary for the reconstruction, stable periodicity of the heart is essential. When beat-to-beat variations in heart rate occur, image quality is degraded significantly. In our experience, multisegment reconstruction works well in patients with high heart rates who are being studied for clinical indications, in whom the highest image quality may not be required (e.g., studies of graft patency, pericardial calcification). For more demanding applications (e.g., native coronary CTA), we still routinely employ beta blockade for heart rates greater than 60 bpm.

Beta Blockade for Heart Rate Control

As suggested earlier, beta blockade is an important component of most cardiac CT examinations. A useful rule of thumb for the target heart rate is, "The first number is a 5"—i.e., an ideal heart rate between 50 and 59 bpm. While this goal is not achieved in every patient, it provides a useful frame of reference. Many surgical patients come to imaging beta blocked as part of their medical therapy. When this is not the case, IV metoprolol is administered routinely in 5-mg increments, given every 5 minutes up to a maximum dose of 25 mg. Doses greater than 15 mg rarely are needed.

ECG Gating

ECG gating refers to the simultaneous acquisition of both the patient's ECG tracing and CT data (Fig. 6-2). With the acquisition of both pieces of information, CT images can be reconstructed using only a short temporal segment periodically located in the R-R interval over multiple cardiac cycles. The duration of the temporal segment is equal to the temporal resolution of the scanner, e.g., 165 ms (330 ms/2) for the Siemens Sensation 64 Cardiac scanner. Each temporal segment of the RR interval is named by its "phase" in the cardiac cycle; the most commonly used nomenclature is to name the percentage of a specific phase with respect to its position in the R-R interval. For example, if a manufacturer enables reconstruction of 20 (equally spaced) phases, they typically would be named 0%, 5%, 10%, . . . 95% beginning with one R wave and ending with the following R wave. The period in which the heart has the least motion usually (but not always) is in middiastole, near a phase between 55% and 75%. Thus, under the assumption that the position of the heart remains consistent over the R-R intervals during which CT data are reconstructed, cardiac motion is minimized by producing images from the same phase over multiple cardiac cycles. This explains why ECG gating typically fails to freeze cardiac motion in patients with an irregular rhythm, such as atrial fibrillation. Consequently, ECG-gated cardiac CT is rarely beneficial in atrial fibrillation patients.

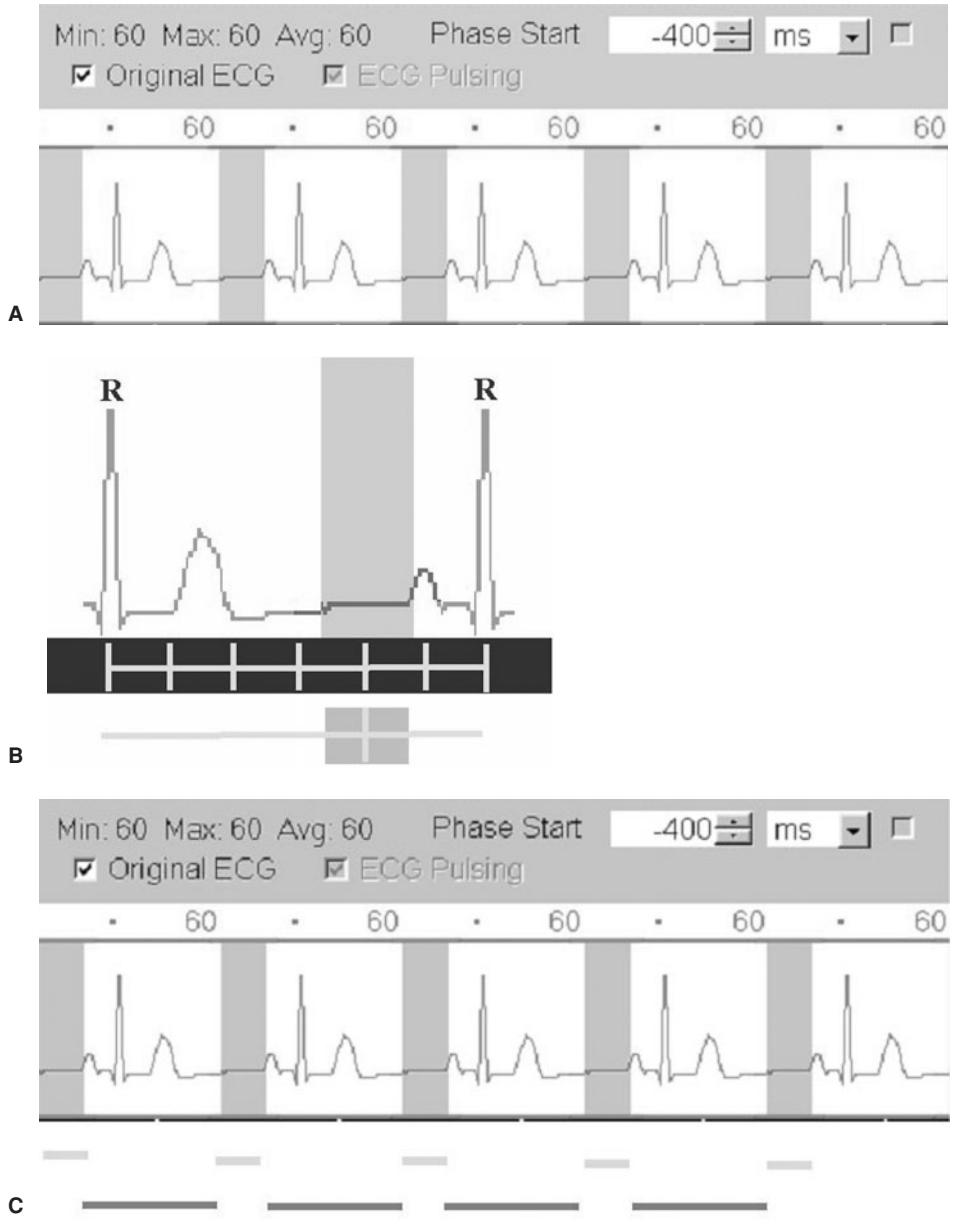

Figure 6-2. (*A*) In gating, the continuous ECG tracing is displayed on the console. In this case, the minimum, maximum, and average heart rate is 60 bpm (R-R interval = 1000 ms). The gray vertical bars indicate that portion of the cardiac cycle used in the reconstruction. As discussed in the text, the width of the gray bar is the temporal resolution of the scan. For this single-segment reconstruction, the width is half the gantry rotation time, or 165 ms. The term "–400 ms" refers to the fact that the center of the gray bars is located 400 ms before the second of the two R waves in the R-R interval. (*B*) Enlarged view of a single R-R interval. To provide a simple demonstration of how the R-R interval is divided, six segments are illustrated. In clinical imaging, CT scanners divide the R-R interval into a number of segments between 10 and 20. The gray block at the very bottom emphasizes that each reconstructed image uses only a small portion of the cardiac cycle. The gray block is positioned in diastole; its center is approximately 65% between the R waves; i.e., for an R-R interval of 1000 ms, 650 ms elapses between the first R wave and the center of the block. This reconstruction is one used most commonly to visualize the left coronary arterial system. If this reconstruction does not provide the most optimal images, additional reconstructions, in either earlier or later phases, are performed. Since the right and left coronary arteries are asynchronous, it is sometimes the case that evaluation of the right side is best performed using images closer to systole. (*C*) Tube current modulation or ECG pulsing. The ECG tracing is identical to the one illustrated in part *A*. The colored bars under the tracing correspond to the gray bars and correlate with current modulation; the optimal (high) tube current will be used. The red lines show times that correspond to portions of the cardiac cycle where the x-ray CT tube current is minimized. ECG pulsing can reduce the patient dose by 30 to 50%.

If only static (as opposed to cine) images are desired, image reconstruction usually can be performed over a small number of phases for which motion is minimized. For native coronary imaging, the reconstructions must account for a synchronous movement of the left and right coronary arterial systems. That is, the phase of the cardiac cycle that proves best for diagnosis of the left main and left anterior descending (LAD) arteries often is different from the phase that proves most diagnostic for the right coronary artery (RCA). Thus it is sometimes the case, particularly when beta blockade is suboptimal, that the reconstruction must include several phases. Within the cardiac cycle, periodic displacement of both saphenous vein grafts (SVGs), radial grafts, and internal mammary artery (IMA) grafts is far less than the motion of the native coronary arteries. Thus, for these vessels, a single reconstruction at middiastole usually is sufficient (Fig. 6-3). However, it is *essential* that the surgeon not only recognizes that motion has degraded image quality but also realizes that additional reconstructions in different phases *can and should be performed.* If the entire course of the graft is not clear to the surgeon on a single image (e.g., 65%), it is almost always the case that another phase can be reconstructed from the CT data (e.g., 50%) for motion-free depiction of the graft segment that was poorly seen. At BWH, open communication between the radiologist and surgeon for every patient has eliminated this pitfall and ensures that the maximum amount of imaging data are incorporated into preoperative planning.

In cine CT, such as imaging the aortic valve over the entire R-R interval, images are reconstructed throughout the cardiac cycle and then played, in cine mode, to demonstrate function. Each individual image (Fig. 6-4) offers an outstanding assessment of the aortic valve and root structure. Cine CT also can be used to assess ventricular wall motion. In comparison with magnetic resonance imaging (MRI), the "gold standard" for global and regional wall motion abnormalities, CT

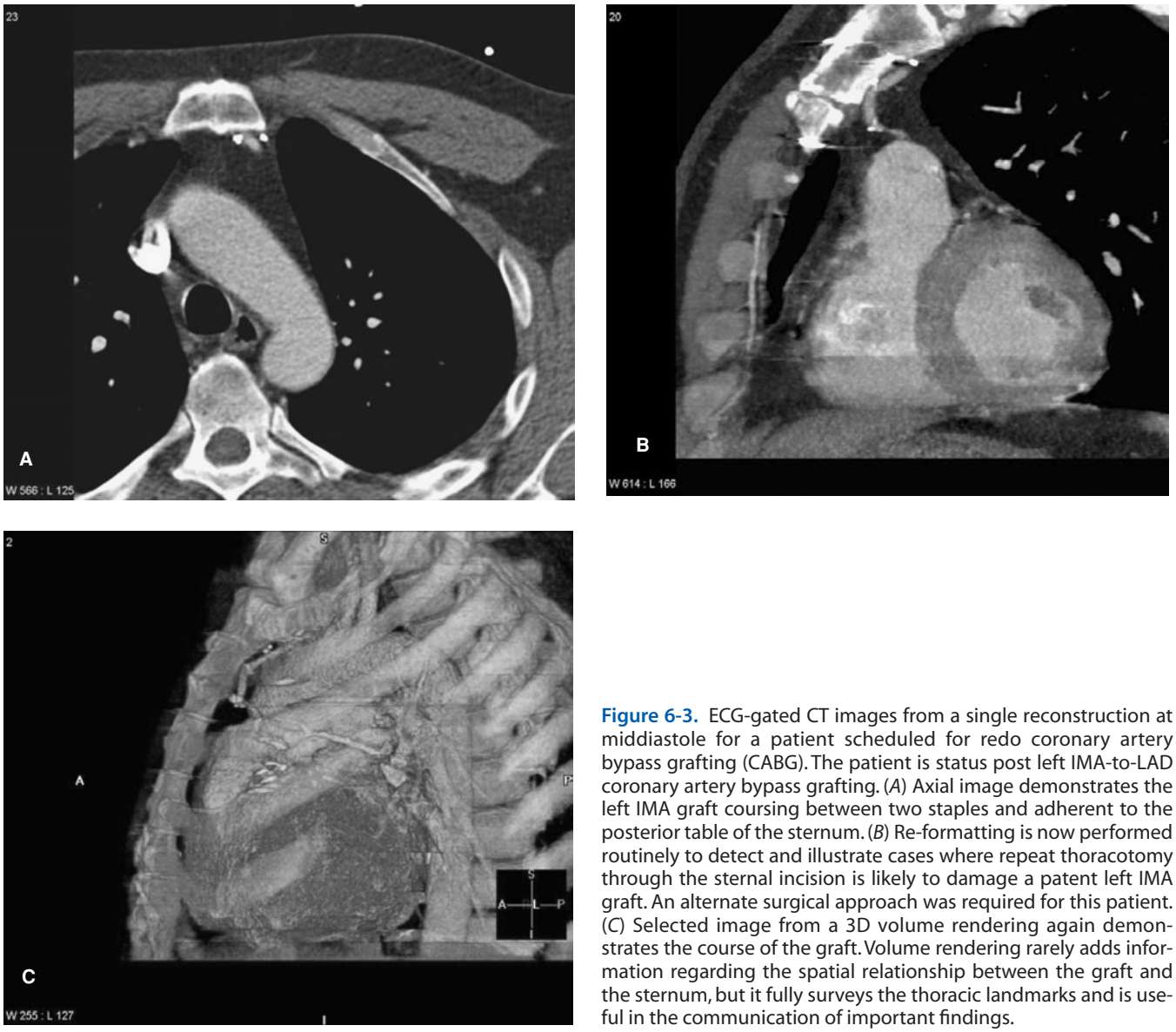

Figure 6-3. ECG-gated CT images from a single reconstruction at middiastole for a patient scheduled for redo coronary artery bypass grafting (CABG). The patient is status post left IMA-to-LAD coronary artery bypass grafting. (*A*) Axial image demonstrates the left IMA graft coursing between two staples and adherent to the posterior table of the sternum. (*B*) Re-formatting is now performed routinely to detect and illustrate cases where repeat thoracotomy through the sternal incision is likely to damage a patent left IMA graft. An alternate surgical approach was required for this patient. (*C*) Selected image from a 3D volume rendering again demonstrates the course of the graft. Volume rendering rarely adds information regarding the spatial relationship between the graft and the sternum, but it fully surveys the thoracic landmarks and is useful in the communication of important findings.

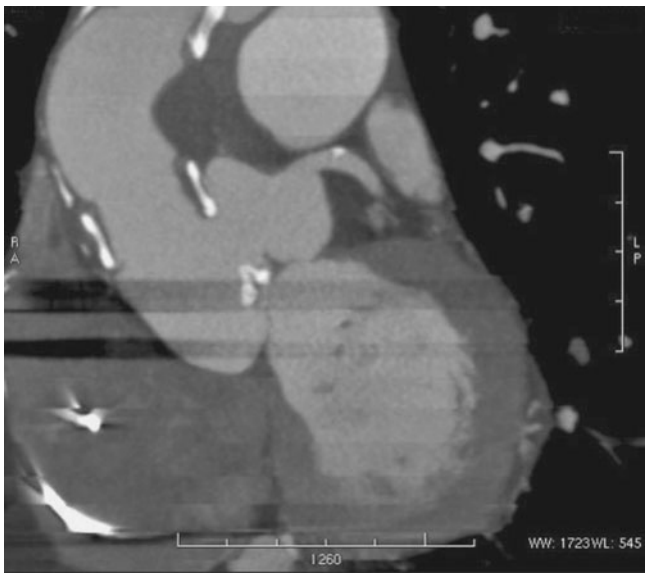

Figure 6-4. ECG-gated CT image through the left ventricle and the aortic valve in a patient status post aortic root repair. Note the pacemaker (right heart wires); MRI was contraindicated. The repair is well visualized and without complication, with only mild aortic valve calcification (cine images showed a tricuspid valve with no significant stenosis). This image also demonstrates a punctate calcified plaque along the superior course of the proximal left main coronary artery without a significant stenosis.

has less contrast to noise, and images typically have greater artifact from the poorer temporal resolution. However, it is important to emphasize that cine CT does not require a separate image acquisition. The entire CT data set (i.e., coronary, valve, myocardium, and pericardium) is acquired in a single breath hold; cine CT is simply part of the image postprocessing.

For surgical patients, CT has the distinct advantage over MRI in that it is by far the best imaging modality to identify and quantify calcification. Also, the most common contraindications for cardiac CT (e.g., impaired renal function as measured by glomerular filtration rate or, alternatively, by serum creatinine) differ from those for MRI (e.g., pacemaker), and thus CT often can be used for patients who cannot have MRI. Finally, newer and future CT equipment with up to 256 slices is expected to perform whole-heart coverage with a single half-gantry (180-degree) rotation. This approach holds the promise of a subsecond cardiac scan. In addition to the fact that patient radiation is decreased, multiple scans can be performed with the same injection of iodinated contrast material, creating the opportunity for a host of additional studies (e.g., myocardial perfusion) that are, at present, largely in the domain of cardiac MRI and nuclear cardiology.

Patient Irradiation

Because ECG gating is required, ascending aorta and cardiac CT delivers more patient irradiation than CT of any other body part. While details regarding cardiac CT dosimetry are beyond the scope of this chapter, discussions regarding CT dose must be based on sound principles. The radiation risk most commonly quoted relates to the probability that the CT scan will result in the development of a fatal radiation-induced neoplasm. Human data for radiation at this low level (the level delivered in ECG-gated cardiac CT) are very sparse; all anecdotal reports support a latency period of no less than 20 years for a radiation-induced neoplasm. For this reason, patients should be separated into two groups: those with a life expectancy of roughly 20 years or less and those with a longer life expectancy. In the former group, the only dose consideration is whether the radiation could cause a skin burn (the only short-term complication of any consequence). X-ray skin burns are extremely uncommon, particularly in CT (even for ECG-gated studies), and typically result from multiple examinations repeated at short-term intervals. Thus, for this subset of patients, *radiation dose should not be a consideration* in determining a modality for coronary imaging.

Current modulation is a strategy to lower the radiation dose for patients with a longer life expectancy and for whom multiple cardiac scanning is anticipated. The tube current (expressed as the milliamperes) is modulated over the course of the cardiac cycle (see Fig. 6-2C) so that the desired (high) diagnostic current is delivered only in diastole. The patient dose is decreased because the tube current is reduced for the remainder of the cardiac cycle. While current modulation is helpful in many cases (e.g., in pediatric patients), the decision to use it should be made after consultation between surgeon and radiologist because the potential drawbacks are significant. Most important, when current modulation is used, images reconstructed during phases with low tube current are noisy (Fig. 6-5) because less tube current is used to generate them. Moreover, current modulation eliminates the potential to reconstruct high-quality cine images. Thus, current modulation is useful only for patients with a long life expectancy in whom repeated imaging is expected and for whom it is anticipated that only static images over a small number of cardiac phases will be sufficient.

Scanning Parameters

The *scan time* refers to the time required to complete the CT acquisition along the *z* axis of the patient. As described earlier, better temporal resolution decreases the scan time, not only decreasing cardiac motion but also enabling breath-hold CT. This is important in cardiac CT because in comparison with nongated CT, ECG gating not only increases patient radiation but also increases the scan time.

In practical terms, a 64-slice ECG-gated cardiac CT scan (i.e., craniocaudal or *z*-axis imaging over ~15 cm) can be performed in roughly 10 seconds versus 20 to 25 seconds with a 16-slice scanner. This is one great benefit of scanners equipped with a larger number of detectors. The number of detectors determines the number of slices obtained per rotation of the CT gantry. Increasing the number of slices, the thickness of the detectors, or both increases the *z*-axis coverage per rotation and thus decreases the scan time.

For example, in a patient who cannot perform the breath hold, using thicker detectors (e.g., 1-mm thickness as

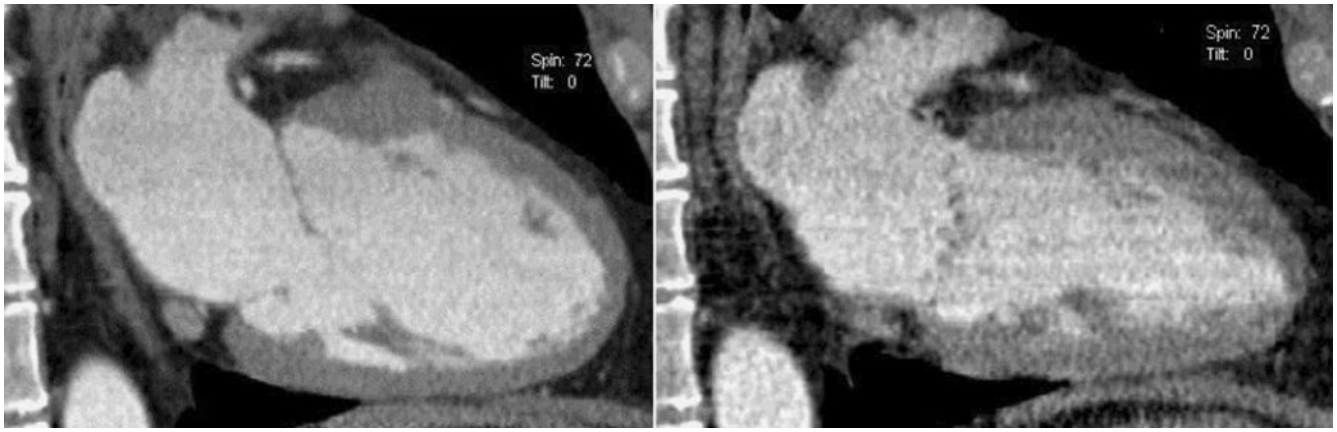

Figure 6-5. Comparison of images obtained without (*left*) and with (*right*) ECG-based tube current modulation or ECG pulsing. The left-hand two-chamber (left atrium and ventricle) view is reconstructed at 65% of the R-R interval. Note that the normal mitral valve is well demonstrated with ECG gating. The right image was reconstructed at 10% of the R-R interval, where the x-ray CT tube current was reduced dramatically. As a result, the right-hand image suffers from high image noise.

opposed to 0.5 mm thickness) will decrease the scan time by providing more *z*-axis coverage per rotation. However, routinely increasing the width of the detectors for cardiac applications is undesirable because it degrades the spatial resolution of the examination. In general, *spatial resolution* refers to the ability to differentiate two structures. In practical terms, the spatial resolution refers to the thinnest axial slices that can be reconstructed from the configuration of the detectors, and thinner detectors translate into better spatial resolution.

Routine consultation between the surgeon and the radiologist is essential to best understand and optimize the tradeoff between scan time and slice thickness. In some cases, as in native coronary CTA, the best spatial resolution is required, and thus the scan time must remain long. To illustrate, consider that the thinnest slices that can be reconstructed are approximately 0.4 mm wide. Therefore, for a perfectly ECG-gated native coronary CTA with no respiratory motion, a normal 3-mm coronary artery spans seven or eight high-quality pixels (3 mm/0.4 mm). If the thinnest slices were 1 mm wide instead of 0.4 mm, the coronary artery would be fully seen on at most three pixels, and thus stenosis evaluation would be severely compromised. On the other hand, myocardial and ascending aortic imaging almost never requires 0.4-mm slices because the pathology is larger. Thus, for dyspneic patients who require only imaging of the ascending aorta, thicker slices are used to cut the scan time. For these more complex cases, routine communication between the surgeon and the radiologist is critical to ensure that imaging meets the diagnostic need for surgical planning or follow-up.

The scanning parameters that primarily determine the number of photons used to create a CT image are termed *effective milliampere-seconds* (effective mA · s) and *kilovolts* (kV). The former is proportional to the x-ray tube current; the latter refers to the voltage applied within the tube. For the surgeon, choosing the best numbers (typical values are 550 to 700 effective mA · s and 120 kV) is far less important than understanding the fact that modern cardiac CT pushes the limits of technology and thus creates tradeoffs with respect to the x-ray CT source. The source generates photons that are either attenuated by the patient or reach the detectors. When more photons reach the detectors, the image quality is higher because there is less noise. The decision to image with thinner slices (e.g., 0.5 mm as opposed to 1 mm) means that fewer photons reach the detector; thus thinner slices have more noise. This is especially important in obese patients because patients with increased body mass absorb more photons than thin patients. For the same scanning parameters, images of obese patients can be degraded dramatically by greater image noise.

If there were no limit to the number of photons that an x-ray CT source could produce, the solution would be simply to increase the number of photons (and the radiation dose) until image noise was satisfactory. Unfortunately, because the x-ray CT tube heats excessively when pushed to its maximum, there is a limit to the number of photons that can be produced. This is why image noise becomes problematic with thin-slice imaging of obese patients. When this is the case, consultation between surgeon and radiologist is important because diagnostic images often can be obtained by increasing the image thickness, scanning a smaller *z*-axis field of view (FOV), or both. The latter can be particularly useful if the examination can be tailored to the most important structure. Scanning a smaller *z* axis means that more photons can be generated and used before the x-ray CT tube reaches its heat limit.

On the other hand, whenever possible, the *z*-axis FOV should be generous because unexpected pathology can extend both cranially and caudally. For example, an ECG-gated cardiac and ascending aorta examination to evaluate extension of the intimal flap into the coronary arteries can reveal extension into the great vessels. Also, scanning must allow for variations in the FOV induced by breath holding. As a general rule, for scanning the native coronary arteries alone, the superior border of the FOV is set at the axial slice

corresponding to the top of the carina. This is typically 2 to 3 cm superior to the origin of the left main coronary artery. The inferior border should scan through the entire inferior wall of the heart and should include several slices of the liver to account for cardiac displacement during breath holding. For bypass graft imaging, the superior border of the FOV must include the subclavian arteries and the origins of both IMAs.

Contrast Material

With the exception of scans performed solely for the assessment of cardiac and aortic calcification, CT examinations are performed with iodinated contrast material. Effective communication between surgeon and radiologist is important in optimizing the use of contrast material, particularly in the decision of whether to use a single or a dual injection system. A single system injects only contrast material, whereas a dual system has two reservoirs to inject contrast material followed by saline. Dual injection is essential for many applications, and it is routine in native coronary artery imaging. The contrast material and saline delivery are timed so that the left side of the heart, aorta, and coronary arteries are opacified with contrast material while the right side of the heart is filled with saline. The use and timing of the saline are essential parts of the examination because artifacts that limit interpretation of the RCA will be induced if the right side of the heart and central veins are densely opacified with contrast material (as opposed to saline). However, for patients in whom imaging requires opacification of both the left and right sides of the heart (e.g., assessment of both the mitral and tricuspid valves), saline cannot be used, and less dense contrast material may be chosen to lessen potential artifacts.

Summary

Advances in technology, such as submillimeter spatial resolution, 64 slices per rotation, and gantry rotation times of less than 1/2 second, have enabled ECG-gated CT to make a positive contribution to the care of cardiac surgery patients. The surgeon must recognize that cardiac protocols push the limit of technology and that therefore CT of the heart is more complicated than a scan of any other body part. Consequently, routine and effective communication between the surgeon and the radiologist will result in the best possible patient outcomes.

APPLICATIONS IN CARDIAC SURGICAL PATIENTS

Native Coronary Artery CTA

One of the most common clinical indications for cardiac CT is to evaluate the native coronary arteries for stenosis (Figs. 6-6 through 6-9). Numerous validation studies have evaluated cardiac CT for this purpose. In these studies, data typically are reported on a per-coronary-artery-segment basis, comparing CTA and DSA. A significant stenosis generally is defined as greater than 50%, determined by quantitative coronary artery angiography. Data are also analyzed on a per-patient basis regarding the value of CTA in ruling in or

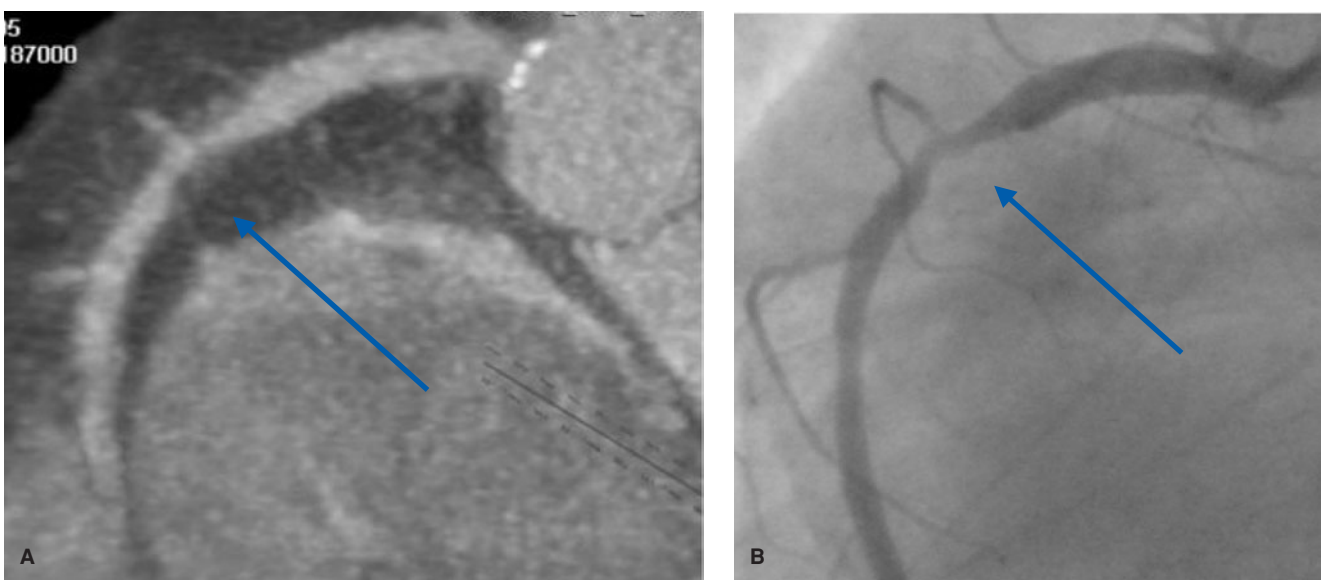

Figure 6-6. Proximal RCA 50% stenosis diagnosed by coronary CTA and confirmed by conventional angiography. Double oblique maximum-intensity projection image (4 mm thick) through proximal RCA (*A*) and LAO projection still image from conventional angiogram (*B*) demonstrate a segment of approximately 50% stenosis (*arrows*).

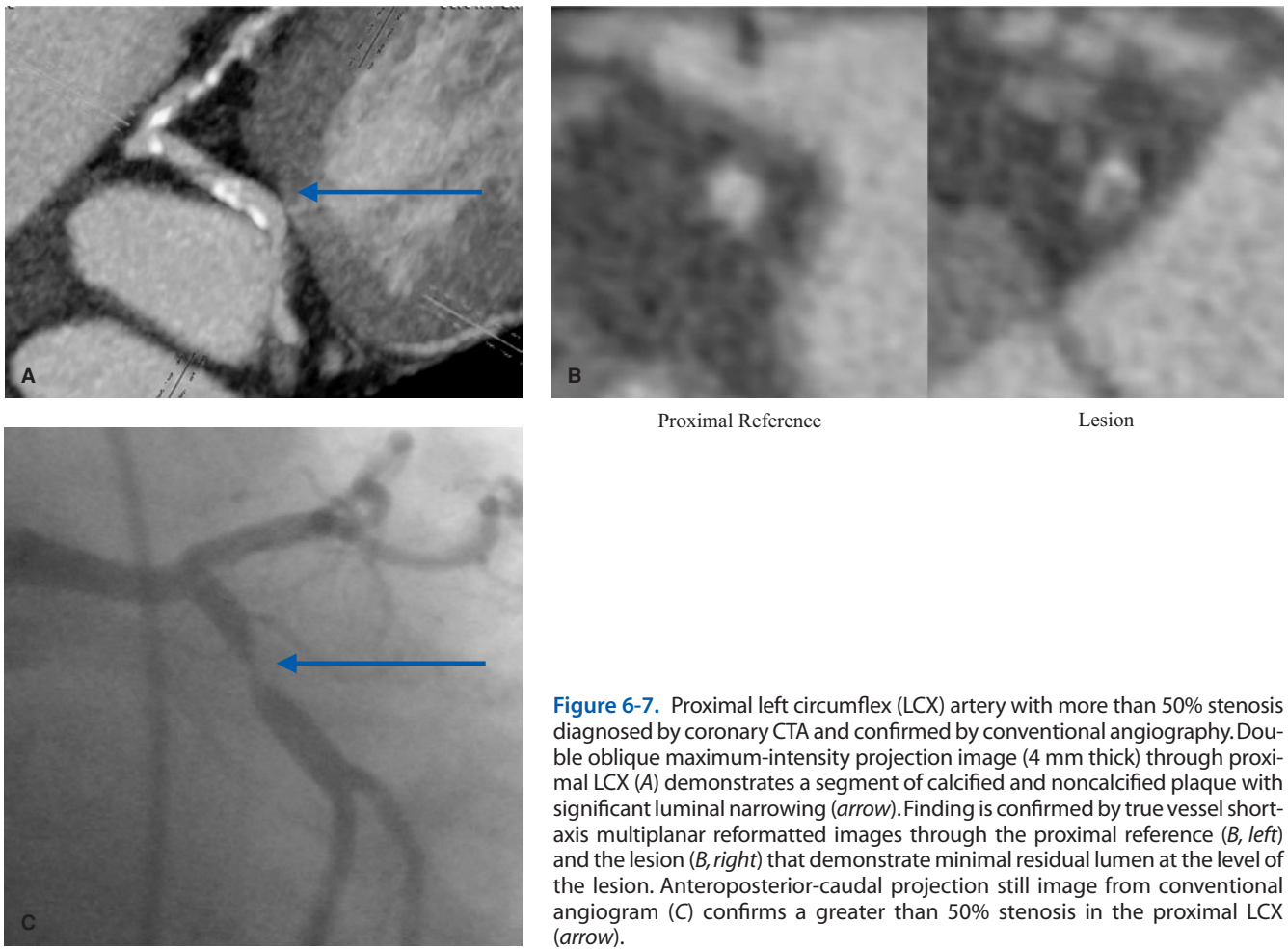

Figure 6-7. Proximal left circumflex (LCX) artery with more than 50% stenosis diagnosed by coronary CTA and confirmed by conventional angiography. Double oblique maximum-intensity projection image (4 mm thick) through proximal LCX (*A*) demonstrates a segment of calcified and noncalcified plaque with significant luminal narrowing (*arrow*). Finding is confirmed by true vessel short-axis multiplanar reformatted images through the proximal reference (*B, left*) and the lesion (*B, right*) that demonstrate minimal residual lumen at the level of the lesion. Anteroposterior-caudal projection still image from conventional angiogram (*C*) confirms a greater than 50% stenosis in the proximal LCX (*arrow*).

excluding coronary artery disease (CAD). Literature to date reports on patient populations with a relatively high prevalence of CAD (i.e., patients already scheduled for DSA).

Table 6-1 summarizes recently published data. The consistently high negative predictive value (NPV) on a per-patient basis (93 to 99%) is the most clinically relevant aspect of presently available data. These data and our experience suggest that cardiac CTA effectively can exclude CAD in patients with a low to intermediate pretest probability of disease. Consequently, CTA has become increasingly useful for the cardiac surgeon in managing patients scheduled for non–coronary artery cardiac surgery. If the clinical suspicion is low but not insignificant, CTA affords the surgeon a method of assessing CAD without subjecting the patient to femoral arterial puncture with its known complications. For example, patients undergoing isolated mitral valve surgery for degenerative myxomatous disease have a low prevalence of CAD, making CTA an ideal alterative to conventional angiography to exclude significant CAD. When the CT protocol described earlier is followed, high-quality imaging is *routine*, and when CTA excludes CAD, some surgeons are beginning to feel comfortable in using CTA alone. In patients in whom image quality is degraded or there is significant disease, CTA then can be followed by DSA and intervention as needed.

Coronary Artery Bypass Graft CTA

Cardiac CT provides the cardiac surgeon with a noninvasive method to assess graft patency after coronary artery bypass grafting (CABG). Studies using 16-slice CT scanners suggest 100% sensitivity and specificity for identifying occluded versus patent grafts.[7–9] In clinical practice, this application is of value in the evaluation of symptomatic patients in the early postoperative period in whom graft failure is being considered (Fig. 6-10). It is particularly useful for the demonstration of patent grafts in patients with a remote surgical history and unknown graft anatomy prior to DSA and in patients in whom conventional angiography fails to demonstrate a known graft (Fig. 6-11). In the reoperative setting, such data have virtually revolutionized decision making and planning prior to surgery in patients who have already undergone CABG.

Patients with recurrent angina after bypass surgery may have developed stenosis or occlusion in bypass grafts or may have progression of native CAD. In these patients, CTA

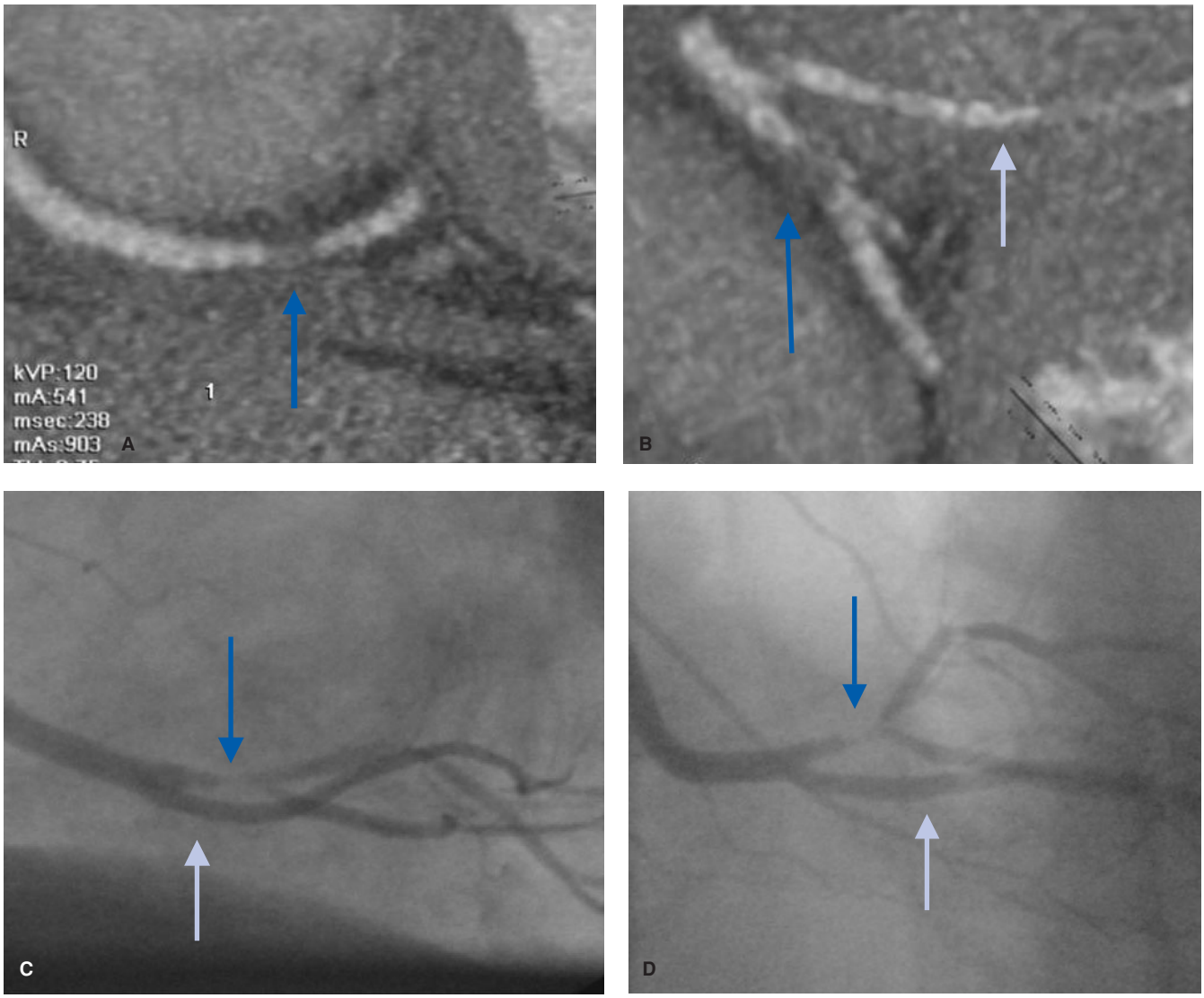

Figure 6-8. Ongoing RCA greater than 50% stenosis diagnosed by coronary CTA and confirmed by conventional angiography. Double oblique maximum-intensity projection images (4 mm thick) through ongoing RCA at 90-degree angles (*A, B*) demonstrate a segment of noncalcified plaque with nonvisualization of lumen (*line arrow*). The PIV is also partially demonstrated (*white arrow*). Finding is confirmed by LAO (*C*) and anteroposterior-cranial (*D*) projection still images via conventional angiogram (*blue arrow*). The PIV is also seen (*white arrow*).

can be more limited. For example, exclusion of significant stenosis in a graft may be problematic owing to metallic surgical clips that cause artifact (Fig. 6-12). Moreover, native CAD in these patients often is advanced and heavily calcified. A large volume of calcium may result in an uninterpretable study for many segments of the native coronary arteries (Fig. 6-13). CTA in such patients may not be definitive; consequently, conventional angiography may be preferred in this population.[10] Obviously, the less calcification and metal artifact present, the more useful CTA is.

In the research context, graft patency is an important outcome in the evaluation of different surgical techniques. Randomized, controlled trials using conventional angiography for assessment of graft patency typically demonstrate a 10 to 20% rate of noncompliance. This noncompliance is at least partly attributable to the invasive nature of the test.[11,12] Cardiac CT is an attractive noninvasive and very accurate method to assess graft patency for clinical trials, again obviating a traditional arterial puncture with its risks and known complications. Cardiac CT also may be used for routine postoperative control of grafts following implementation of a new surgical technique in a local center practice (Fig. 6-14).

The Aorta: The Root, the Ascending Aorta, the Arch, and the Descending Aorta

Surgery of the aortic root, the ascending aorta, the arch, and the descending aorta is becoming increasingly commonplace

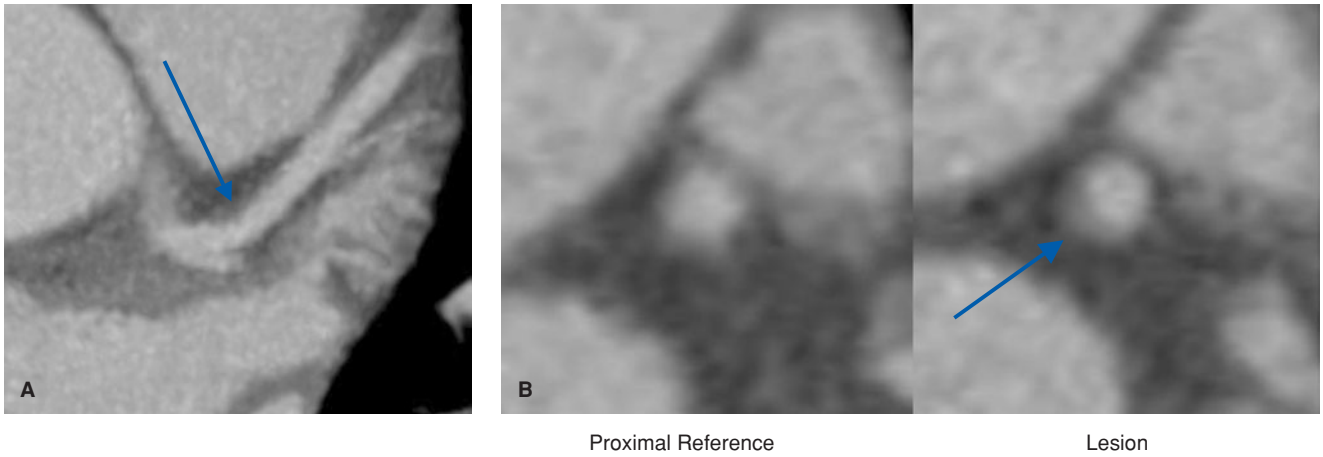

Figure 6-9. Proximal less than 50% stenosis diagnosed by coronary CTA. Double oblique maximum-intensity projection image (4 mm thick) through proximal LAD (*A*) demonstrates a segment of noncalcified plaque that is not associated with any significant luminal narrowing (*arrow*). True vessel short-axis multiplanar reformatted images through the lesion (*B, right*) and through the proximal reference segment (*B, left*) confirm minimal luminal narrowing. Low-density "noncalcified" plaque with positive vessel remodeling is seen (*arrow*). This case highlights the ability of CTA to detect early stages of subclinical atherosclerosis. This lesion may not have been detected during a conventional angiogram.

as the population ages. CT has been used for many years to assess the thoracic aorta. Non–ECG-gated CT is highly accurate in assessment of the aortic arch and descending thoracic aorta because they are not subject to significant cardiac motion. However, ECG-gated cardiac CT adds motion-free imaging of the aortic root and ascending aorta. Without question, any surgery involving the aorta (whether the root, the arch, the ascending, or the descending portion) requires preoperative CTA for surgical decision making. The superior imaging of ECG-gated CTA better defines the pathology and hence facilitates preoperative planning. For example, CTA is by far the best imaging modality to define aortic calcification clearly.

If portions of the aorta are calcified on CTA, then aortic cross-clamping and cannulation for cardiopulmonary bypass at those sites are contraindicated in order to avoid

Table 6–1.

Author	MDCT	Study	*N*	Sens by seg	Spec by seg	Not eval	NPV by patient
Mollet[1]	16	*JACC* 2005 All segments >2 mm	51	95%	98%	n/a	99%
Kuettner[2]	16	*Heart* 2005 All segments	120	85%	98%	7%	96%
Hoffman[3]	16	*JAMA* 2005 All segments >1.5 mm	103	95%	98%	6.4%	95%
Achenbach[4]	16	*Eur Heart J* 2005 All segments >1.5 mm	50	93%	95%	5%	99%
Leschka[5]	64	*Eur Heart J* 2005 All segments	57	94%	97%	n/a	99%
Raff[6]	64	*JACC* 2005 All segments	70	86%	95%	12%	93%

Sens = sensitivity; spec = specificity; seg = segment; eval = evaluable; NPV = negative predictive value.

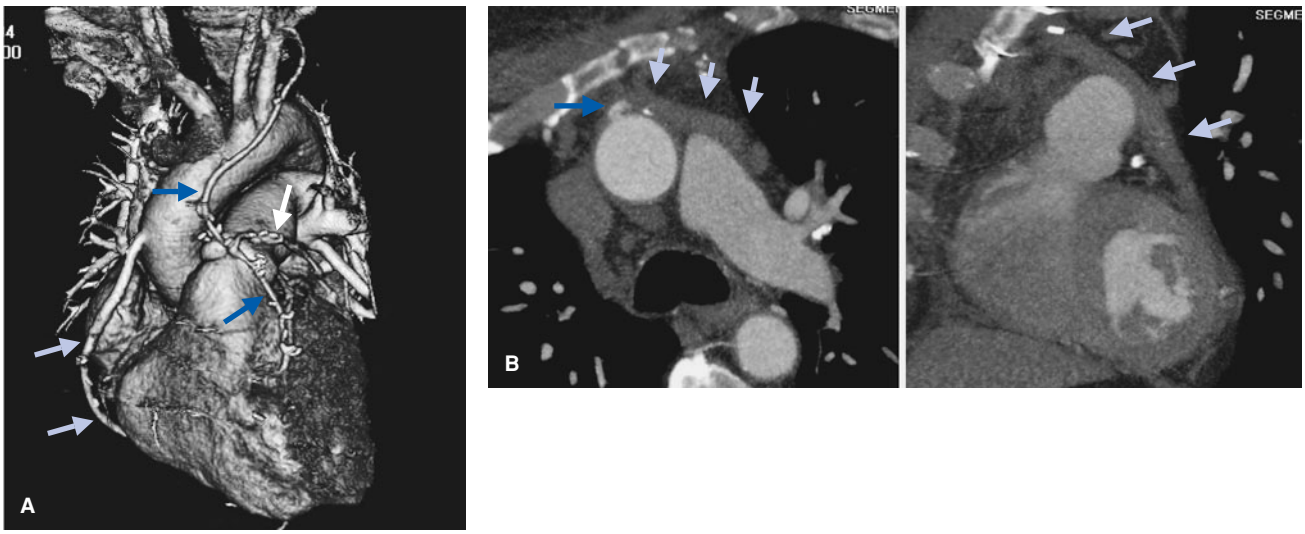

Figure 6-10. Cardiac CT performed for evaluation of graft patency in the postoperative setting. Three-dimensional volume-rendered image demonstrates patent left IMA to LAD (*blue arrows*), T-graft right IMA to obtuse marginal (*white arrow*), and SVG to RCA (*gray arrows*). This study was obtained in a patient 1 day following off-pump CABG. The patient had developed recurrent chest pain and elevated troponin. Cardiac CT ruled out early graft failure as a cause for the patient's presentation. Oblique multiplanar reformatted images (*B*) in a second patient demonstrate an acutely occluded saphenous vein graft to obtuse marginal. Note the patent graft stump (*blue arrow*) and thrombosed graft body (*gray arrows*).

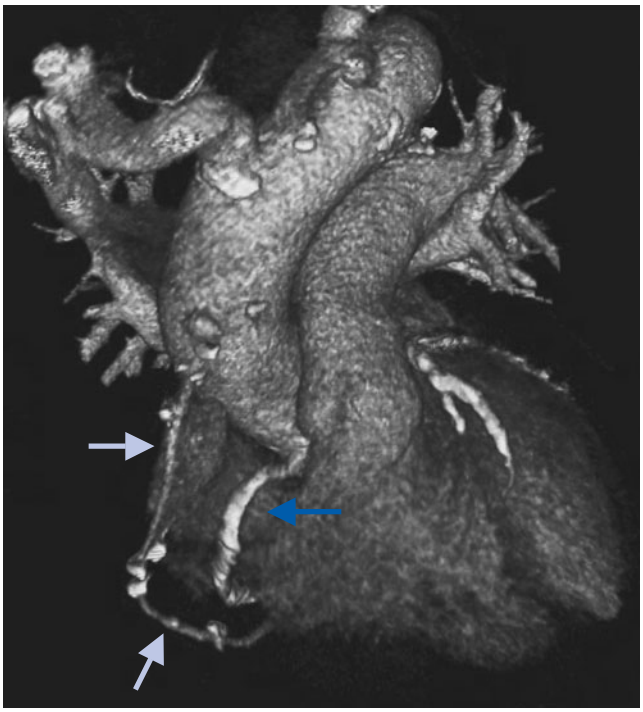

Figure 6-11. Cardiac CT performed to evaluate possible radial graft occlusion. The patient had surgery 1 month prior and presented with recurrent angina. The radial-to-RCA graft could not be selectively catheterized at conventional angiography and also was not seen at aortic root injection. Three-dimensional volume-rendered image demonstrates patent radial graft (*gray arrows*) to RCA (*blue arrow*). The anastomosis is not seen on this orientation.

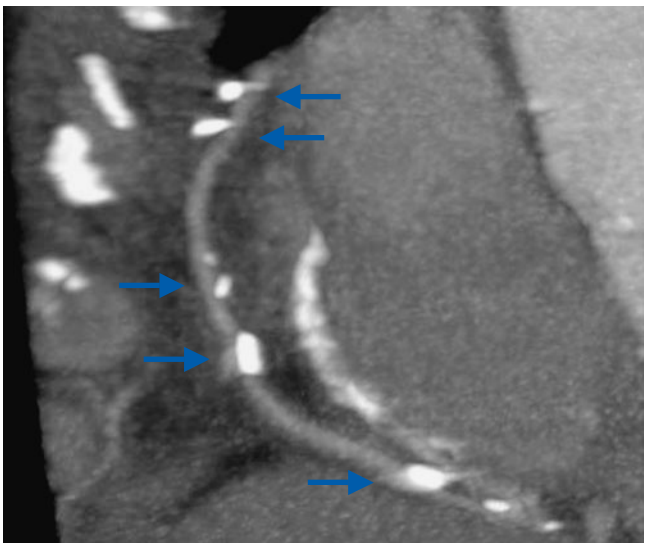

Figure 6-12. Surgical clip artifacts can limit cardiac CT evaluation of coronary bypass grafts significantly. Double oblique maximum-intensity projection image (10 mm thick) demonstrates multiple surgical clips placed along the length of a radial-to-PIV graft (*blue arrows*). Artifact from these metallic clips can partially or completely obscure the adjacent vessel lumen, precluding evaluation of these segments for the presence or absence of stenosis. Although CT can unequivocally demonstrate graft patency, surgical clip artifact usually does not allow complete graft evaluation to rule out graft stenosis.

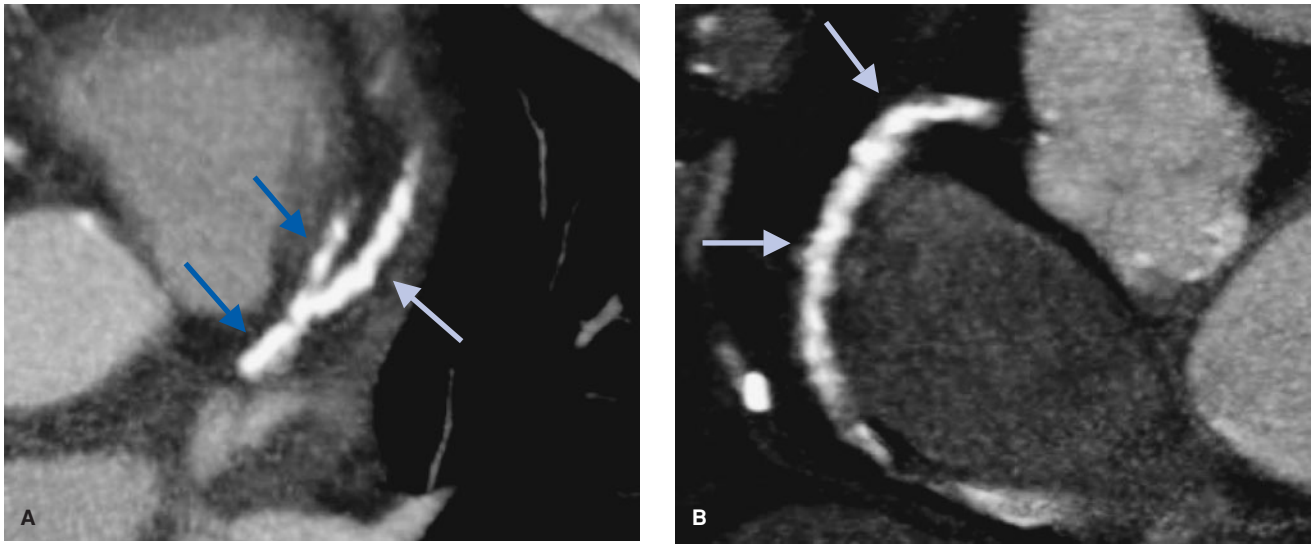

Figure 6-13. Cardiac CT often is limited in its evaluation of native coronary arteries in the post-CABG patient owing to the presence of advanced and heavily calcified coronary atherosclerosis. Double oblique maximum-intensity projection image (4 mm) demonstrates (*A*) the proximal LAD (*blue arrows*) and a large first diagonal branch (*gray arrow*) and (*B*) the proximal right coronary artery (*gray arrows*). The white areas represent calcification. All vessel segments shown are heavily calcified. The extent of calcification completely obscures the vessel lumen, and the presence or absence of stenosis cannot be assessed reliably.

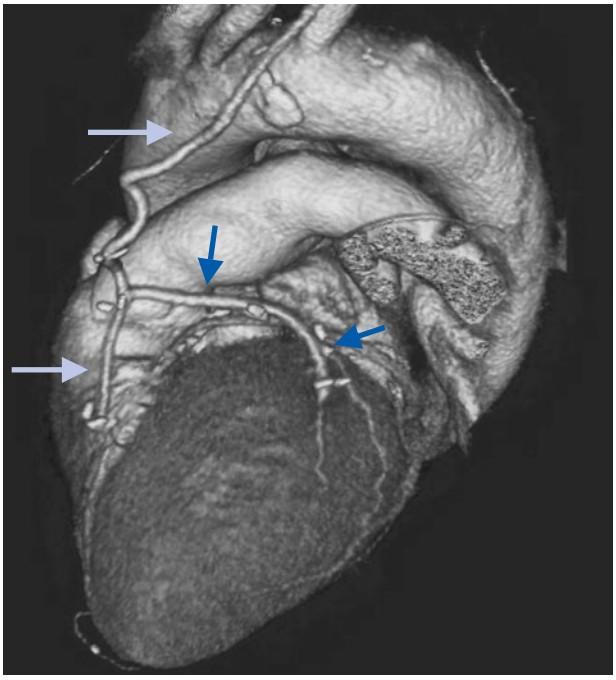

Figure 6-14. Cardiac CT obtained for postoperative graft control in a patient who underwent MVST. Three-dimensional volume-rendered image demonstrates patent left IMA-to-LAD (*gray arrows*) and radial T-graft to obtuse marginal (*blue arrow*).

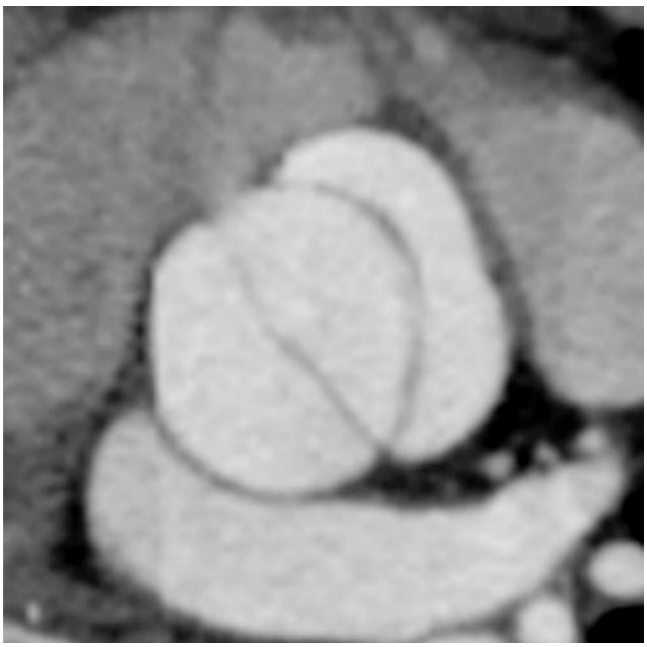

Figure 6-15. Demonstration of aortic root and aortic valve. Axial oblique multiplanar reformatted image from a systolic data set demonstrates an open bicuspid aortic valve. Note the precise definition of the aortic wall, free from the cardiac motion–related artifacts that are present in conventional thoracic CT scanning. Aortic root size measurements are highly accurate owing to a lack of motion artifacts and the high spatial resolution of the cardiac CT scanning (<0.5 mm).

embolic phenomena and stroke. Thus preoperative cardiopulmonary bypass strategy and myocardial protection often are altered critically by preoperative CTA.

As with calcification, CT is the most accurate modality to evaluate the aortic root, with both two-dimensional (2D) and three-dimensional (3D) visualization (Fig. 6-15). Not only can the aortic root be sized from multiple imaging planes, but also the exact location of the aneurysmal pathology with respect to the valve and sinotubular junction often can be defined. This assessment is critical for preoperative decision making and surgical planning. In patients with ascending aortic aneurysms, if the aortic root is determined to be aneurysmal near the coronary ostia, surgical decision making changes from a simple tube-graft repair for the aneurysm to a much more complex composite root repair with coronary reimplantation. In addition, motion-free images obtained with ECG gating allow for definitive exclusion of type A dissection (Fig. 6-16). Three-dimensional volume rendering optimally depicts other aortic root pathologies such as coronary artery anomalies or a sinus of Valsalva

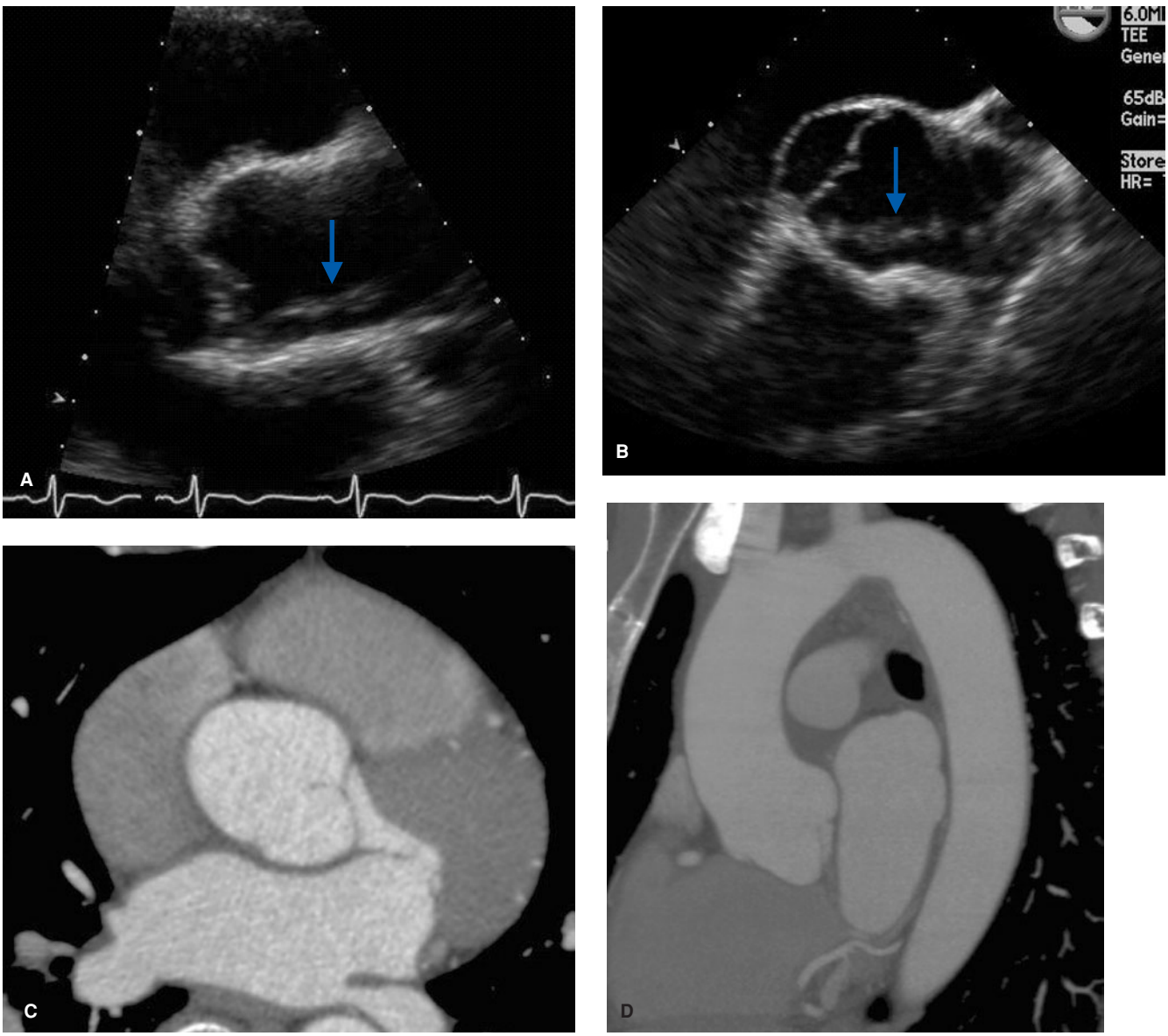

Figure 6-16. Although multiple modalities may be used for evaluation of the aortic root, with recent technical advances, cardiac CT is the "gold standard" for the exclusion of type A dissection. Parasternal long-axis image from transthoracic echocardiogram (*A*) demonstrates a linear area of echogenicity (*white arrow*) above the noncoronary cusp of the aortic valve, concerning for an intimal flap. The finding was detected incidentally in a patient with recent stroke and possible patent foramen ovale. Subsequent transesophageal echocardiogram (*B*) again demonstrates the finding. Axial image from cardiac CT scan (*C*) provides excellent visualization of the aortic root and excludes the presence of an intimal flap. Sagittal oblique maximum-intensity projection image (*D*) shows the aortic root and ascending aorta to be normal. Echocardiographic findings were presumed to be due to artifact.

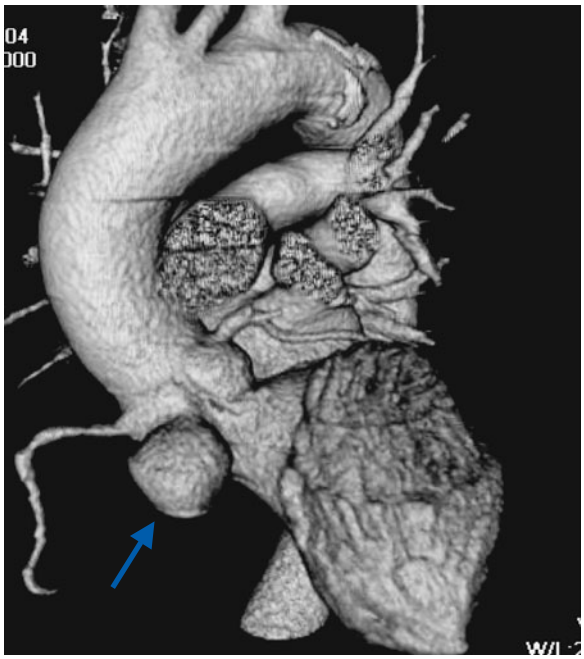

Figure 6-17. Cardiac CT provides optimal visualization of complex aortic root pathology. Prior echocardiogram suggested the entire aortic root to be aneurysmal at more than 4.5 cm in this patient. Three-dimensional volume-rendered image from cardiac CT demonstrates a 2.6-cm sinus of Valsalva aneurysm arising off the right coronary sinus (arrow). The remainder of the aortic root is normal. Using saline flush and thresholding techniques for image display, high-resolution unobstructed visualization of such lesions is possible.

aneurysm (Fig. 6-17). In patients with a sinus of Valsalva aneurysm, as opposed to a root aneurysm, CT alters surgical strategy for repair.

For known ascending aortic aneurysms that do not meet size criteria for surgery, CTA represents the optimal study for periodic assessment of size or change. For patients who require surgery, CTA with 3D volume-rendered images provides the surgeon with preoperative visualization of aneurysm size and extent. The extension of an ascending aortic aneurysm into the arch can be demonstrated, and as mentioned earlier, the expected location of aortic cross-clamping can be determined preoperatively (Fig. 6-18). The location of normal aorta distally and the extent of arch involvement preoperatively will determine the arterial cardiopulmonary bypass cannulation site as well as the need for concomitant arch repair, circulatory arrest, or selective antegrade perfusion. Selective antegrade cerebral perfusion itself depends on intact right axillary and innominate arteries, and CTA is optimal for defining this anatomy. Since the success of a procedure can be compromised by unexpected intraoperative findings, CT has contributed enormously to surgical planning by defining anatomy that would not be visualized preoperatively with any other imaging modality.

In patients with aortic dissection, CTA allows the surgeon to understand the extent of the intimal flap. In particular, ECG-gated CT offers information regarding dissection of the ascending aorta (the proximal extent of the dissection flap and its relationship to the coronary arteries and the aortic valve) that was not available before gating was performed routinely. The location of the true and false lumen is critical in the preoperative planning, the operative sequence, and the extent of repair. For example, in dissection of the descending aorta, end-organ perfusion is assessed by demonstrating contrast enhancement of individual organs and related compromise of the celiac, superior mesenteric, inferior mesenteric, or renal artery. As is the case for a nonsurgical aneurysm, if a descending thoracic aortic dissection is stable and to be followed expectantly, CTA remains the "gold standard" for periodic assessment.

Cardiac Masses

Cardiac MRI is the modality used most commonly for high–spatial-resolution cross-sectional imaging to evaluate cardiac

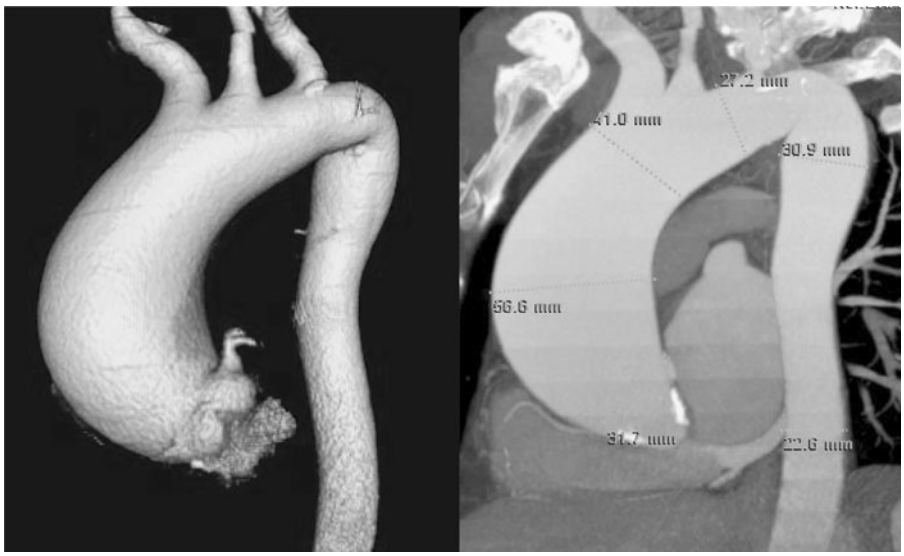

Figure 6-18. Comprehensive evaluation of ascending aortic aneurysm for preoperative planning. On the left, three-dimensional volume-rendered image demonstrates an aneurysmal ascending aorta. Sagittal oblique maximum-intensity projection image (20 mm thick) can be used to demonstrate aortic size measurements. The aneurysm can be seen to extend into the aortic arch. Since the entire ascending aorta and proximal arch needed to be replaced, cross-clamping could not occur proximal to the innominate artery in this patient and would have to occur in the middistal arch, altering the surgical risk of the procedure.

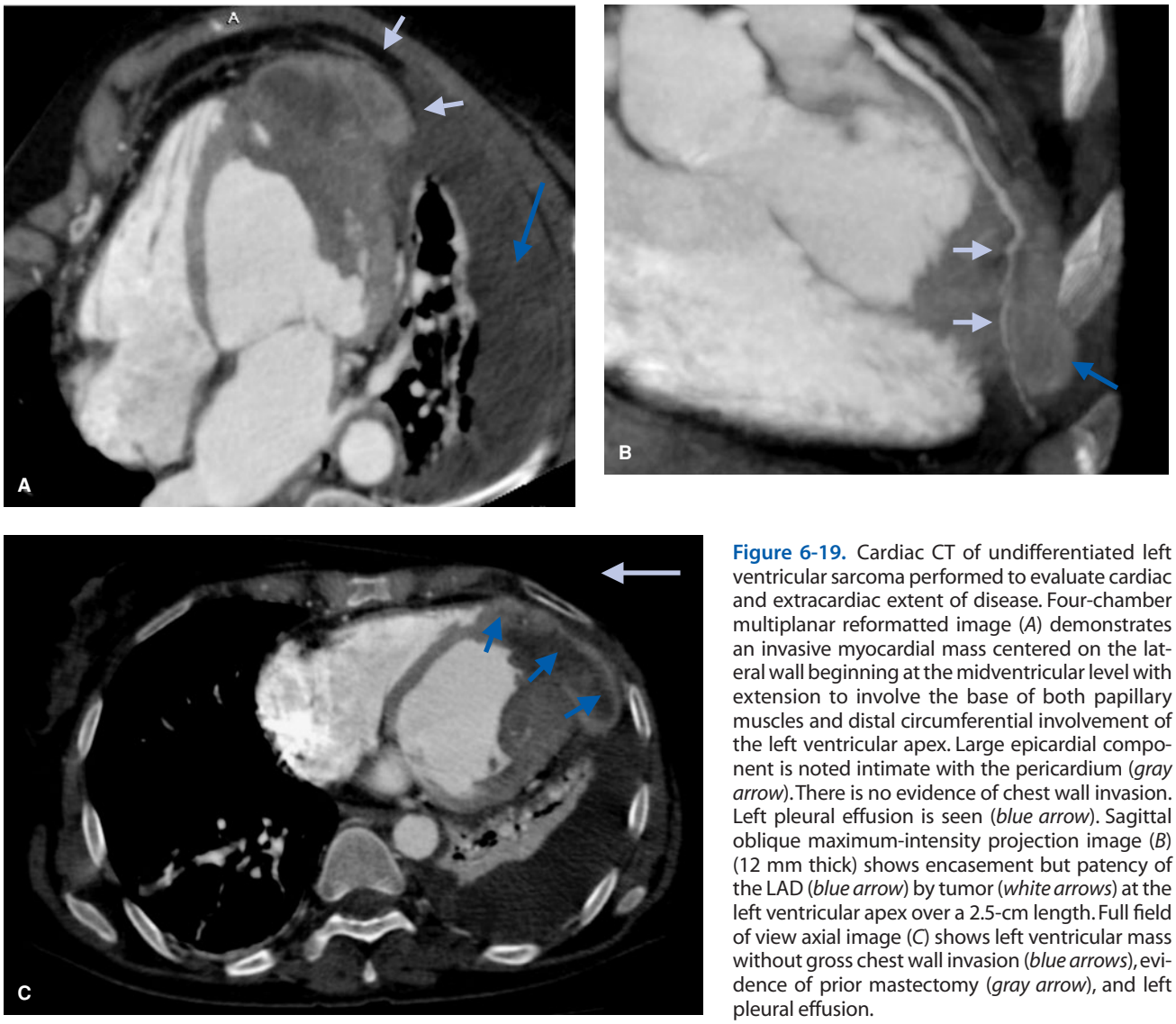

Figure 6-19. Cardiac CT of undifferentiated left ventricular sarcoma performed to evaluate cardiac and extracardiac extent of disease. Four-chamber multiplanar reformatted image (*A*) demonstrates an invasive myocardial mass centered on the lateral wall beginning at the midventricular level with extension to involve the base of both papillary muscles and distal circumferential involvement of the left ventricular apex. Large epicardial component is noted intimate with the pericardium (*gray arrow*). There is no evidence of chest wall invasion. Left pleural effusion is seen (*blue arrow*). Sagittal oblique maximum-intensity projection image (*B*) (12 mm thick) shows encasement but patency of the LAD (*blue arrow*) by tumor (*white arrows*) at the left ventricular apex over a 2.5-cm length. Full field of view axial image (*C*) shows left ventricular mass without gross chest wall invasion (*blue arrows*), evidence of prior mastectomy (*gray arrow*), and left pleural effusion.

and pericardial masses. However, CT may be preferred if the mass is known to extend into the mediastinum, chest wall, or lung or if the patient has a contraindication to MRI. CT also evaluates extracardiac thoracic structures with high spatial resolution; thus it can define the full extent of disease (Fig. 6-19). CT is also useful as a single follow-up examination in patients with metastases to the heart and lungs because it avoids the need for periodic assessment with both conventional chest CT and cardiac MRI. Fat-containing lesions are very amenable to evaluation by CT because lesions have a characteristic appearance, appearing black relative to water (Fig. 6-20).

Imaging of the Pericardium

In patients with clinically suspected constrictive pericarditis, cardiac MRI or CT can be used to confirm and measure pericardial thickening. In comparison with MRI, CT far better demonstrates the presence and extent of calcification. This may be of value in confirming chronic calcific pericardial thickening, supporting the diagnosis of constrictive pericarditis (Fig. 6-21). In these cases, 3D volume rendering to illustrate regional localization of pericardial abnormality functions as an outstanding preoperative planning tool prior to pericardial stripping (Fig. 6-22).

Valve Imaging

In patients with suspected valve dysfunction based on echocardiography, cine CT provides valuable additional data. As discussed earlier, reconstruction is performed for all phases of the cardiac cycle, and the reformatted data can be played in a cine loop. For example, cardiac cine CT permits high-resolution functional evaluation of mechanical aortic valve prostheses (Fig. 6-23).

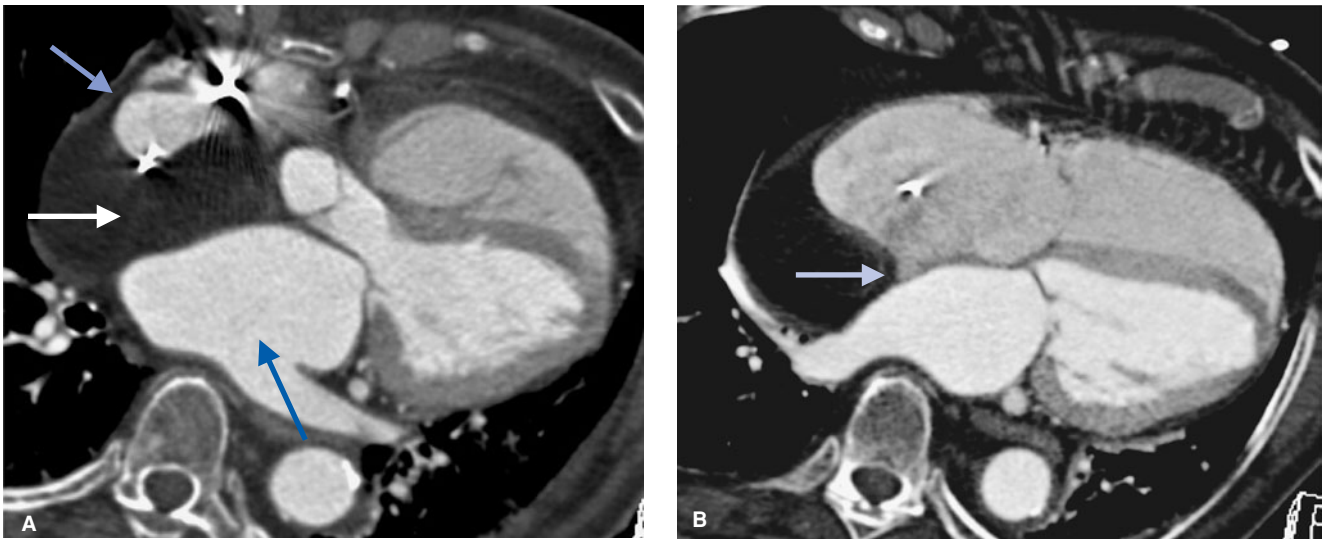

Figure 6-20. Lipomatous hypertrophy of the interatrial septum. Oblique axial multiplanar reformatted image (*A*) demonstrates a low-attenuation mass (*white arrow*) insinuated between the SVC (*gray arrow*) and the left atrium (*blue arrow*). Second more caudal image (*B*) demonstrates characteristic sparing of the fossa ovalis (*gray arrow*). This lesion is nonencapsulated and can be quite extensive, as in this case. Note the presence of leads from pacemaker, which precluded an MRI.

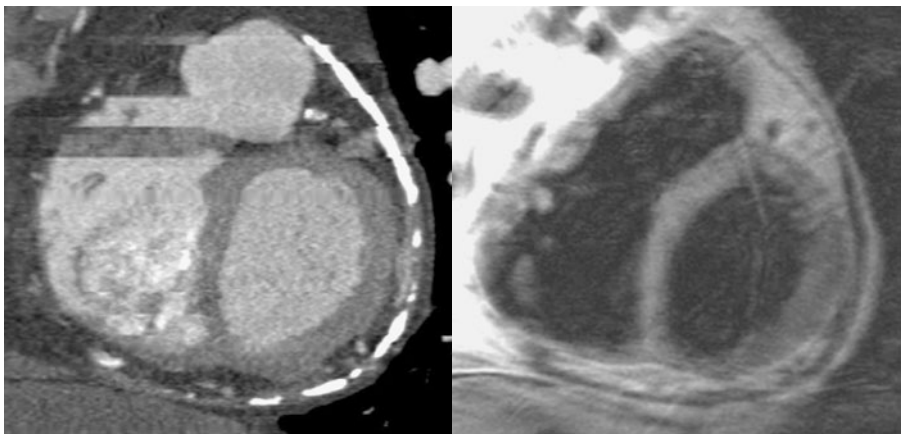

Figure 6-21. Calcific constrictive pericarditis. Short-axis multiplanar reformatted image from cardiac CT demonstrates extensive thickening and calcification involving left-sided pericardium. In the appropriate clinical setting, these findings would support the diagnosis of constrictive pericarditis. Short-axis double inversion recovery fast–spin-echo image from cardiac MRI in the same patient also shows abnormal pericardial thickening but is insensitive to calcification.

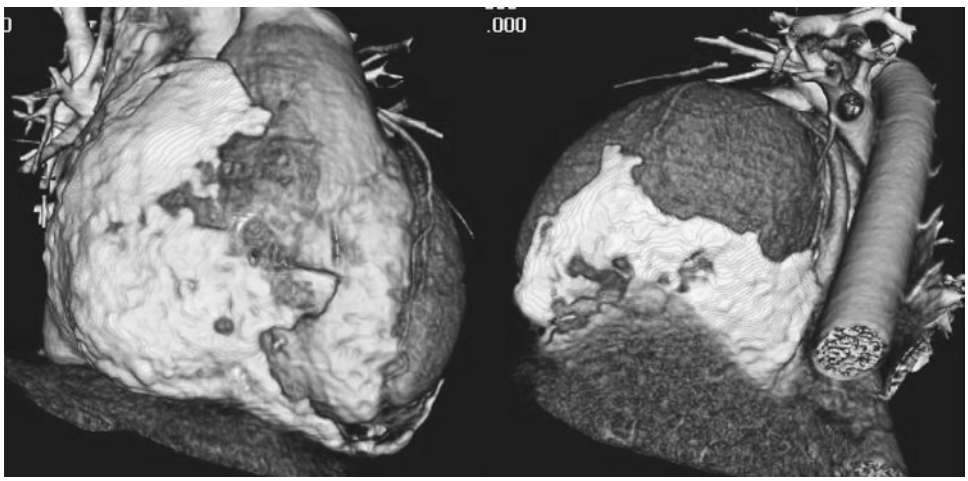

Figure 6-22. Preoperative evaluation of chronic calcific pericardial thickening prior to pericardial stripping. Three-dimensional volume-rendered images from cardiac CT demonstrate extensive regional pericardial calcification (*white areas*). This includes over the right ventricular outflow tract, right ventricle, right atrium, and entire inferior wall extending inferolaterally. Anterior and anterolateral pericardium was normal.

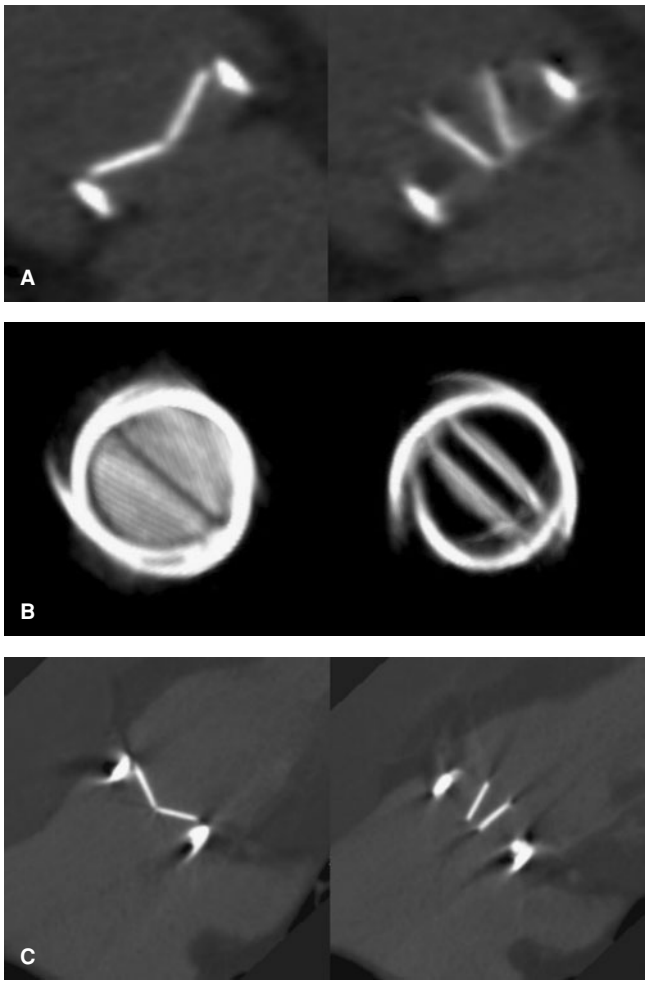

Figure 6-23. Evaluation of mechanical valve function with cardiac CT. Coronal oblique multiplanar reformatted images (*A*) demonstrate closed and open positions of mechanical AVR in a patient with suspected valve dysfunction based on echo-Doppler. Axial oblique slab maximum-intensity projection images (*B*) demonstrate closed and open positions of mechanical AVR in a patient in atrial fibrillation at the time of cardiac CT. Although image quality is degraded by arrhythmia, optimization of the data set with ECG editing can result in diagnostic-quality images. Four-chamber oblique multiplanar reformatted images (*C*) demonstrate closed and open positions of a mechanical MVR. Images can be generated over the cardiac cycle and displayed in a cine movie format to allow dynamic evaluation of valve function. Since the study is performed with contrast material, thrombus or perivalvular abscess also can be identified, if present.

Preoperative Planning and Surgical Guidance

Reoperative surgery

Reoperative cardiac surgery with live coronary artery grafts after previous CABG represents one of the most difficult problems in cardiac surgery. Reoperative sternotomy is challenging secondary to adhesions, loss of tissue planes, and the potential for injury to patent grafts, the aorta, and the right ventricle. Injury to a patent left internal thoracic artery graft to the LAD is associated with a mortality of 50%.[13,14] Cardiac CT has been revolutionary in precisely defining the relationship of important structures (e.g, the aorta, right ventricle, or live grafts) to the midline and sternum for re-entry planning (Fig. 6-24). At BWH, every reoperative surgery includes a preoperative CTA with *z*-axis coverage to include all grafts and the entire course of the IMAs. Preoperative identification of all structures at risk is mandatory, and different, specific operative approaches always remain in consideration.[15] Recent reported experience suggests that preoperative cardiac CT will lead to a modification in surgical strategy for 1 in 5 patients undergoing redo cardiac surgery.[16] For example, if CT demonstrates a patent left IMA is close to the midline or a right ventricle directly adherent to the posterior table of the sternum, cardiopulmonary bypass is instituted prior to reentry. Definition of live grafts with respect to their proximal placement on the aorta is instrumental in determining, *before the operation,* the precise manner in which those grafts will be handled. For example, in reoperative surgery for aortic valve replacement (AVR) in the setting of live grafts, CTA allows the surgeon to plan preoperatively whether or not those grafts will have to be divided in carrying out the aortotomy for the AVR. As described earlier, CT also allows the cardiac surgeon to plan the precise location of the aortotomy itself preoperatively.

Minimally invasive surgery: CABG

Minimally invasive CABG surgery is becoming an alternative to open surgery. With limited intraoperative access for direct visualization, aspects of coronary artery anatomy such as vessel diameter, extent of calcification, and presence of intramyocardial segments become even more important to define preoperatively (Fig. 6-25). In addition, 3D models that combine visualization of a partially transparent thoracic cage over mediastinal structures allow the surgeon to obtain detailed preoperative understanding of the patient's cardiothoracic anatomy (Fig. 6-26). Preoperative CT has demonstrated usefulness for MIDCAB[17] and totally endoscopic coronary artery bypass surgery.[18] CT is also expected to become invaluable for procedures such as multivessel small thoracotomy coronary artery revascularization.

CT versus MRI of the Heart

Throughout this chapter, comparisons between CT and MRI have illustrated the strengths and limitations of each. Both modalities give the surgeon valuable pre- and postoperative information. While the modality best suited for specific clinical indications evolves with the technology, at present, certain generalizations can be made. Cardiac CT is invaluable in reoperative cardiac surgery because it offers higher-quality noninvasive angiography of native coronary arteries and bypass grafts. Since 3D volume rendering with CT has higher quality and better spatial resolution, it is preferred for preoperative planning for reoperative CABG or minimally invasive cardiac surgery. All calcification is poorly seen with MRI and superbly seen with CT, and thus CT is far superior in demonstrating coronary, myocardial,

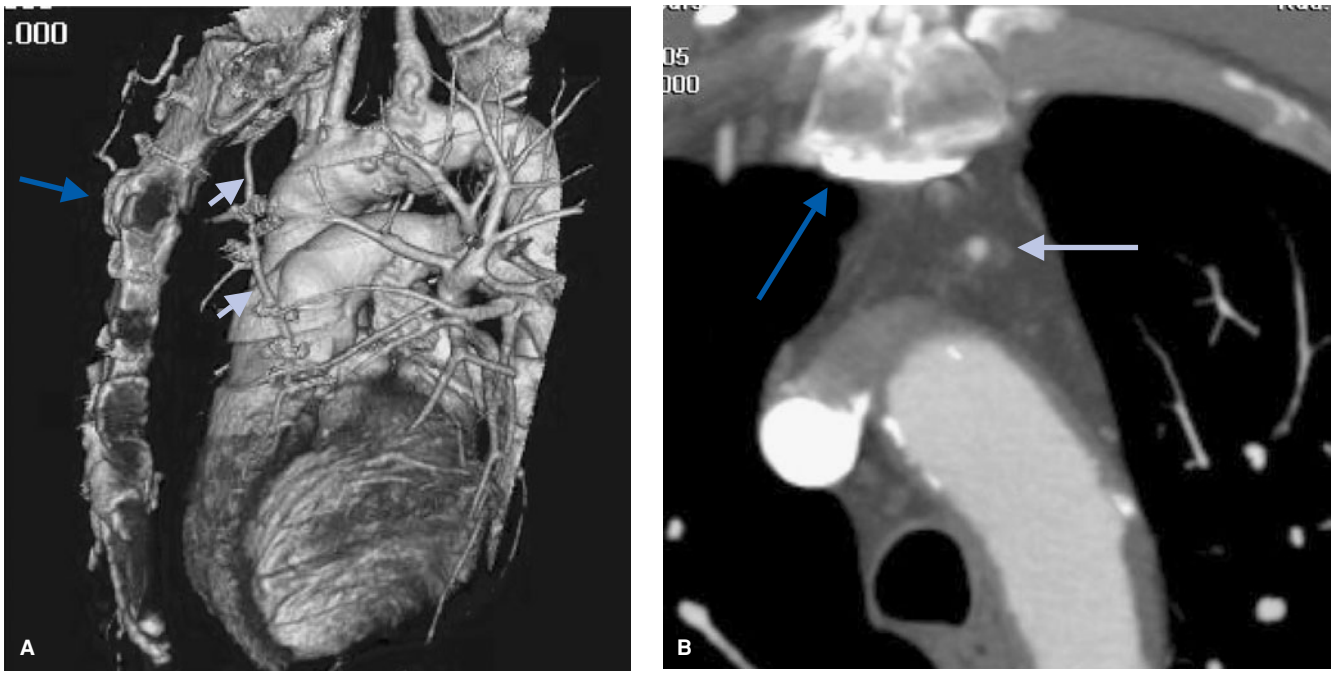

Figure 6-24. Planning for reoperative CABG. Laterally oriented 3-D volume-rendered image (*A*) from a patient who had previously undergone left IMA coronary bypass grafting. The left IMA (*gray arrows*) is grafted to the LAD coronary artery. Note the relatively large distance between the grafted left IMA and the sternum (*blue arrow*). Axial image (*B*) clearly shows the left IMA graft (*gray arrow*) to be clear of the midline and well posterior to the sternum (*blue arrow*). Since the most common surgical approach in a redo CABG is repeat thoracotomy through the sternal incision, this study demonstrates that surgical revascularization through sternal re-entry has no significant risk of damage to the patent left IMA graft.

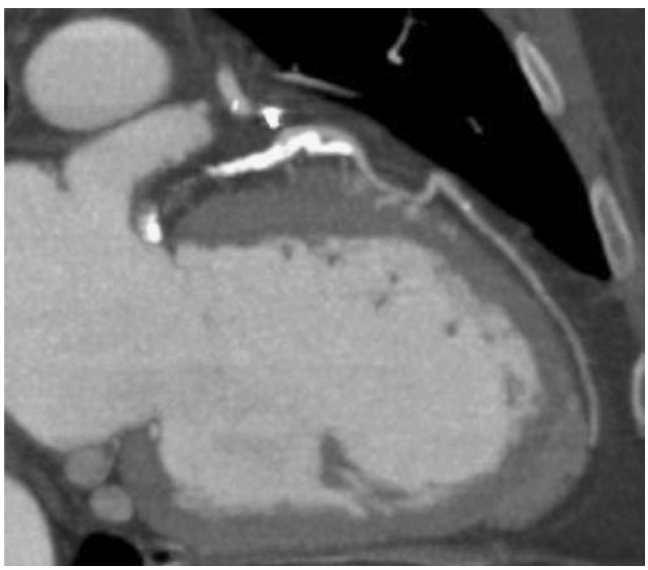

Figure 6-25. Preoperative planning for minimally invasive cardiac surgery (MIDCAB). Two-chamber plane maximum-intensity projection image (6 mm thick) demonstrates the LAD. A segment of heavy calcification is identified in the proximal vessel that corresponds to the site of the stenotic lesion. No significant calcification is present in the remainder of the vessel. An intramyocardial segment is present immediately beyond the calcified segment.

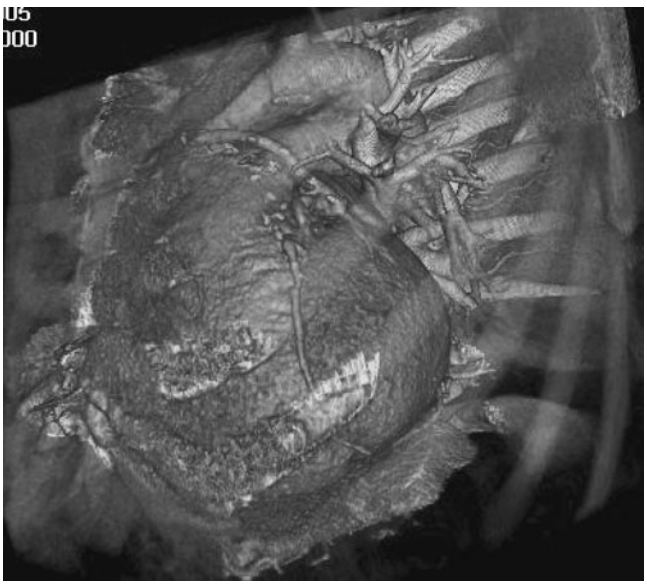

Figure 6-26. Preoperative planning for minimally invasive cardiac surgery (MIDCAB). Specialized display protocols for 3-D volume-rendered images can be used to provide combined visualization of a semitransparent thoracic cage and underlying cardiac and mediastinal structures. These models can be rotated and viewed from any angle or degree of magnification. With cardiac CT, 3-D localization of target vessels, accessibility from proposed incision site, and position of left ventricular apex with respect to chest wall all can be understood preoperatively.

pericardial, and valvular calcification. The same is true for mechanical valve prostheses; because of large areas of artifact on MRI images, functional evaluation is possible only with CT. Finally, all patients with a surgical problem of the aorta require evaluation with CT.

The strengths of MRI include higher temporal resolution, greater blood–myocardial image contrast, multiparametric functional evaluation, and techniques for myocardial tissue characterization. In addition, cardiac MRI is invaluable in assessing myocardial function, contractility, and actual tissue perfusion and viability. For these reasons, MRI remains the "gold standard" to assess biventricular volumes and function and myocardial mass. A number of MRI pulse sequences can delineate areas of chronic myocardial infarction accurately, identify certain specific cardiomyopathies, and confirm the presence of neoplasm. With the use of parallel imaging techniques to increase the speed of the MRI acquisition, very high temporal resolution (20 to 30 ms) can be obtained to study bioprosthetic and native valve function. In addition, measurements of flow parameters through a vessel cross section can be used, for example, to quantify valvular regurgitant lesions accurately.

One distinct advantage of MRI over CT is that MRI delivers no patient radiation. As detailed earlier, the radiation exposure in ECG-gated CT is higher than that for CT of any other body part. In younger patients, who typically have less comorbid disease and may require multiple follow-up examinations over years or decades, MRI should be used when possible.

CONCLUSIONS

Dramatic progress in CT technology has enabled advanced cardiac imaging for cardiac surgery patients. As the newest cardiac imaging modality to enter clinical practice, cardiac CT has rapidly demonstrated broad-ranging applicability, and in particular, CT has revolutionized the preoperative assessment of patients for reoperative surgery. Understanding the technical considerations will allow the surgeon to appreciate the inherent strengths and weaknesses of cardiac CT and to optimally communicate with the radiologist. This, in turn, will result in the best-quality diagnostic examination in the vast majority of cardiac surgery patients.

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CHAPTER 7

Risk Stratification and Comorbidity

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HISTORICAL PERSPECTIVES AND THE PURPOSE OF OUTCOME ASSESSMENT

Hunter, Nightingale, Codman, and Cochrane

> It may seem a strange principle to enunciate as the very first requirement in a Hospital that it should do the sick no harm. It is quite necessary, nevertheless, to lay down such a principle, because the actual mortality in hospitals . . . is very much higher than . . . the mortality of the same class of diseases among patients treated out of hospital.
>
> Florence Nightingale, 1863

From the dark ages until the 1700s, medicine advanced little. Remedies such as blood letting, cathartics, emetics (purges), and blistering were used to treat everything from gunshot wounds to smallpox. These were the only options and not only were ineffective but also often made things worse. As is so often true, before progress can be made, it is necessary to recognize where we stand at present. Arguably, it took at least one person to do this, John Hunter. He was relatively uneducated by the standards of the time. He came to London from his family farm in Scotland to work for his brother, a physician. His brother gave him the task of securing cadavers for anatomy experiments. This often involved illicit actions such as robbing freshly dug graves and associating with the seedier parts of London society. John Hunter had two qualities that allowed him to succeed and become the preeminent surgeon of the time and the father of modern surgery.[1] He had the ability to see things as they really were, and he had great technical skill. He recognized right away that the current remedies of the time were ineffective and that it was often better to do nothing than to subject patients to the current interventions. He was one of the earliest surgeons to recognize that human illness has anatomic causes and explanations. More important, he was unwilling to accept hypothetical abstract explanations of illness such as "humors" or "spirits." He required that he verify causes of illness himself and that he could explain them on the basis of anatomy. For example, treatment of venereal disease was an important part of a physician's practice in the mid-1700s. Hunter was outspoken about the failure of the majority of medications claiming to cure gonorrhea. He was quoted as saying that "gonorrhea could be cured by the most ignorant, since gonorrhea mostly cures itself." He even performed an ingenious test by treating some of his patients with pills made of bread. He recorded the results, and almost all the patients had resolution of gonorrhea. This was one of the first trials documenting the placebo effect. In Hunter's time, gonorrhea and syphilis were thought to be different manifestations of the same infection. Hunter injected himself with what he thought was gonorrhea in order to study the natural history of the disease.[1] Hunter's approach often was unpopular, and it took a person who was not brought up in the mold of the current physicians of the time to stand back and ask these important questions about illness, disease, and outcomes. John Hunter's friends and patients included Benjamin Franklin, Edward Jenner, Lord Byron, Casanova, and Adam Smith. His list of enemies probably was equally distinguished. What is clear is that the assessment of outcomes of illness could not advance without the likes of someone like John Hunter.

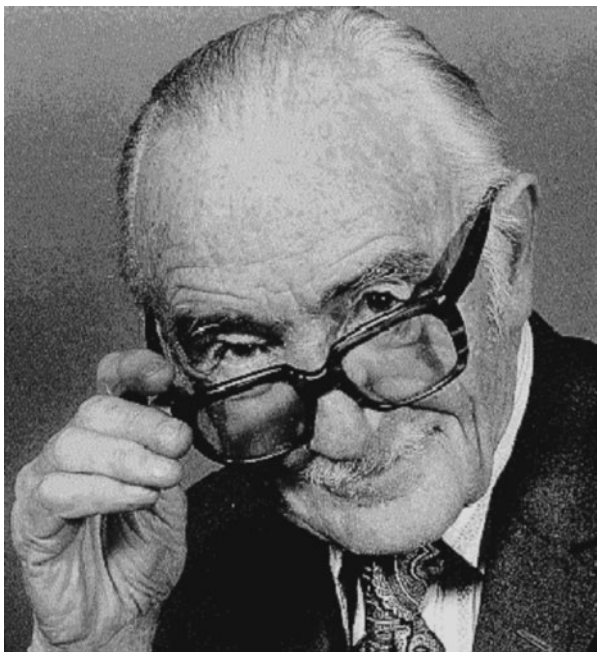
The formal assessment of patient care had its beginnings in the mid-1800s. One of the earliest advocates of analyzing outcome data was Florence Nightingale, who was troubled by observations that hospitalized patients died at higher rates than those treated out of hospital.[2] She also noted that there was a vast difference in mortality rates among different hospitals, with London hospitals having as high as a 90% mortality rate and smaller rural hospitals having a much lower mortality rate (12 to 15%). Although England had tracked hospital mortality rates since the 1600s, the

analysis of these rates was in its infancy. Yearly mortality statistics were calculated by dividing the number of deaths in a year by the average number of hospitalized patients on a single day of that year. Nightingale made the important observation that raw mortality rates were not an accurate reflection of outcome because some patients were sicker when they presented to the hospital and therefore would be expected to have a higher mortality. This was the beginning of risk adjustment based on severity of disease. She was able to carry her observations to the next level by suggesting simple measures such as improved sanitation, less crowding, and location of hospitals distant from crowded urban areas that ultimately would result in dramatic improvement in patient outcomes—an example of a quality improvement project (see below).

Ernest Amory Codman, a Boston surgeon, was one of the most outspoken early advocates of outcome analysis and scrutiny of results. Codman was a classmate of Harvey Cushing and became interested in the issues of outcome analysis after a friendly bet with Cushing about who had the lowest complication rate with the delivery of anesthesia. In the early 1900s as medical students, they were responsible for administering anesthesia. Since vomiting and aspiration were common on induction of anesthesia, many operations were over before they started. Cushing and Codman compared their results and kept records concerning the conduct of anesthesia while they were medical students. This effort not only represented the first intraoperative patient records but also served as a foundation for Codman's later interest in (almost passion for) documentation of outcomes. Codman actually paid a publisher to disseminate the results obtained in his privately owned Boston hospital.[3] Codman was perhaps the first advocate of searching for a cause of all complications. He linked specific outcomes to specific interventions (or errors). He felt that most bad outcomes ultimately were the result of errors or omissions on the part of the physician and completely ignored any contribution to outcome from hospital-based and process-related factors. His efforts were not well received by his peers, and eventually his private hospital closed because of lack of referrals.

Both Codman and Nightingale viewed outcome analysis as an intermediate step in the improvement of patient care. It was not enough to know the rates of a given outcome. For these early clinicians, outcome analysis became meaningful only when it helped to improve patient care. While it is axiomatic that any valid comparison of quality of care or patient outcome must account for patients' severity of illness, this is only the initial step toward improving patient outcome.

Further definition of outcome assessment occurred in the mid-1900s. As more and more therapeutic options became available to treat the diseases that predominated in the early twentieth century (e.g., tuberculosis), a need arose to determine the best alternative of multiple therapies—thus the advent of the controlled, randomized trial and tests of effectiveness of therapy. One of the earliest randomized trials was conducted to determine whether streptomycin was effective against tuberculosis.[4] Although the trial proved the effectiveness of streptomycin against tuberculosis, it stimulated a great deal of controversy. After World War II, several clinicians advocated the use of randomized, controlled trials (RCTs) to better identify the optimal treatment to provide the best outcome. Foremost among these was Archie Cochrane. Every physician should know about Archie Cochrane (Fig. 7-1). He is as close to a true hero as a physician can get, but there may be those who see him as the devil incarnate. As you can see from some of the highlights of his career (see Fig. 7-1), he lived during an exciting time. In the 1930s, Professor Cochrane was branded as a Trotskyite because he advocated a national health system for Great Britain. His advocacy was tempered by 4 years as a prisoner of war in multiple German prisoner of war (POW) camps. He saw soldiers die from tuberculosis,



- 1934–36: Medical student, University College Hospital, London.
- 1936: International Brigade, Spanish Civil War.
- 1939–46: Captain, Royal Army Medical Corps.
- 1941: Taken prisoner of war in June 1941 in Crete; POW medical officer in Salonica (Greece) and Hildburghausen, Elsterhorst, and Wittenberg-am-Elbe (Germany).
- 1947–48: Studied the epidemiology of tuberculosis at Henry Phipps Institute, Philadelphia, USA.
- 1948–60: Member, Medical Research Council Pneumoconiosis Research Unit, Penarth, Wales.
- 1960–69: David Davies Professor of Tuberculosis and Chest Diseases, Welsh National School of Medicine, Cardiff, Wales.
- 1960–74: Director, Medical Research Council Epidemiology Research Unit, Cardiff, Wales.
- 1972: Publication by the Nuffield Provincial Hospitals Trust of his book *Effectiveness and Efficiency—Random Reflections on Health Services.*

Figure 7-1. Portrait of Archie Cochrane with brief biography. (*Used with permission from the Cochrane Collaboration.*)

and he was never sure what the best treatment was. Believe it or not, he did have some alternate therapies to offer the soldiers in the POW camps. He could choose between collapse therapy, bed rest, supplemental nutrition, or even high-dose vitamin therapy. A quote from his book sums up his frustration:

> I had considerable freedom of clinical choice of therapy: my trouble was that I did not know which to use and when. I would gladly have sacrificed my freedom for a little knowledge.[5]

His experience with the uncertainty about the best treatment for tuberculosis and other chest diseases continued after the war when he became a researcher in pulmonary disease for the Medical Research Council of Great Britain. Still with an interest in tuberculosis, now heightened by the fact that he had contracted the disease, Archie wanted to know the best drug therapy for tuberculosis because drugs were now available that could treat this disease—streptomycin being the first really effective drug against *Mycobacterium tuberculosis*.[4] He was a patron of RCTs, to test important medical hypotheses. He used the evidence gained from these RCTs to make decisions about the best therapy based on available evidence—the beginning of *evidence-based practice*. He felt that RCTs are the best form of evidence to support medical decision making (so-called class 1 evidence). Initially, he was a voice in the wilderness, but this changed little by little. In 1979 he criticized the medical profession for not having a critical summary, organized by specialty and updated periodically, of relevant RCTs. In the 1980s at Oxford, a database of important RCTs dealing with perinatal medicine was developed. In 1987, the year before Cochrane died, he referred to a systematic review of RCTs of care during pregnancy and childbirth as "a real milestone in the history of randomized trials and in the evaluation of care" and suggested that other specialties should copy the methods used. This led to the opening of the first Cochrane center (in Oxford, UK) in 1992 and the founding of the Cochrane Collaboration in 1993. Today, the Cochrane Collaboration is a repository of RCTs, both disease-specific and specialty-specific. Clinicians and lay people can go to the Cochrane Web site (www.cochrane.org/) and find summaries of all available RCTs on a wide range of medical subjects. From the preceding discussion, it is fair to call Archie Cochrane the "father of evidence-based medicine." Evidence-based medicine has, at its heart, the imperative to improve outcomes by comparing alternative therapies to determine which is best. Evidence-based studies that involve RCTs have the advantage of being able to infer cause and effect (i.e., a new therapy or drug *causes* improved outcome). On the other hand, observational studies (or retrospective studies) such as those of Hunter, Nightingale, and Codman are only able to define associations between therapies and outcome, not prove cause and effect. The ascendancy of RCTs represents a major step forward in outcome assessment.

DEFINITIONS

Risk Stratification: Arranging Patients According to Severity of Illness

Implicit in the assessment of process of care or of outcomes is the ability to arrange patients according to their severity of illness. In its simplest form, this is *risk stratification*. Implicit in this definition is the ability to predict outcomes from a given intervention based on preexisting risk—i.e., patients who are sicker to start with are expected to have worse outcome from an intervention than are those who are less sick. *Risk stratification* therefore is defined as the ability to predict outcomes from a given intervention by arranging patients according to severity of illness. The usefulness of any risk-stratification system arises from how the system links severity to a specific outcome. Risk stratification is implicit in any assessment of clinical outcomes.

There have been numerous attempts at describing severity of illness by means of a tangible score or number. Table 7-1 is a partial listing of some of the severity measures used commonly in risk assessment of cardiac surgical patients. This list is not meant to be comprehensive but does give an overview of the types of risk-stratification schemes that have been used for cardiac patients. The risk-stratification systems listed in Table 7-1 are in constant evolution, and the descriptions in the table may not reflect current or future versions of these systems. All these severity measures share two common features. First, they are all linked to a specific outcome. Second, all measures view a period of hospitalization as the episode of illness. The severity indices listed in Table 7-1 define severity predominantly based on clinical measures (e.g., risk of death, clinical instability, treatment difficulty, etc.). At least two of the severity measures shown in the table (MedisGroups used in the Pennsylvania Cardiac Surgery Reporting System and the Canadian Provincial Adult Cardiac Care Network of Ontario) define severity based on resource use (e.g., hospital length of stay, cost), as well as on clinical measures.[6,7] Of the nine severity measures listed in the table, only one, the APACHE III system, computes a risk score independent of patient diagnosis.[8] All the others in the table are diagnosis-specific systems that use only patients with particular diagnoses in computing severity scores.

Each of the risk-stratification measures shown in Table 7-1 has been tested against a validation set of patients and found to be an adequate measure of the risk of operative mortality or of other outcome. However, assessing the validity and performance of various risk-adjustment methods entails more than simple cross-validation. No severity tool will ever perfectly describe patients' risks for death, complications, or increased resource use. The most important reason that risk-adjustment methods fail to predict outcomes completely is that the data set used to derive the risk score comes from retrospective, observational data that contain inherent selection bias; i.e., patients were given a certain treatment that resulted in a particular outcome because a clinician had a certain

Table 7–1.

Examples of Risk Stratification Systems Used for Patients Undergoing Cardiac Surgical Procedures

Severity system	Data source	Classification approach	Outcomes measured
APACHE III[8]	Values of 17 physiologic parameters and other clinical information	Integer scores from 0 to 299 measured within 24 hours of ICU admission	In-hospital death
Pennsylvania	Clinical findings collected at time of admission	Probability of in-hospital death ranging from 0 to 1 based on logistic regression model and MediQual's Atlas admission severity score	In-hospital death and cost of procedure
New York	Condition-specific clinical variables from discharge record	Probability of in-hospital death ranging from 0 to 1 based on logistic regression model	In-hospital death
Society for Thoracic Surgeons	Condition-specific clinical variables from discharge record	Bayesian algorithm used to assign patient to risk interval (percent mortality interval); more recently converted to logistic regression model	In-hospital death and morbidity
EuroSCORE	Condition-specific clinical variables from discharge record	Additive logistic regression model with scores based on presence or absence of important risk factors	30-day and in-hospital mortality
Veterans Administration	Condition-specific clinical variables measured 30 days after operation	Logistic regression model used to assign patient to risk interval (percent mortality interval)	In-hospital death and morbidity
Parsonnet	Condition-specific clinical variables from discharge record	Additive multiple regression model with scores between 0 and 158 based on 14 weighted risk factors	Death within 30 days of operation
Canadian	Condition-specific clinical variables entered at time of referral for cardiac surgery	Range of scores from 0 to 16 based on logistic regression odds ratio for six key risk factors	In-hospital mortality, ICU stay, and postoperative length of stay
Northern New England	Condition-specific clinical variables and comorbidity index entered from discharge record	Scoring system based on logistic regression coefficients used to calculate probability of operative mortality from 7 clinical variables and 1 comorbidity index	In-hospital mortality
Cleveland Clinic	Condition-specific clinical variables from discharge record	Range of scores from 0 to 33 based on univariate odds ratio for each of 13 risk factors	In-hospital death or death within 30 days of operation

Pennsylvania = Pennsylvania Cost Containment Committee for Cardiac Surgery; New York = New York State Department of Health Cardiac Surgery Reporting System; Society for Thoracic Surgeons = Society of Thoracic Surgeons Risk Stratification System; Veterans Administration = Veterans Administration Cardiac Surgery Risk Assessment Program; Parsonnet = Parsonnet Risk Stratification Model; Canadian = Ontario Ministry of Health Provincial Adult Cardiac Care Network; Northern New England = Northern New England Cardiovascular Disease Study Group; Cleveland Clinic = Cleveland Clinic Foundation Risk Stratification System.

selection bias about what treatment that particular patient should receive. In observational data sets, patients are not allocated to a given treatment in a randomized manner. In addition, clinician bias is not always founded in evidence-based data. An excellent review of the subtleties of evaluating the performance of risk-adjustment methods is given in the book by Iezzoni, and this reference is recommended to the interested reader.[9] More attention is paid to the quality of risk-adjustment systems in subsequent sections.

Outcomes and Risk Stratification

There are at least four clinical outcomes of interest to surgeons dealing with cardiac surgical patients: *mortality, serious nonfatal morbidity, resource utilization,* and *patient satisfaction.* Which patient characteristics constitute important risk factors may depend largely on the outcome of interest. For example, Table 7-2 lists the multivariate factors and odds ratios associated with various clinical outcomes of interest for patients having cardiac operations.[10–12] The clinical variables associated with increased resource utilization after operation are different from those associated with increased mortality risk. As a generalization, the risk factors associated with in-hospital death are likely to reflect concurrent disease-specific variables, whereas the factors associated with increased resource utilization reflect serious comorbid illness.[13–15] For example, mortality risk after coronary artery bypass grafting (CABG) is associated with disease-specific factors such as ventricular ejection fraction, recent myocardial infarction, and hemodynamic instability at the time of operation, whereas risk factors for increased resource utilization (as measured by length of stay and hospital cost) include comorbid illnesses such as peripheral vascular disease,

Table 7–2.

Multivariate Factors Associated with Various Outcomes of Cardiac Surgery[10,11]

	Relative risk of outcome			
Variable	**Serious morbidity (95% CI)**	**Mortality (95% CI)**	**Decreased cost (95% CI)**	**Decreased LOS (95% CI)**
Congestive heart failure	4.81 (2.16–5.98)	9.20 (6.02–14.0)	0.56 (0.51–0.63)	0.79 (0.73–0.85)
NYS predicted mortality risk		1.28 (1.16–1.41)	0.93 (0.89–0.97)	0.78 (0.76–0.80)
Type of operation		6.04 (3.48–10.5)	0.43 (0.40–0.47)	0.53 (0.48–0.59)
Creatinine > 2.5 mg/100 mL			0.40 (0.33–0.49)	0.47 (0.38–0.58)
Priority		18.6 (7.42–46.6)	0.53 (0.50–0.56)	
Age/RBC volume (per 0.01 unit increase)	6.93 (3.21–11.5)		0.61 (0.55–0.67)	0.32 (0.30–0.36)
Reoperative procedure			0.68 (0.62–0.76)	
Preoperative IABP			0.65 (0.56–0.75)	
Hypertension	5.62 (2.11–15.2)		0.86 (0.81–0.92)	0.83 (0.78–0.89)
More than one prior MI			0.83 (0.75–0.91)	
Dialysis-dependent renal failure			0.61 (0.47–0.78)	
Peripheral vascular disease				0.85 (0.71–0.94)
Prior CNS disease	3.41 (2.99–4.91)			0.81 (0.72–0.92)
COPD				0.87 (0.79–0.94)

CNS = central nervous system; COPD = chronic obstructive pulmonary disease; IABP = intra-aortic balloon counterpulsation; LOS = length of stay; MI = myocardial infarction; RBC = red blood cell.

renal dysfunction, hypertension, and chronic lung disease (Table 7-2). It is not surprising that comorbid conditions are important predictors of hospitalization charges because patients with multiple comorbidities often require prolonged hospitalization not only for treatment of the primary surgical illness but also for treatment of complicating comorbid conditions.

Operative mortality is an easily defined, readily measured outcome, and its value to patients is undeniable. Most studies that have attempted to define effective care have focused on mortality as an outcome for the preceding reasons. Other outcomes such as resource utilization or quality-of-life indicators may be more relevant postoperative outcomes in many instances. Outcome measures other than operative mortality are particularly important when deciding how to spend health care dollars wisely.[16,17]

Measures of Comorbidity

Comorbidities are coexisting diagnoses that are indirectly related to the principal surgical diagnosis but that may alter the outcome of operation. Clearly, physicians or hospitals that care for patients with a higher prevalence of serious comorbid conditions are at significant disadvantage in unadjusted comparisons. The prevalence of comorbid illness in patients with cardiac disease has been well demonstrated. In one series of patients with myocardial infarction, 26% also had diabetes, 30% had arthritis, 6% had chronic lung problems, and 12% had gastrointestinal disorders.[18]

Several indices of comorbidity are available. Table 7-3 compares five commonly used comorbidity measures: the Charlson index, the Rand Corporation index, the Greenfield index, the Goldman index, and the APACHE III scoring system.[18–25] There are many limitations of comorbidity indices, and they are not applied widely in studies of efficacy or medical effectiveness. Perhaps the most serious drawback of comorbidity scoring systems is the imprecision of the databases used to form the indices. Most of the data used to construct the indices come from two sources: (1) administrative databases in the form of computerized discharge abstract data and (2) out-of-hospital follow-up

Table 7–3.

Five Comorbidity Indices

Comorbidity index	Data source and purpose	Classification approach	Most significant comorbidities
Charlson[19]	Abstract of medical records and follow-up data used to predict death at 1 year	Weighted relative risks from Cox proportional hazards model used to create comorbidity index	AIDS, metastatic tumor, and moderate to severe liver disease
APACHE III[21]	In-patient ICU records used to develop chronic health evaluation as part of overall index	Scores ranging from 0 to 299 created from logistic regression model with in-hospital mortality as outcome	AIDS, severe liver failure, lymphoma/leukemia, metastatic tumor
Keeler/RAND[22]	Medicare administrative database used to evaluate 30-day mortality risk	Weights assigned based on regression coefficients of significant logistic regression variables	Cancer, chronic renal failure, hypoalbuminemia, disease of the thorax, and use of nasogastric tube
Goldman[25]	Preoperative examination of patients undergoing noncardiac operations	Weights assigned for comorbidities based on discriminant analysis	Third heart sound, MI within 6 months, nonsinus rhythm, aortic stenosis, type of operation
Greenfield/ ICED[18,23,24]	Abstracts of medical records and outpatient follow-up to assess functional status 1 year after acute event	Combines measures of physiologic derangement and impairment related to comorbidity; variables derived from clinical experience	Functional status, acute exacerbation of comorbid condition, and baseline comorbidities, including metastatic cancer, liver disease, renal failure, and cardiac disease

MI = myocardial infarction.

reports. Discharge abstracts include clinical diagnoses that often are assigned by nonphysicians who were not involved in the care of the patient. Comprehensive entry of correct diagnoses is not a high priority for most clinicians, and problems with discharge coding have been identified by Iezzoni and others.[26–28] These authors found that many conditions that are expected to increase the risk of death actually are associated with a lower mortality. The presumed explanation for this paradoxical finding is that less serious diagnoses are unlikely to be coded for in the most seriously ill patients. Likewise, the accuracy of out-of-hospital follow-up studies is hard to validate, and such studies may contain significant inaccuracies. Despite these shortcomings, analyses that compare physician or hospital outcomes and that do not provide adequate adjustment for patient comorbidity are likely to discriminate against providers or hospitals that treat disproportionate numbers of elderly patients with multiple comorbid conditions. A vivid example of failure to adjust for patient severity occurred when the leaders of the Health Care Financing Administration (HCFA) released hospital mortality figures in March 1986. One hundred and forty-two hospitals had significantly higher death rates than predicted. At the facility with the most aberrant death rate, 87.6% of Medicare patients died compared with a Medicare average of 22.5%. What was not taken into account was that this facility was a hospice caring for terminally ill patients.[29] The HCFA model had not accounted for patient risks and comorbidities adequately.

Risk adjustment for severity of illness and comorbidity is equally important for patients undergoing stressful interventions such as surgical operations or chemotherapy. For example, Goldman and colleagues reported that preexisting heart conditions and other comorbid diseases were important predictors of postoperative cardiac complications for patients undergoing noncardiac procedures.[25] The Goldman scoring system is used commonly by anesthesiologists in assessing patients preoperatively, especially prior to noncardiac procedures.[25,30]

Outcome versus Process and Structural Measures of Quality

In 2000, the Institute of Medicine issued a report that was highly critical of the U.S. health care system, suggesting that between 50,000 and 90,000 unnecessary deaths occur yearly because of errors in the health care system.[31] This Institute of Medicine report created a heightened awareness of more global aspects of quality. For most of the history of cardiac surgery, quality generally was equated with operative mortality (i.e., outcome measure). As the new millennium got underway, a distinct change in the landscape of quality assessment occurred. The narrow focus on operative mortality gave way to a broader analysis that also included operative morbidity. The emphasis on these *outcomes measures* was further expanded to include the *process* of surgical care delivery. *Process measures* were developed to monitor the process of care. These measures typically include the choice of medication, timing of administration, and other interventions considered appropriate for optimal care. *Structural measures* such as health information technology (HIT) and organizational design also were considered important elements in this more global model of medical quality. Donabedian is credited with recognizing that outcome measures, process measures, and structural measures all contribute to quality of care.[32] In keeping with the well-accepted Donabedian model, outcome measures, process measures, and structural measures generally are termed *performance measures.*

The following definitions are adapted from those proposed by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO):

performance measure A quantitative entity that provides an indication of an organization's performance in relation to a specified process or outcome.
outcome measure A measure that indicates the results of process measures. Examples are operative mortality and the frequency of postoperative mediastinitis, renal failure, myocardial infarction, etc.
process measure A measure that focuses on a process leading to a certain outcome. Intrinsic in this definition is a scientific basis for believing that the process will increase the probability of achieving a desired outcome. Examples include the rate of internal mammary artery (IMA) use in CABG patients or the fraction of CABG patients placed on beta-blocking agents postoperatively.
structural measure A measure that assesses whether an appropriate number, type, and distribution of medical personnel, equipment, and/or facilities are in place to deliver optimal health care. Examples include enrollment in a national database or procedural volume.

Although there are numerous proposed criteria for an ideal performance measure, the following are universally accepted attributes:

- The measure must be clearly linked to quality of care.
- The measure must be objective, evidence-based, and risk-adjusted if possible.
- The physician must have the ability to influence the measure in a clinical setting.
- The measure must be sufficiently well defined to permit practical measurement.

Several national organizations are specifically devoted to the rigorous development of performance measures. Perhaps the most visible of these is the National Quality Forum (NQF), a quasi-governmental organization that uses a process of exhaustive, evidence-based scrutiny of candidate measures to determine those that are truly indicative of quality outcome. The value of the NQF process lies in the fact that process measures subject to this "trial by fire" are endorsed at a national level and thereby have a high level of credibility not otherwise possible.

TOOLS OF RISK STRATIFICATION AND OUTCOME ASSESSMENT

Databases

Perhaps the most important tool of any outcome-assessment endeavor is a database that is made up of a representative sample of the study group of interest. The accuracy of the data elements in any such database cannot be overemphasized.[33,34] Factors such as the source of data, the outcome of interest, the methods used for data collection, standardized definitions of the data elements, data reliability checking, and the time frame of data collection are essential features that must be considered when either constructing a new database or deciding about using an existing database.[33,34] The quality of the database of interest must be evaluated.

Data obtained from claims databases are less reliable than those obtained from clinical databases. Because claims data are generated for the collection of bills, their clinical accuracy is inadequate, and it is likely that these databases overestimate complications for billing purposes.[35] Furthermore, claims data underestimate the effects of comorbid illness and contain major deficiencies in important prognostic variables for CABG, namely, left ventricular function and number of diseased vessels.[36] The Duke Databank for Cardiovascular Disease found major discrepancies between clinical and claims databases, with claims data failing to identify more than half the patients with important comorbid conditions such as congestive heart failure (CHF), cerebrovascular disease, and angina.[37] The HCFA used claims data to evaluate variations in the mortality rates in hospitals treating Medicare patients. After an initially disastrous effort at risk adjustment from claims data,[38,39] new algorithms were developed. Despite these advances, the HCFA halted release of the 1993 Medicare hospital mortality report because of concerns about the database and fears that the figures would unfairly punish inner-city public facilities.[40] The quality of databases used to generate comparisons cannot be overemphasized.

Analytic Tools of Risk Stratification

Implicit in risk adjustment is some analytic technique used to develop significant risk factors that are predictive of the outcome of interest. The current shift to outcomes analysis carries with it a more intensive reliance on statistical techniques that are capable of evaluating large populations with multiple variables of interest in an interdependent manner—i.e., multivariate analyses. A modicum of statistical knowledge helps to unravel the intricacies of simple statistics and risk adjustment.[41] This knowledge provides confidence in the results of risk-adjustment methodologies. It is not our intention to provide the reader with exhaustive knowledge of the statistics of outcome analysis but rather to provide a resource for critical assessment of these methods and to stimulate the interest of readers to learn more about this important field. Perhaps the biggest single benefit of risk adjustment for outcome analysis will come from physicians increasing their knowledge base about these analytic techniques and gaining confidence in the methodology such that physician practices will be altered favorably by the results of risk-adjusted outcome assessment, with the ultimate goal being improved patient care.

Regression Analysis

The starting point for understanding multivariate statistical methods is to have a firm grasp of elementary statistics.[41] Several basic texts on statistics are available that are enjoyable reading for the interested health care professional.[42–44] These texts are a painless way to become familiar with the basic terminology regarding variable description, simple parametric (normally distributed) univariate statistics, linear regression, analysis of variance, nonparametric (not normally distributed) statistical techniques, and ultimately, multivariate statistical methods.

A statistical technique that is used commonly to describe how one variable (the dependent or outcome variable) depends on or varies with a set of independent (or predictor) variables is *regression analysis*. The dependent or outcome variable of interest can be either continuous (e.g., hospital cost or length of stay) or discrete (e.g., mortality). Discrete outcome variables can be either dichotomous (two discrete values such as alive or dead) or nominal (multiple discrete values such as improved, unimproved, or worse). The relationship between the outcome variable and the set of descriptor variables can be linear or any other nonlinear mathematical relationship. Two books, one by Glantz and Slinker and the other by Harrell, provide an enjoyable primer on regression analysis and are geared to the biomedical sciences.[44,45] They are recommended to the interested reader.

Regression analysis means determining the relationship (also termed *constructing a model*) that describes how an outcome variable depends on (or is associated with) a set of independent predictor variables. Put in simple terms, multivariate regression analysis is *model building*. The resulting model is useful only if it predicts outcomes accurately for patients by determining significant risk factors associated with the outcome of interest—i.e., risk adjustment of outcome. When the outcome variable of interest is a continuous variable such as hospital cost, linear multivariate regression often is used to construct a model to predict outcome. A multivariate linear regression model contains a set of dependent variables that are linearly related to and can be used to predict an outcome variable. These significant dependent variables are termed *risk factors,* and knowledge of these risk factors allows separation of patients according to their degree of risk—i.e., risk stratification. There are two important features of this linear regression model and any regression model for that matter. First, the model allows one to estimate the expected risk of a patient based on his or her risk characteristics. Second, various health care providers can be compared by comparing their observed outcomes to the expected outcomes that would be predicted from consideration of the risk factors of the patients they treat.

Statistical terminology used to describe variables and variable distribution patterns is particularly important in understanding linear regression statistical modeling. An important concept is *statistical variance* (R^2). R^2 is a summary measure of performance of the statistical model. R^2 often is described by saying that it is the fraction of the total variability of the dependent variable explained by the statistical model. Most investigators routinely report R^2 as a measure of the performance of linear regression risk-adjustment models.[46] For example, the APACHE III risk-adjustment scoring system described in Table 7-1 can be used to predict intensive-care unit (ICU) length of stay. When this is done, the model is associated with an R^2 value of 0.15.[21,46] This implies that 15% of the variability in ICU length of stay can be explained by the variables encompassed in the APACHE III score. Another way of saying this is that 85% of the variability in ICU length of stay is *not* explained by the APACHE III scoring system. This R^2 value does not rate the APACHE III scoring system very highly for predicting ICU length of stay. The APACHE III scoring system uses patient data obtained within 24 hours of admission to the ICU to predict outcome and was developed to predict in-hospital mortality, not hospital costs or length of stay. Ferraris and Propp found that the outcome of patients admitted to the ICU depends on things that happen after admission (especially iatrogenic events occurring in the ICU) more so than patient characteristics present on admission to the ICU.[47] Hence it is not surprising that the APACHE III score does not account for all the variability in ICU length of stay. In addition, it is not clear what level of R^2 can be expected when using APACHE III in a very different context than the one for which it was designed. Shwartz and Ash give an excellent review of evaluating the performance of risk-adjustment methods using R^2 as a measure of model performance, and their work provides an enlightening insight into the tools of risk adjustment.[48] An R^2 value of 0.15, as exhibited by the preceding APACHE III model, is not as horrible as it sounds. Hartz and colleagues point out that it is unlikely that any large multivariate regression model will completely account for all the variability of any complex outcome.[49] These authors constructed a so-called perfect model of simulated mortality data for CABG and found that this model only accounted for 31% of the variation in the mortality rate. The APACHE III value for R^2 looks somewhat better when compared with these standards. Ideally, refinements in any regression model should be an ongoing process that ultimately results in improvement in the regression diagnostics, therefore maximizing the value of R^2.

Logistic Regression

When the outcome variable of interest is a discrete variable (e.g., mortality), then nonlinear regression analysis is used. *Logistic regression* is the nonlinear method used most widely to model dichotomous outcomes in the health sciences. Logistic regression predicts the probability that an indicator variable is equal to 1. To be precise, the logistic regression equation does not directly predict the probability that the indicator is equal to 1. It predicts the log odds that an observation will have an indicator equal to 1. The *odds* of an event are defined as the ratio of the probability that an event occurs to the probability that it fails to occur. Thus

$$\text{Odds (indicator} = 1) = \text{probability (indicator} = 1)/[1 - \text{probability (indicator} = 1)]$$

or

$$\text{Odds (indicator} = 1) = \text{probability (indicator} = 1)/\text{probability (indicator} = 0)$$

The log odds is just the (natural) logarithm of the odds. Probabilities are constrained to lie between 0 and 1, with 1/2 as a neutral value for which both outcomes are equally likely. The constraints at 0 and 1 make it impossible to construct a linear equation for predicting probabilities. Logistic regression equations (i.e., models) compute the set of linear variables that best fits the observed log odds. Unlike a linear least-squares regression equation, which can be solved explicitly, logistic regression equations are solved with computer-intensive iteration steps by trial and error. A trial equation is fitted and adjusted repeatedly in steps until the equation describes the results accurately. Iterations stop when the improvement from one step to the next is very small. A typical logistic regression equation that describes the relationship of age to operative mortality might look as follows:

$$\text{Log odds (death)} = -4.353 + 0.038\ \text{(age)}$$

or

$$\text{Probability (death)}/[1 - \text{probability (death)}] = \exp[-4.353 + 0.038\ \text{(age)}]$$

or

$$\text{Probability (death)} = 1/(1 + \exp^{-[-4.353\ +\ 0.038\ \text{(age)}]})$$

The value –4.353 + 0.038 (age), sometimes called the *logit* or the *log odds,* in the expression is the linear sum of predictor variables (either continuous or discrete) and the value of $1/1 + e^{-x}$ is the probability of outcome between 0 (e.g., survival) and 1 (e.g., death) for any value of predictor variables. With more extensive modeling and with sufficiently large databases, computer iteration techniques produce a model consisting of a set of independent variables that best predicts the occurrence of a dichotomous outcome variable. The significant independent variables identified by the logistic regression model are risk factors that allow risk stratification of patients according to their risk of experiencing the dichotomous outcome (e.g., survival versus death).

The performance of logistic regression models can be assessed in several ways. However, there is less agreement about how best to measure performance for models that predict binary outcomes than there is about the use of R^2 to evaluate linear regression models. One commonly used parameter to evaluate the performance of logistic regression models is the *c*-statistic.[50] The *c*-statistic is equal to the area

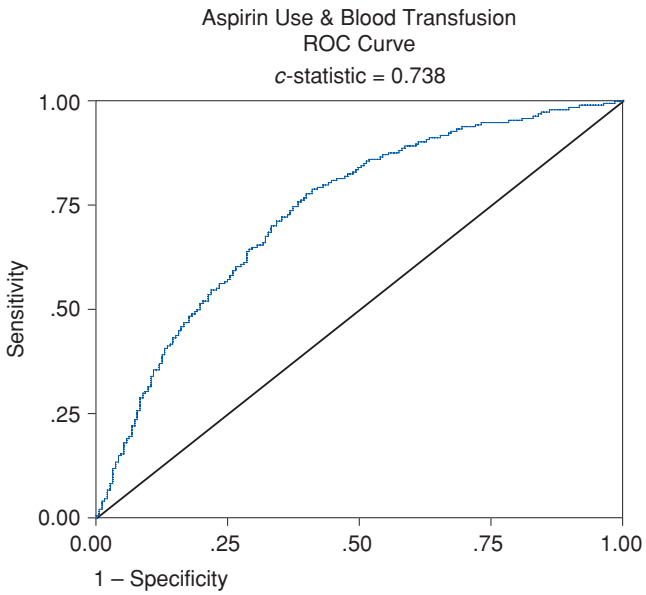


Figure 7-2. Receiver operating characteristics (ROC) curve demonstrating association of preoperative aspirin use in 2606 patients before CABG with postoperative blood transfusion. For this analysis, postoperative transfusion was considered a dichotomous variable (patients either received a transfusion or they did not). The area between the diagonal line and the upper curve represents the *c*-statistic.[51]

under the receiver operator characteristic (ROC) curve (e.g., Fig. 7-2) and can be generated from the sensitivity and specificity of measurements of any dichotomous outcomes. Table 7-4 shows a 2 × 2 table generated from a hypothetical logistic regression model used to predict dichotomous outcomes, and Table 7-5 describes the statistical terms of interest that can be derived from the predicted and observed outcomes.

Figure 7-2 depicts the ability of a logistic regression model to predict patients who will receive a blood transfusion after CABG based on preoperative variables including preoperative aspirin use.[51] This figure is an ROC curve derived from a plot of the sensitivity versus 1 minus the specificity (same as a plot of the correct positive prediction rate on the *y* axis versus the false-positive rate on the *x* axis). The ROC curve in Fig. 7-2 is produced by assuming a particular cutpoint for a predicted probability of one outcome (e.g., patients with a predicted probability of greater than 0.5 of receiving any transfusion after CABG are considered to be positive for receiving a blood transfusion). The *c*-statistic for the prediction model is 0.738, suggesting only a fair ability of the model to predict postoperative blood transfusion. To put this in perspective, a *c*-statistic of 1.0 indicates perfect discrimination of the model, and a *c*-statistic of 0.5 indicates no discrimination. Thus a *c*-statistic of 0.738 is about halfway between perfect and worthless. An excellent critique of the various methods used to assess the performance of regression models of dichotomous outcomes is given by Ash and Shwartz in the book by Iezzoni.[52]

Logistic regression models are used to develop risk profiles for providers (both hospitals and individual surgeons)—so-called report cards.[53–60] This has caused anguish on the part of providers[61] and concern on the part of statisticians and epidemiologists.[53,54] The typical form that report cards take is to grade surgeons by their operative mortality for CABG. In order to grade a provider, the expected number of deaths (*E*, or expected rate), calculated from deaths observed in the entire provider group, is compared with the observed number of risk-adjusted deaths for the provider (*O*, or observed rate). This gives an *O:E* ratio, or a ratio of the risk-adjusted observed mortality rate to the expected mortality rate, based on the group logistic model. In order to make comparisons between providers, a confidence interval (usually the 95% confidence interval) is assigned to the observed mortality rates, and the between-provider mortality rates are presented as a range of values for each provider (Fig. 7-3*A*). The expected mortality rates are assumed to be independent of the observed mortality rates—an incorrect assumption. Furthermore, no sampling error is attached to the expected values—another incorrect assumption. The effect of making these two assumptions is to identify too many outliers (in either direction). Statistical methodology is available and has been available for many years to account for these incorrect assumptions. The methodology involves construction of hierarchical regression models.

Table 7–4.

Two-by-Two Table Comparing Predicted Versus Observed Dichotomous Outcomes

	Observed outcome		
Predicted outcome	**Dead**	**Alive**	**Totals**
Dead	*A*	*B*	*A* + *B*
Alive	*C*	*D*	*C* + *D*
Totals	*A* + *C*	*B* + *D*	*A* + *B* + *C* + *D*

Table 7–5.

Definitions of Important Quantities for Analysis of Risk-Adjusted Dichotomous Outcomes*

Statistical term	Definition from values in Table 7-4
True-positive cases	A
False-positive cases	B
True-negative cases	D
False-negative cases	C
Prevalence	$(A + C)/(A + B + C + D)$
Positive predictive value (PPV)	$A/(A + B)$
Negative predictive value (NPV)	$D/(C + D)$
Sensitivity (rate of correct positive predictions)	$A/(A + C)$
Specificity (rate of correct negative predictions)	$D/(B + D)$

**Capital letters in the table are from Table 7-4.*

Hierarchical Models versus Logistic Regression

One of the most controversial applications of logistic regression models is *provider profiling,* the determination and comparison of risk-adjusted outcomes for hospitals and physicians.[53,62] Such outcome reports may be mandated by states,[64,65] in which case the results usually are published as report cards. The statistical methodology used previously to develop most such report cards is both simple and straightforward. The probability of mortality for each of a provider's patients during a given time period is estimated using logistic regression, and then these probabilities are aggregated to determine that provider's expected mortality *E.* The observed mortality *O* is simply the counted number of deaths. A ratio of observed to expected mortality (*O:E*) then is calculated, and it has a value close to 1 if the performance is what would be predicted from the model. Ratios greater than 1 imply worse-than-expected performance, and ratios less than 1 suggest better-than-expected performance. Often the *O:E* ratios are multiplied by the state-unadjusted mortality rate to obtain the *risk-adjusted mortality.*

It has long been recognized by statisticians that this intuitively appealing approach, aggregating patient-level data to make inferences about providers, is not appropriate.[65–68] This type of study is inherently multilevel, and in such situations, simply aggregating or disaggregating between levels may lead to erroneous conclusions.[69,70] This was recognized long ago in education, where the analogous situation would be the inappropriate aggregation of pupil test scores to evaluate teacher performance. Multilevel or hierarchical models have been developed for such situations, and these models also found application in longitudinal studies, meta-analyses, and small-area variation studies. These models address most of the major concerns regarding the use of standard models for multilevel scenarios. For example, the sample sizes from various providers often differ substantially and for low-volume providers may be rather small. In the latter situation, the observed point estimates of observed mortality are a much less accurate reflection of their true but unobserved mortality. Hierarchical models "shrink" the observed mortality rates of lower-volume providers toward the mean of the overall population of providers, a way of borrowing strength or pooling the data. The resulting estimates are more accurate and stable. Another concern with the use of nonhierarchical models for profiling is clustering of observations. Standard methods assume independent observations, but patients within a given hospital (and students within a given school) are likely to be more similar to each other than they would be if drawn randomly from the larger population. This "clustering" of patients, referred to mathematically as *intraclass correlation,* reduces the effective sample size, increases standard errors, and makes false outlier identification more likely. Finally, standard logistic models do not partition the various levels of variability (between and within providers) accurately, which is one of the central questions to be answered by profiling. Hierarchical models partition this variability correctly, they account for sample size and clustering, and through their shrinkage effect, they also compensate for multiple comparisons.

Numerous studies have investigated the difference in the results of provider profiling obtained from traditional logistic regression versus hierarchical modeling using data

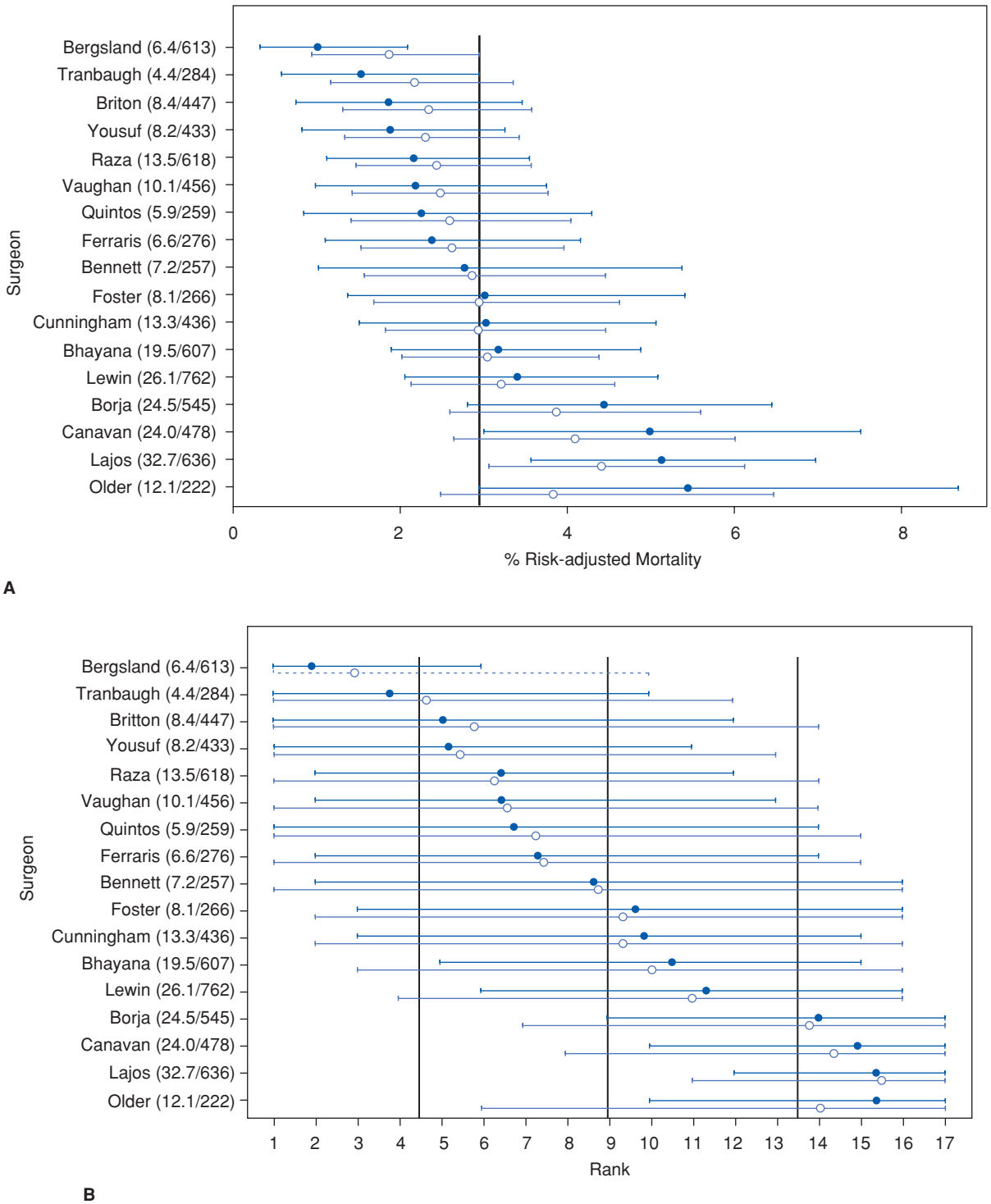


Figure 7-3. Comparison of classic statistical point and interval estimates (*A*) to estimates from hierarchical models (*B*) for a sample of New York surgeons performing coronary artery bypass grafting.[67] (*Used with permission from* Journal of the Royal Statistical Society.)

from New York,[67,71,72] Pennsylvania,[73] Oregon,[54] and Massachusetts.[65] In all but one of these, profiling based on hierarchical models yielded appropriately more conservative results. For example, in the classic work of Goldstein and Spiegelhalter, use of a hierarchical model reduced the number of New York outliers from three to one[67] (see Fig. 7-3*A*, *B*). Hannan's own New York analysis[72] found no significant difference between the results obtained using the two methodologies, but the number of cases per hospital sample was large enough that this is not surprising. The absence of a significant difference in results in this study does not negate the value of hierarchical modeling in other settings, and at

the very least it is comforting to know that the most appropriate model (i.e., a hierarchical model) is being employed. A more significant objection to the use of hierarchical models is that by reducing the chance of false outlier identification, they also may reduce the sensitivity to detect true outliers. Ultimately, this tradeoff is a health policy and regulatory decision.

Two impediments to widespread use of hierarchical models are the absence of the necessary large data sets and the lack of readily available easy-to-use software packages. There are statistical work-arounds that adjust data sets to obtain similar results to those obtained from hierarchical models, but it is unclear if such adjustment produces a qualitatively different result from standard hierarchical analysis. At present, hierarchical regression is the "gold standard" for risk adjustment of dichotomous outcomes and producing provider report cards. Unfortunately, this gold standard is used rarely. Hierarchical models are complex and require not only extensive computer resources but also close planning and oversight by a statistician experienced in these methods. However, most investigators regard them as the best model for profiling providers, and hierarchical modeling has been adopted for use recently both by the state of Massachusetts and by the Society of Thoracic Surgeons.

Statistics of Survival

When the outcome of interest is a time-dependent variable (e.g., hospital length of stay or survival after valve implantation), then regression modeling may be a more complex but still manageable process. Regression models for time-dependent outcome variables can be developed using computer iteration methods. Several excellent texts are available that cover the gamut of technical information from the relatively simple[74,75] to the complex.[76–78] One model that is used extensively in the biomedical sciences is the Cox proportional hazards regression model.[76] In some regression models, such as logistic regression, the dependent or outcome variable is known with precision. With time-dependent outcome variables, the possibility exists that only a portion of the survival time is observed for some patients. Thus the data available for analysis will consist of some outcomes that are incomplete or "censored." Some regression models, such as logistic regression, do not adapt easily to censored data. Cox's model overcomes these technical problems by assuming that the independent (predictor) variables are related to survival time by a multiplicative effect on the hazard function—thus a *proportional hazards* model. The hazard function is defined as the slope of the survival curve (or the time-decay curve) for a series of time-dependent observations. In the Cox model, one assumes that the hazard functions are proportional, a reasonable assumption when comparing survival in two or more similar groups. Hence it is not necessary to know the underlying survival function in order to determine the relative importance of independent variables that contribute to the overall survival curve. Table 7-6 shows an example of the use of Cox regression to evaluate the independent variables that are predictive of hospital length of stay (a time-dependent outcome variable) for patients undergoing CABG.[11] For the purposes of this analysis, hospital deaths were considered censored observations. The independent variables shown in Table 7-6 are considered risk factors for increased length of stay and can be used to stratify patients into groups with varying risk of prolonged hospitalization.

Measures of the performance of Cox regression models are less well developed than those for logistic regression or for multivariate linear regression. Simple methods of checking the predictive value of Cox models usually are reported in the medical literature. One of the most commonly used methods is called *cross-validation,* or *jackknife analysis.* This consists of using Cox regression to determine significant independent variables predictive of outcome in a "training set" of data. The significant variables and their coefficients from the Cox model are then used to compute values of the outcome variables in a different data set (called the *validation set,* or the *jackknife set*). The agreement between the predicted values and the observed values in the validation set is used as an index of the performance of the Cox model. Figure 7-4 shows a cross-validation set of data used to check the results of the Cox regression described in Table 7-6. This figure shows fair "validation" of the Cox model using a relatively small data set (1200 patients operated on during 1994 at a single institution). Performance of Cox models also can be expressed in terms of ROC curves and the *c*-statistic as for logistic regression models.

Bayesian Analysis: Models Based on Experience

Thomas Bayes was a nonconformist minister and mathematician who is given credit for describing the probability of an event based on knowledge of prior probabilities that the same event has already occurred.[79] Using the Bayesian approach, three sets of probabilities are defined: (1) the probability of an event before the presence of a new finding is revealed (*prior probability*), (2) the probability that an event is observed given that an independent variable is positive (*conditional probability*), and (3) the probability of an event occurring after the presence of a new finding is revealed (*posterior probability*). The mathematical relationship between the three probabilities is Bayes' theorem. The prior and posterior probabilities are defined with respect to a given set of independent variables. In the sequential process common to all Bayesian analyses, the posterior probabilities for one finding become the prior probabilities for the next, and a mathematical combination of prior and conditional probabilities produces posterior probabilities. Bayes' theorem can be expressed in terms of the nomenclature of Table 7-5 as

$$P_{\text{Bayes}} = (\text{sensitivity} \times \text{prior probability})/(\text{sensitivity} \times \text{prior probability}) + [\text{false-positive rate} \times (1 - \text{prior probability})]$$

Table 7–6.

Cox Proportional Hazards Regression Model for Significant Predictor Variables Associated with Increased Hospital Length of Stay in 938 Patients Undergoing CABG during 1993[11]

Risk factor (patients with risk factor)	Observed LOS	95% CI	Odds ratio	Chi^2 improvement
None (40 patients)*	5.9 days	0.7 days	1.00	
Age/RBCVOL (385 patients with ≥ mean value of 0.0390)	10.0 days	0.98 days	1.83 per 0.01 unit of age/RBCVOL	72.907
CHF (91 patients)	11.6 days	2.3 days	4.34	17.729
Hypertension (646 patients)	9.0 days	0.6 days	2.31	12.296
Peripheral vascular disease (74 patients)	10.1 days	1.4 days	3.01	8.053
Renal dysfunction (17 patients)†	12.8 days	3.8 days	5.64	6.904
COPD (213 patients)	9.4 days	0.9 days	2.23	7.259
Previous stroke (51 patients)	11.1 days	2.2 days	3.20	5.017

**For purposes of calculating zero risk factor scores, age/RBCVOL was assumed to be less than 0.0250 (one standard deviation below the mean).*
†Serum creatinine ≥ 2.5 mg/% but not dialysis-dependent.
Age/RBCVOL = age in years divided by red blood cell volume obtained from nomogram of patient height, weight, gender, and preoperative hematocrit; CHF = congestive heart failure immediately preceding CABG; COPD = chronic obstructive pulmonary disease; LOS = length of stay.

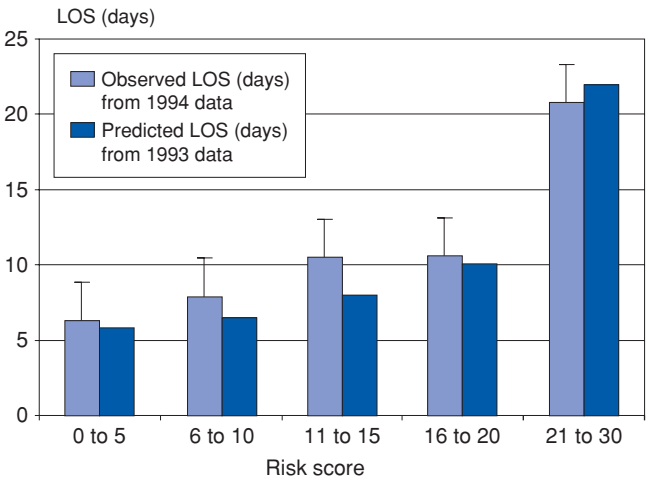


Figure 7-4. Cross-validation of Cox regression model used to predict hospital length of stay (LOS) after CABG. Data from patients operated on in 1993 were used as the "training" data set to predict values for LOS in patients undergoing operation in 1994 ("validation set"). Risk scores were generated by assigning numerical weights to significant variables in the Cox model based on regression coefficients shown in Table 7-8. The methods used to derive the patient risk scores are described in refs. 11 and 278. (*Used with permission from the* Journal of Thoracic and Cardiovascular Surgery.)

where P_{Bayes} is defined as the probability of a given outcome if prior probabilities are known. The principles of Bayesian statistics have been used widely in decision analysis[80] and are also used to generate multivariate regression models based on historical data about independent variables.[81–84] Bayesian multivariate regression models are generated using computer-based iterative techniques[81,84–86] and have been used, in the past but not at present, to develop the risk-stratification analysis for the Society of Thoracic Surgeons National Cardiac Database.[85,87] Evaluation of the performance of the Bayesian statistical regression models usually is done by cross-validation studies similar to those used to validate the Cox survival regression model in Fig. 7-4. Performance of Bayesian models also can be expressed in terms of ROC curves and the *c*-statistic as for logistic regression models. Marshall and colleagues showed that Bayesian models of risk adjustment give comparable results and similar ROC curves to conventional models generated from logistic regression analysis.[88]

Meta-Analysis

An implicit part of assessing outcome is the development of a best standard of care for a given illness or disease process. Once the most efficacious treatment is known, then comparisons with or deviations from the standard can be assessed—a process called *benchmarking* and an important component

in the generation of treatment guidelines. As mentioned earlier, the "best standard" is not always known. Meta-analysis is a quantitative approach for systematically assessing the results of multiple previous studies to determine the best or preferred outcome. The overall goal of meta-analysis is to combine the results of previous studies to arrive at a consensus conclusion about the best outcome. Stated in a different way, meta-analysis is a tool used to summarize efficacy studies (preferably RCTs) of an intervention in a defined population with disease in order to determine which intervention is likely to be effective in a large population with a similar disorder. Meta-analysis is a tool that can relate efficacy studies to effectiveness of an intervention by summarizing available medical evidence.

In summarizing available medical evidence on a given subject, information retrieval is king. Nowhere is this more evident than in the Cochrane Collection of available randomized trials on various medical subjects. For example, a recent Cochrane review (www.update-software.com/abstracts/ab002138.htm) found 17 trials that evaluated postoperative neurologic deficit in patients having hypothermic cardiopulmonary bypass (CPB) compared with normothermic CPB.[89] This compares with a recently published meta-analysis on a similar topic that found only 11 trials on which to perform a similar analysis.[90] It is important to understand how the Cochrane reviewers found these 17 observational studies and RCTs. One has to realize that only about a third of the world's medical literature appears on large computer databases such as MEDLINE, so it is not good enough simply to search MEDLINE for the RCTs of interest. Computerized databases such as MEDLINE are incomplete, especially in areas of subspecialization such as cardiothoracic surgery. The Cochrane reviewers perform an exhaustive search of all available literature, not only MEDLINE but also unpublished trials and so-called fugitive literature (e.g., government reports, proceedings of conferences, published Ph.D. theses). The average thoracic surgeon has not heard of "publication bias," but the Cochrane reviewers are acutely aware of it. They realize that RCTs that have a negative result are less likely to pass the peer-review editorial process into publication than RCTs with a significant treatment effect—so-called publication bias in favor of positive clinical trials.[91] Thus, for each of the Cochrane reviews, attempts are made to find unpublished and/or negative trials to add to the body of evidence about a given subject.

If information retrieval is king in summarizing available medical evidence on a given subject, then statistical analysis of the retrieved studies (including RCTs) shares the throne. It must be obvious that all trials or observational studies that address the same outcomes of a given intervention are not the same. There are almost always subtle differences in study design, sample size, analysis of results, and inclusion/exclusion criteria. The object of comparing multiple observational studies and RCTs on the same treatment outcome is to come up with a single summary estimate of the effect of the intervention. Calculating a single estimate in the face of such diversity may give a misleading picture of the truth. There are no statistical tricks that account for bias and confounding in the original studies. Heterogeneity of the various RCTs and observational studies on the same or similar treatment outcome is the issue. This heterogeneity makes comparison of RCTs a daunting task, about which volumes have been written.[17] There are at least two types of heterogeneity that confound summary estimates of multiple RCTs—clinical heterogeneity and statistical heterogeneity. *Statistical heterogeneity* is present when the between-study variance is large; i.e., similar treatments result in widely varying outcomes in different trials. This form of heterogeneity is easiest to measure. For example, Berlin and colleagues evaluated 22 separate meta-analyses and found that only 14 of 22 had no evidence of statistical heterogeneity.[92] Three of the remaining 8 comparative studies gave different results depending on the type of statistical methods used for the analysis—the more statistical heterogeneity, the less certain are the statistical inferences from the analysis.

Clinical heterogeneity of groups of RCTs that assess similar outcomes is much more difficult to assess. Measurement of treatment outcomes has plagued reviewers who try to summarize RCTs. Many RCTs address similar treatment options (e.g., hypothermic CPB versus normothermic CPB) but measure slightly different outcomes (e.g., stroke or neuropsychological dysfunction). For example, the Cochrane Heart Group found 17 RCTs that addressed the effect of CPB temperature on postoperative stroke.[89] Only 4 of these 17 RCTs measured neuropsychological function, whereas all 17 measured neurologic deficit associated with CPB. In summarizing the results of multiple RCTs comparing a given treatment, it is necessary to match "apples with apples" when looking at outcomes. In this analysis by the Cochrane Heart Group, there was a trend toward a reduction in the incidence of nonfatal strokes in the hypothermic group [odds ratio (OR) 0.68 (0.43, 1.05)]. Conversely, there was a trend for the number of non–stroke-related perioperative deaths to be higher in the hypothermic group [OR 1.46 (0.9, 2.37)]. When pooling all "bad" outcomes (i.e., stroke, perioperative death, myocardial infarction, low output syndrome, and intra-aortic balloon pump use), there was no significant advantage of either hypothermia or normothermia [OR 1.07 (0.92, 1.24)]. This suggests that there is clinical heterogeneity among the various RCTs evaluated. There are statistical "tricks" that can investigate and explore the differences among studies, such things as stratification or regression, but it is unlikely that clinical heterogeneity can be removed completely from the meta-analysis. Importantly, the Cochrane Group concludes from this work that there is no definite advantage of hypothermia over normothermia in the incidence of clinical events following CPB. This constitutes good evidence (i.e., multiple well-done RCTs) to support the notion that normothermic and hypothermic CPB have equal efficacy for most outcomes. An expert panel reviewing the Cochrane evidence might suggest that there is class I evidence [according to the American College of Cardiology/American Heart Association (ACC/AHA) guideline nomenclature shown in Table 7-7] that both normothermic and

Table 7–7.

1999 AHA/ACC Guidelines for CABG in ST-segment elevation (Q-wave) MI

Indication and clinical condition	Definition of level of evidence
Class I None	Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class IIa 1. Ongoing ischemia/infarction not responsive to maximal nonsurgical therapy	Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or efficacy of a procedure
Class IIb 1. Progressive LV pump failure with coronary stenosis compromising viable myocardium outside the initial infarct area	Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy
2. Primary reperfusion in the early hours (⩽6 to 12 hours) of an evolving ST-segment elevation MI	Class IIb: Usefulness/efficacy is less well established by evidence/opinion
Class III 1. Primary reperfusion late (>12 hours) in evolving ST-segment elevation MI without ongoing ischemia	Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

AHA = American Heart Association; ACC = American College of Cardiology; MI = myocardial infarction; LV = left ventricle.

hypothermic CPB are equally safe and result in a similar incidence of perioperative complications. This is an entirely different conclusion from that made by Bartels and colleagues in their meta-analysis about the same interventions. These authors suggest that there is little evidence to support the usefulness/efficacy of hypothermia in CPB.[90] Which meta-analysis is closer to the truth is hard to say. Much depends on the details of the meta-analyses, but logic suggests that the higher-quality study including more available RCTs and statistically rigorous analysis such as used by the Cochrane group comes closer to the scientific truth.

There is some concern about the findings of meta-analyses.[93–95] LeLorier and colleagues found significant discrepancies between the conclusions of meta-analyses and subsequent large RCTs.[94,95] On review of selected meta-analyses, Bailar found that "problems were so frequent and so serious, including bias on the part of the meta-analyst, that it was difficult to trust the overall 'best estimates' that the method often produces."[96,97] Great caution must be used in the interpretation of meta-analyses, but the technique has gained a strong following among clinicians because it may be applied even when the summarized studies are small and there is substantial variation in many of the factors that may have an important bearing on the findings.

Breakthrough Statistics[98]

The use of complex statistics is becoming more common in assessing medical data. Arguably, the understanding of this complex material on the part of clinicians has not advanced at a similar rate. In an attempt to address this knowledge gap, Blackstone coined the term *breakthrough statistics* to denote newer methods that are available to handle complex but clinically important research questions.[98] His goal was to acquaint clinicians with the methods in a nontechnical fashion "so that [they] . . . may read reports more knowledgeably, interact with [their] . . . statistical collaborators more closely, or encourage [their] . . . statistician to consider these methods if they are applicable to [their] . . . clinical research."[98] These worthy goals have direct relevance to outcomes assessment and risk stratification.

Balancing scores

One of Blackstone's breakthrough statistical methods deals with a very common problem—the assessment of nonrandomized comparisons. Observational studies, or nonrandomized comparisons, can detect associations between risk and outcome but cannot, strictly speaking, determine which risks *cause* the particular outcome. Traditionally, only RCTs have been able to determine cause and effect. A so-called breakthrough technique to allow nonrandomized comparisons to come closer to inferring cause and effect is the use of *balancing scores.*

Simple comparison of two nonrandomized treatments is confounded by selection factors. This means that a clinician decided to treat a particular patient with a given treatment for some reason (not always obvious and not always

evidence-based). The selection factors used in this nonrandomized situation are difficult to control, and RCTs eliminate this type of bias. However, RCTs often are not applicable to the general population of interest because they are very narrowly defined.[99] Use of nonrandomized comparisons is more versatile and less costly. One of the earliest methods used to account for selection bias was patient matching. Two groups who received different treatments were matched as closely as possible for all factors except the variable of interest. Balancing scores were developed as an extension of patient matching. In the early 1980s, Rosenbaum and Rubin introduced the idea of balancing scores to analyze observational studies.[100] They called the simplest form of a balancing score a *propensity score*. Their techniques were aimed at drawing causal inference from nonrandomized comparisons. The propensity score is a probability of group membership. For example, in a large group of patients having CABG, some receive aspirin before operation and others do not. One might ask whether preoperative aspirin causes increased postoperative blood transfusion. The propensity score is a probability between 0 and 1 that can be calculated for each patient, and this score represents their probability of getting aspirin before operation. If one matches the aspirin and nonaspirin patients by their propensity scores, the patients will be as nearly matched as possible for every preoperative characteristic excluding the outcome of interest. Not all the patients may be included in the analysis because some aspirin users may have a propensity score that is not closely matched with that of a nonaspirin user. But those aspirin users who have a matching propensity score with a nonaspirin user will be very closely matched for every variable except for the outcome variable of interest. This is as close to a randomized trial comparison as you can get without actually doing the randomized trial.

How is the propensity score calculated? The relevant question asked to construct the propensity score is which factors predict group membership (e.g., who will receive aspirin and who will not). The probability of receiving aspirin is a dichotomous variable that can be modeled like any other binary variable. For example, logistic regression can be used to identify factors associated with aspirin use. In the logistic regression analysis to develop the propensity score, as many risk factors as possible are included in the model, and the logistic equation is solved (or modeled) for the probability of being in the aspirin group. This probability is the propensity score. An example of the results obtained from this type of analysis is shown in Table 7-8.[51] In this analysis, 2606 patients (1900 preoperative aspirin users and 606 nonusers) were "balanced" according to their propensity scores. The group was divided into five equal quintiles according to their propensity scores (i.e., their tendency to receive aspirin before operation). Quintile 1 had the least chance of receiving aspirin, whereas quintile 5 had the greatest chance of receiving aspirin before operation. Within each quintile, the patients are matched as closely as possible for all variables except for the outcome variable of interest,

Table 7–8.

Effect of Aspirin (ASA) on Postoperative Blood Transfusion Using Propensity Score–Matched Quintiles.

	Quintile									
	1 (n = 521)		2 (n = 521)		3 (n = 521)		4 (n = 521)		5 (n = 521)	
	ASA	No ASA	ASA	No ASA	ASA	No ASA	ASA	No ASA	ASA	No ASA
Total Patients	267	254	335	166	381	141	423	98	444	77
% receiving blood transfusion	31*	14	27	25	18	22	21	16	21	19
% women	43	43	34	34	25	23	23	25	19	16
% with renal insufficiency	5.2	5.1	3.6	3.1	1.9	2.5	2.5	2.6	1.7	0
Age (s.d.)	64 (11)	65 (10)	63 (11)	62 (11)	63 (10)	62 (10)	62 (10)	63 (11)	63 (10)	64 (10)
Weight in kg (s.d.)	79 (15)	78 (16)	84 (19)	84 (17)	84 (17)	86 (17)	86 (18)	85 (17)	88 (21)	90 (21)
CPB time, min (s.d.)	162 (81)	162 (63)	144 (51)	148 (51)	144 (62)	141 (51)	135 (52)	143 (43)	137 (47)	136 (41)

*$p < .001$, chi-square, compared to no ASA in quintile 1.
s.d. = standard deviation.

Table 7–9.

Recently Published Risk Models for Coronary Bypass Surgical Mortality

Risk model	NYS	Canada	USA	Emory	VA	Australia	Canada2	Cleveland	Israel	Duke	NNE	Stroke	Parsonnet	
Number of patients	174,210	57,187	50,357	17,128	13,368	12,712	12,003	7,491	4,918	4,835	3,654	3,055	2,152	
Number of risk factors	29	16	13	7	6	9	5	9	7	9	9	10	8	Sum
Age	X	X		X	X	X	X	X	X	X	X	X	X	12
Gender	X	X	X	X	X		X	X		X		X		9
Surgical urgency	X		X		X	X		X		X	X	X		8
Ejection fraction	X	X			X		X	X		X	X	X		8
Renal dysfunction/ creatinine	X	X	X	X						X	X		X	7
Previous CABG	X		X	X				X			X	X		6
NYHA class	X	X	X	X		X				X				6
Left main disease	X	X						X		X	X	X		6
Diseased coronary vessels	X	X			X			X		X		X		6
Peripheral vascular disease	X		X			X		X	X					5
Diabetes mellitus	X	X			X					X			X	5
Cerebrovascular disease	X		X	X		X								4
Intraop/postop variables			X				X		X				X	4
Myocardial infarction	X	X	X	X										4
Body size	X	X										X		3
Preoperative IABP	X	X				X								3
Cardiogenic shock/unstable	X	X									X			3
COPD	X	X												2
PTCA	X		X											2
Angina		X					X							2

Intravenous nitrates	X				X							2
Arrhythmias	X						X					2
History of heart operation		X			X							2
Hemodynamic instability	X										X	2
Charison comorbidity score								X	X			2
Dialysis dependence	X	X										2
Pulmonary hypertension	X										X	2
Diuretics	X				X							2
Systemic hypertension						X						1
Serum albumin							X					1
Race	X											1
Previous CHF								X				1
Myocardial infarction timing	X											1
Cardiac index							X					1
LV end-diastolic pressure									X			1
CVA timing	X											1
Liver disease			X									1
Neoplasia/metastatic disease			X									1
Ventricular aneurysm			X									1
Steroids	X											1
Digitalis	X											1
Thrombolytic therapy											X	1
Arterial bicarbonate							X					1
Calcified ascending aorta											X	1

Note: Mortality risk models are sorted horizontally by the number of patients. The risk factors are sorted vertically by the sum of their appearances in these models.
CABG = coronary artery bypass grafting; CHF = congestive hearrt failure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; IABP = intra-aortic balloon pump; LV = left ventricular; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.
Source: Reprinted by permission from ref. 54.

i.e., receiving any blood transfusion after CABG, almost like a randomized trial. Notice that within each quintile, aspirin users and nonusers are closely matched for other variables such as preoperative renal function, gender, and CPB time. This indicates that the propensity score matching did what it was supposed to—i.e., matched the patients for all variables except for the outcome variable of interest (i.e., postoperative transfusion). The results show that the propensity-scored quintiles are asymmetric—i.e., there is not a consistent association between aspirin and blood transfusion across all quintiles. In the strata that are least likely to receive preoperative aspirin, there are patients who are more likely to receive postoperative transfusion (i.e., patients in quintile 1 have the longest CPB time, the greatest number of women, and the largest number of patients with preoperative renal dysfunction). This implies that some patients may have been recognized as high risk preoperatively and were not given aspirin—i.e., selection bias exists in the data set. The corollary is that if this high-risk cohort received aspirin, there was an increased likelihood of receiving postoperative blood transfusion. These results suggest that certain high-risk aspirin users are at increased risk for receiving a postoperative blood transfusion. These results do not replace RCTs for determining cause and effect, but they do represent an economical and versatile way to address the problem with results comparable with those of RCTs. There is some evidence that well-done observational studies give comparable results to RCTs dealing with similar outcomes,[101,102] and balancing scores provide optimal means of analyzing nonrandomized studies.

Bootstrapping

The importance of risk factor identification for comparing outcomes already has been stressed. Risk factor identification for a given outcome has become commonplace in medicine. A problem arises from this dependence on risk factor analysis, especially logistic regression. Different observers analyzing the same risk factors to predict outcome get different results. Table 7-9 is an example of the variability in risk factor identification that can result. In this table, Grunkemeier and colleagues compared 13 published multivariate risk models for mortality following CABG.[54] The number of independent risk factors cited by any one model varied from 5 to 29! Naftel described 9 factors that contribute to different investigators obtaining different models to predict outcome (i.e., different sets of risk factors associated with the same outcome).[103] Some or all of these factors may affect the risk models listed in Table 7-9. One of Naftel's factors that is important in differentiating various models of CABG mortality is variable selection. In Table 7-9, 13 different groups found 13 different variable patterns that apparently adequately predicted operative mortality. How can this be? Recent breakthrough statistical methods address variable selection in statistical modeling.

In the early 1980s, the ready availability of computers began to surface to the consciousness of investigators. Efron and colleagues popularized computer-intensive computational techniques that were not readily available until computers were on every investigator's desk.[104–107] They coined the term *bootstrap* to describe these computer-intensive methods. *Bootstrap analysis* is a data-based simulation method for statistical inference. Efron's group and others found that by taking repeated random samples from a data set (1000 random samples is typical) and determining risk factors for an outcome from each random new data set using statistical modeling, the predictor variables obtained from all the 1000 random samples usually were different but that some variables were never selected in the model and others were selected consistently. The frequency of occurrence of risk factors among the 1000 or more models provides variables that have a high degree of reproducibility and reliability as independent risk factors of the given outcome. This process is called *bootstrap bagging*[108] and has formalized the development of model building that previously was more of an art than a science. As a result of this work with bootstrap analysis, model building and risk adjustment will be held to a more rigorous scientific standard.

USES OF OUTCOMES ASSESSMENT AND RISK STRATIFICATION

There are multiple areas where the tools of risk stratification and outcome analysis can be used to judge effectiveness of care and to aid providers in quality improvement, including the following: (1) cost containment, (2) patient education, (3) effectiveness-of-care studies, and (4) improving provider practices. Table 7-10 provides an idealized list of some of the potentially beneficial uses and goals of risk stratification.

Improving the Quality of Care

The ultimate goal of risk stratification and outcomes assessment is to account for differences in patient risk factors so that patient outcomes can be used as an indicator of quality of care. A major problem arises in attaining this goal because uniform definitions of quality of care are not available. This is particularly true of cardiovascular disease. For example, there are substantial geographic differences in the rates at which patients with cardiovascular diseases undergo diagnostic procedures, and incidentally, there is little, if any, evidence that these variations are related to survival or improved outcome. In one study, coronary angiography was performed in 45% of patients after acute myocardial infarction in Texas compared with 30% of patients in New York State ($p < .001$ for comparison between states).[109] In these patient populations, the differences in the rate of coronary revascularization were not as dramatic, but the survival in these patients was not related to the type of treatment or diagnostic procedures. Regional variations of this sort suggest that a rigorous definition of the "correct" treatment of acute myocardial infarction, as in other cardiovascular disease states, is elusive and that the definition of quality of care for such patients is imperfect. Similar imperfections exist for

Table 7–10.

Uses of Risk Stratification and Outcome Assessment

Risk-stratification goal	Example of methodology	Potential benefit
Cost containment	Risk-adjusted patient care costs determined and tracked over time	Cost-efficient institution's or physician's benefit from savings and patients benefit from decreased cost
Improve physician practices	Physician-specific risk-adjusted outcomes determined and made available to practitioners in a nonpunitive way	Physicians improve practice patterns by careful analysis of risk-adjusted data
Improve patient education	Risk-adjusted provider profiles (both hospital- and physician-specific) made available to the public in a nonthreatening, nonpunitive manner	Patients understand the risks of a given procedure and have more accurate expectations about given intervention; patients have better understanding of "high risk"
Evaluate effectiveness of care	Risk stratification of population-based retrospective studies used to identify high-risk subsets	Efficacy trials devised and implemented to test benefit in high-risk subsets; with refinements, may allow comparison among providers with goal of improving outliers

nearly all outcomes in patients with cardiothoracic disorders. Risk-adjustment methodologies can isolate patient risk factors that are associated with poor outcome, but what to do about these risk factors and how to improve outcomes based on risk stratification are uncertain. Much more work is required to define optimal outcomes and treatment standards based on risk profile.

Recognizing the difficulties in defining "best practices" for a given illness, professional organizations have opted to promote practice guidelines or "suggested therapy" for given diseases.[63,110,111] These guidelines represent a compilation of available published evidence, including RCTs and risk-adjusted observational studies, as well as consensus among panels of experts proficient at treating the given disease.[112] For example, the practice guideline for CABG is available for both practitioners and the lay public on the Internet (www.acc.org/clinical/guidelines/bypass/execIndex.htm). Table 7-7 summarizes the 1999 AHA/ACC guidelines for CABG in patients with acute (Q-wave) myocardial infarction. These guidelines were developed using a summation of available RCTs, risk-adjusted observational studies, and expert consensus. They are meant to provide clinicians with accepted standards of care that most would agree on, with an ultimate goal of limiting deviations from accepted standards.

Guideline development represents a work in progress. The methodology for developing guidelines for disease treatment is evolving. Many published guidelines do not adhere to accepted standards for developing guidelines.[113] The area where greatest improvement is needed is in the identification, evaluation, and synthesis of the scientific evidence. For example, guidelines for the management of bleeding during cardiac procedures are available but are relatively unsuccessful in limiting nonautologous blood transfusion.[114] There is still marked variability in transfusion practices and blood-conservation interventions.[115] There are at least two reasons for this failure of guidelines. First, accurate and timely information about the platelet and coagulation status of patients in the operating room or in the ICU is difficult to obtain. Second, and possibly most important, patient, physician, and institutional variability in decisions about transfusion (e.g., transfusion trigger) is difficult to control and manage. These limitations in the effectiveness of guidelines in altering physician practices are a drawback of guideline efforts. The most important aspect of practice guidelines is implementation of the guidelines themselves.

Efficacy Studies versus Effectiveness Studies

There are many efficacy studies relating to cardiothoracic surgery. These studies attempt to isolate one procedure or device as beneficial for patient outcome. The study population in efficacy studies is chosen specifically to contain as uniform a group as possible. Typical examples of efficacy studies include randomized, prospective, clinical trials comparing use of a procedure or device in a well-defined population with an equally well-defined control population.

Efficacy studies are different from effectiveness studies.[5] The latter deal with whole populations and attempt to

determine the best treatment option that provides optimal outcome in a population that typically would be treated by a practicing surgeon. An example of an effectiveness study is a retrospective study of outcome in a large population treated with a particular heart valve. Risk stratification is capable of isolating associations between outcome and risk factors. Methodologic enhancements in risk adjustment are capable of reducing biases inherent in population-based retrospective studies[98] but can never eliminate all confounding biases in observational studies.

One reasonable strategy for using risk stratification to improve patient care is to isolate high-risk subsets from population-based retrospective studies (i.e., effectiveness studies) and then to test interventions to improve outcome in high-risk subsets using RCTs. This is a strategy that ultimately should lead to the desired goal of improved patient care. For example, a population-based study on postoperative blood transfusion revealed that the following factors were significantly associated with excessive blood transfusion (defined as more than 4 units of blood products after CABG): (1) template bleeding time, (2) red blood cell volume, (3) CPB time, and (4) advanced age.[116] Cross-validation of these results was carried out on a similar population of patients undergoing CABG at another institution. Based on these retrospective studies, it was reasonable to hypothesize that interventions aimed at reducing blood transfusion after CABG were most likely to benefit patients with prolonged bleeding time and low red blood cell volume. A prospective clinical trial then was performed to test this hypothesis using two blood-conservation techniques, platelet-rich plasma saving and whole-blood sequestration, in patients undergoing CABG. The results of this stratified, prospective clinical trial showed that blood-conservation interventions were beneficial in the high-risk subset of patients.[117] The implications of these studies are that more costly interventions such as platelet-rich plasma saving are only justified in high-risk patients, with the high-risk subset being defined by risk-stratification methodologies. Other strategies have been developed that use risk-adjustment methods to improve quality of care, and these methods will be discussed below.

Other Goals of Outcome Analysis (Cost Containment and Altering Physician Practices)

Financial factors are a major force behind health care reform. America's health care costs amount to 15 to 20% of the gross national product, and this figure is rising at a rate of 6% annually. Institutions that pay for health care are demanding change, and these demands are fueled by studies that suggest that 20 to 30% of care is inappropriate.[118] Charges of inappropriate care stem largely from the observation that there are wide regional variations in the use of expensive procedures.[119,120] This resulted in a shift in emphasis, with health care costs being emphasized on equal footing with clinical outcomes of care. Relman suggested that concern about clinical outcomes will be used by patients, payors, and providers as a basis for distribution of future funding of health care.[121] While wide differences in use of cardiac interventions initially fueled charges of overuse in certain areas,[122] recent evaluations suggest that underuse of indicated cardiac interventions [either percutaneous transluminal coronary angioplasty (PTCA) or CABG] may be a cause of this variation.[122–127] Whether caused by underuse or overuse of cardiovascular services, regional variations in resource utilization make it difficult to use outcomes assessment as an indicator of quality of care.

If the causes of regional variations in the use of cardiac interventions seem puzzling, then physician practice behavior might seem bizarre. One study showed that there were unbelievably large variations in care delivered to patients having cardiac surgery.[128] Among six institutions that treated very similar patients (Veterans Administration medical centers), there were large differences in the percentage of elective, urgent, and emergent cases at each institution, ranging from 58 to 96% elective, 3 to 31% urgent, and 1 to 8% emergent.[128] There was also a 10-fold difference in the preoperative use of intra-aortic balloon counterpulsation for control of unstable angina, varying from 0.8 to 10.6%.[128] Similar variations in physician-specific transfusion practices,[129] ordering of blood chemistry tests,[130] anesthetic practices,[131] treatment of chronic renal failure,[132] and use of antibiotics[133] are observed. This variation in clinical practice may reflect uncertainty about the efficacy of available interventions or differences in practitioners' clinical judgment. Some therapies with proven benefit are underused.[131,132] Whatever the causes of variations in physician practice, they distort the allocation of health care funds in an inappropriate way. Solutions to this problem involve altering physician practice patterns, something that has been extremely difficult to do.[134] How can physician practice patterns be changed in order to improve outcome? Evidence suggests that the principal process of outcome assessment, the case-by-case review [traditionally done in the morbidity and mortality (M&M) conference format], may not be cost-effective and may not improve quality.[135] Health care experts suggest that the M&M conference should be replaced by profiles of practice patterns at institutional, regional, or national levels. One proposed model for quality improvement involves oversight that emphasizes the appropriate balance between internal mechanisms of quality improvement (i.e., risk-adjusted outcomes analysis) and external accountability.[135] Risk adjustment is an essential element of this type of outcomes management and assessment. Quality improvement projects (see below) that employ risk stratification to identify patients at high risk for adverse outcomes are essential components of internal review to improve physician-driven variations in resource utilization. Likewise, external accountability, as painful as it may be, relies on accurate risk assessment for fairness and for acceptance by the stakeholders in the process. It remains for the tools of risk stratification and outcomes assessment to be used accurately and effectively for the full potential of these methods to be recognized.

Rewarding High Performers ("Pay for Performance")

Performance measures are regarded as the cornerstone of a new paradigm in quality assessment. In this approach, a quality initiative takes this general form:

1. A patient population is specified.
2. Process measures are developed to serve as quality metrics for this population.
3. The process measures are collected.
4. Compliance with performance measures is tracked for participating centers.
5. Aggregate results are used to establish norms and benchmarks.
6. Participating centers receive data feedback compared with benchmarks.
7. Participating centers are evaluated through this monitoring process.

It becomes immediately apparent that the validity of this approach depends primarily on the validity of the performance measures. This recognition led to the emergence of several national organizations specifically devoted to the rigorous development of performance measures, most notably the National Quality Forum (NQF).

Using the NQF protocol, the Society of Thoracic Surgeons (STS) played a central role in developing national consensus standards for adult cardiac surgery. This process yielded 21 performance measures (Table 7-11). These measures constitute a unique set of nationally accepted tools that can be used to determine the quality of care in cardiac surgical programs. The significance of this set of measures should be emphasized. Prior to their development, there was no general agreement on the specific parameters that are linked to "quality" in cardiac surgery. With development of the NQF measures, these parameters can be identified using the most objective process currently available. NQF measures provide the "toolbox" for quality measurement in cardiac surgery. Any meaningful quality initiative in cardiac surgery should be based on these performance measures.

The STS Database provides benchmark values for all but three of these performance measures. In the most direct application of NQF measures, an institution simply compares its values against the benchmark values. This process allows providers to pinpoint opportunities for improvement so that resources can be directed specifically to areas of greatest need with the expectation that payors will provide increased resources to the institutions that meet the standards.

More sophisticated approaches involve the development of *quality models* that account for the net impact of some or all of the measures. These quality models can be used to develop rating systems or scorecards that allow relative quality comparisons between individual institutions or between an institution and a national benchmark. Models of this sort are in the early stages of development and, as discussed elsewhere, must be understood fully and applied carefully in this context.

Table 7–11.

National Standards for Cardiac Surgery Based on NQF Consensus

1.	Participation in a systematic database for cardiac surgery
2.	Surgical volume for CABG, valve surgery, and CABG + valve surgery
3.	Timing of prophylactic antibiotic administration
4.	Selection of prophylactic antibiotic
5.	Preoperative beta blockade
6.	Use of internal mammary artery
7.	Duration of prophylactic antibiotic
8.	Prolonged intubation (<24 hours postoperatively)
9.	Deep sternal wound infection rate
10.	Stroke/cerebrovascular accident
11.	Postoperative renal insufficiency
12.	Surgical reexploration
13.	Antiplatelet medications at discharge
14.	Beta blockade at discharge
15.	Antilipid treatment at discharge
16.	Risk-adjusted operative inpatient mortality for CABG
17.	Risk-adjusted operative mortality for CABG
18.	Risk-adjusted operative mortality for aortic valve replacement (AVR)
19.	Risk-adjusted operative mortality for mitral valve replacement (MVR)
20.	Risk-adjusted operative mortality for MVR + CABG
21.	Risk-adjusted operative mortality for AVR + CABG

Source: (www.qualityforum.org/docs/cardiac_care/webcardiacPUBLIC02-07-05.pdf.

Many people believe that additional incentives for quality improvement can be obtained by linking quality scores with reimbursement. This concept, commonly called *pay for performance* (P4P), or *value-based purchasing*, has gained a groundswell of support from a variety of organizations. Effective performance-based payments have shown positive results in the private sector, and despite the absence

of convincing evidence, there is widespread belief that similar results can be obtained in medicine.

P4P has become particularly popular among third-party payors. Historically, payment was based on the number and the complexity of services provided to patients, but with P4P, some portion of payment will be determined by the quality rather than the quantity of services. It remains to be seen whether reimbursement incentives will lead to meaningful improvements in quality of care.

There are several reimbursement models, the most common of which is the *tournament model.* In the tournament approach, there are unequivocal winners and losers: Top performers are provided bonuses, which come from reduced payments to the lower performers. Although popular because of its simplicity, this budget-neutral approach, in that one "robs Peter to pay Paul," is subject to considerable criticism because it penalizes precisely the group that most needs financial resources for improvement. Regardless of the mode of implementation, it is obvious that *performance measures* are destined to be an important and intrinsic part of the surgical milieu in upcoming years.

RISKS OF CARDIAC OPERATIONS

Risks for Operative Mortality

By far the bulk of available experience with risk stratification and outcomes analysis in cardiothoracic surgery deals with risk factors associated with operative mortality, particularly in patients undergoing coronary revascularization. Most of the risk-stratification analyses shown in Tables 7-1 and 7-9 are used to evaluate life or death outcomes in surgical patients with ischemic heart disease in part because mortality is such an easy endpoint to measure and track. As mentioned previously, each of the risk-stratification systems shown in Tables 7-1 and 7-9, with the exception of the APACHE III system, computes a risk score based on risk factors that depend on patient diagnosis. For the diagnosis of ischemic heart disease, Table 7-9 shows the significant risk factors found to be important for a spectrum of the risk-stratification systems. The definition of operative mortality varies among the different systems (either 30-day mortality or in-hospital mortality), but the risk factors identified by each of the stratification schemes in Table 7-9 show many similarities. Some variables are risk factors in almost all stratification systems; some variables are never significant risk factors. Each of the models has been validated using separate data sets; hence there is some justification in using any of the risk-stratification methods both in preoperative assessment of patients undergoing CABG and in making comparisons among providers (either physicians or hospitals), but certain caveats exist about the validity and reliability of these models (see below). At present, it is not possible to recommend one risk-stratification method over another. In general, the larger the sample size, the more risk factors can be found. An ideal model would include more variables than even the most robust model in Table 7-9.

There are a large number of patient variables other than those shown in Table 7-9 that have been proposed as risk factors for operative mortality following coronary revascularization. Such variables as serum blood urea nitrogen (BUN) concentration,[136] cachexia,[137] oxygen delivery,[138] human immunodeficiency virus (HIV) infection,[139] case volume,[140] low hematocrit on bypass,[141] use of the internal mammary artery,[142] the diameter of the coronary artery,[143] and resident involvement in the operation[144,145] fit this description. On the surface, the clinical relevance of these variables may seem undeniable in published reports, but very few of these putative risk factors have been tested with the rigor of the variables shown in Table 7-9. The regression diagnostics (e.g., ROC curves and cross-validation studies) performed on the models included in Tables 7-1 and 7-9 suggest that the models are good, but not perfect, at predicting outcomes. In statistical terms, this means that all the variability in operative mortality is not explained by the set of risk factors included in the regression models. Hence it is possible that inclusion of new putative risk factors in the regression equations may improve the validity and precision of the models. New regression models and new risk factors must be scrutinized and tested using cross-validation methods and other regression diagnostics before acceptance. It is uncertain whether inclusion of many more risk factors will improve the quality and predictive ability of regression models significantly. For example, the STS risk-stratification model described in Tables 7-1 and 7-9 includes many predictor variables, whereas the Toronto risk-adjustment scheme includes only five predictor variables. Yet the regression diagnostics for these two models are similar, suggesting that both models have equal precision and predictive capabilities. This suggests that the models are effective at predicting population behavior but not necessarily suited for predicting individual outcomes. Further work needs to be done both to explain the differences in risk factors seen between the various risk-stratification models and to determine which models are best suited for studies of quality improvement.

There are many critical features of any risk-adjustment outcome program that must be considered when determining quality of the risk-stratification method or when comparing one with another (see below). Daley provides a summary of the key features that are necessary to validate any risk-adjustment model.[33] She makes the point that no clearcut evidence exists that differences in risk-adjusted mortalities across providers reflect differences in the process and structure of care.[146] This issue needs further study.

Risk Factors for Postoperative Morbidity and Resource Utilization

Patients with nonfatal outcomes following operations for ischemic heart disease make up more than 95% of the pool of patients undergoing operation. Of approximately 500,000 patients having CABG yearly, between 50% and 75% have what is characterized by both the patient and the provider as an uncomplicated course following operation. The complications

Table 7–12.

Risk Factors Associated with Either Increased Length of Stay (L) or Increased Incidence of Organ Failure Morbidity (M) or Both (L/M) Following Coronary Revascularization

Risk factor	STS[147]	Boston[278]	Albany[11]	VA[194, 279]	Canada[7]
Demographics					
Advanced age	M	L		M	L
Low preoperative red blood cell volume	M		L/M		
Female gender	M				L
Disease-specific diagnoses					
CHF	M	L	L/M	M	
Concomitant valve disease	M			M	L
Reoperation	M			M	L
LV dysfunction (ejection fraction)	M				L
Surgical priority	M			M	L
IABP preop	M	L			
Active endocarditis				M	
Comorbid conditions					
Obesity		L			
Renal dysfunction	M	L	L	M	
Peripheral vascular disease	M		L	M	
Chronic obstructive lung disease	M		L		
Cerebrovascular disease	M		L/M		
Hypertension	M		L/M		

CHF = congestive heart failure; LV = left ventricular; IABP = intra-aortic balloon counterpulsation.

occurring in surviving patients range from serious organ system dysfunction to minor limitation or dissatisfaction with lifestyle and account for a significant fraction of the cost of the procedures. We estimate that as much as 40% of the yearly hospital costs for CABG is consumed by 10 to 15% of the patients who have serious complications after operation.[11] This is an example of a statistical principle called the *Pareto principle* (see below) and also suggests that reducing morbidity in *high-risk* cardiac surgical patients has a significant impact on cost reduction.

A great deal of information exists on nonfatal complications after cardiac operations. Several large databases identify risk factors for both nonfatal morbidity and increased resource utilization. Table 7-12 is a summary of some of the risk factors identified by available risk-stratification models that are associated with either serious postoperative morbidity or increased resource utilization as measures of undesirable outcomes.

The STS Risk Model for Postoperative Morbidity

For many years, operative *mortality* was the sole criterion for a successful CABG procedure. This concept has given way to a broader focus on the entire hospitalization associated with CABG. There is universal agreement that nonfatal complications play a central role in the assessment of CABG quality,

but many morbidity outcomes are relatively difficult to define and track. Risk adjustment is particularly difficult because of the fact that risk factors for most complications are not well established. The low frequency of some complications also creates statistical challenges.

Shroyer and colleagues used part of the large national experience captured in the STS Database to examine five important postoperative CABG complications: stroke, renal failure, reoperation within 24 hours after CABG, prolonged (>24 hours) postoperative ventilation, and mediastinitis.[147] For each of these complications, risk factors were identified using univariate screening followed by multivariate logistic regression analysis (Table 7-12). Predictive models were developed for each of the five complications, thereby allowing one to use specific patient risk factors to adjust for severity of illness and determine *O:E* ratios for providers. This, in turn, allows for meaningful comparisons of risk-matched populations between hospitals or between an institution and a national benchmark.

For the purposes of morbidity estimates, over 500,000 patients from the STS Database were examined.[147] This allowed an accurate estimate of the frequency of each of these five postoperative complications. For example, the morbidity estimates in CABG patients from this large database are as follows: (1) stroke, 1.63%; (2) renal failure requiring dialysis, 3.53%; (3) prolonged postoperative ventilation, 5.96%; (4) mediastinitis, 0.63%; and (5) reoperation within 24 hours, 7.17%. Predictor variables from the logistic regression for each complication demonstrated considerable overlap, but there were substantial differences in odds ratios associated with individual risk factors. The relative importance of specific risk factors differed depending on the outcome measure. For each of the complications, preoperative shock was invariably a major risk factor, as was any form of diabetes. Redo operations were associated with a high odds ratio of most postoperative morbidities, particularly for prolonged postoperative ventilation.

These models were associated with *c*-index values ranging from 0.76 (renal failure) to 0.64 (reoperation within 24 hours), indicating reasonable reliability of the models. The *c*-indices are generally less than those seen with typical models of CABG operative mortality. Nevertheless, the ability to use validated models to risk stratify patients in this context is invaluable. It should be mentioned that NQF and other national quality initiatives clearly have placed a high premium on the need for risk adjustment for most outcome measures, including both mortality and morbidity outcomes.

Risk Factors That Do Not Predict Outcome

Occasionally, studies appear that suggest that a particular patient variable is *not* a risk factor for a particular patient outcome. Care must be exercised in interpreting negative results. Many putative risk factors labeled as "no different from control" in studies using inadequate samples have not received a fair test. For example, Burns and associates studied preoperative template bleeding times in 43 patients undergoing elective CABG.[148] They found no increased postoperative blood loss in patients with prolonged skin bleeding times. Their study reports 5 patients whose bleeding times were prolonged greater than 8 minutes. In this small sample, there was a trend toward more units of blood transfused, but differences between high and low bleeding time groups were reported as "not significant" by the authors at the $\alpha = 5\%$ level (i.e., $p = .05$). Using the authors' data, it is possible to compute a β error for this negative observation of less than 0.5. This means that there is as much as a 50% chance that the negative finding is really a false-negative result. This high false-negative rate occurs because of the small sample size and the wide variation in bleeding time values. We have found elevated bleeding time (>10 minutes) to be a significant multivariate risk factor for excessive blood transfusion after CABG in two different studies.[116,117] Although there is controversy about the value of bleeding time as a screening test,[149,150] it is possible that discarding the bleeding time after an inconclusive negative trial, such as that of Burns and colleagues, may ignore a potentially important risk factor. Care must be taken in the interpretation of a negative finding, especially in a small study group. A similar cautionary note was sounded by Freiman and colleagues after reviewing the medical literature over a 10-year period. These authors found that 50 of 71 "negative" RCTs could have missed a 50% therapeutic improvement from intervention because the sample size studied was too small.[151] Their conclusions were that many therapies discarded as ineffective after inconclusive negative trials still may have a clinically important effect. Negative findings in a literature report require scrutiny and an understanding of type II statistical errors.[41]

Patient Satisfaction as an Outcome

Other post-CABG outcomes, such as patient satisfaction and sense of well-being, have been less well studied. The increasing importance of patient-reported outcomes reflects the increasing prevalence of chronic disease in our aging population. The goal of therapeutic interventions is often to relieve symptoms and improve quality of life rather than to cure a disease and prolong survival. This is especially important in selecting elderly patients for operation. One report from the United Kingdom suggests that as many as a third of patients over the age of 70 did not have improvement in their disability and overall sense of well-being after cardiac operation.[152] Risk-stratification methodology may prove to be important in identifying elderly patients who are optimal candidates for revascularization based on quality-of-life considerations.

Surprisingly little published information is available regarding long-term functional status or patient satisfaction following CABG. One comparative study found no difference between patients older than 65 years and younger than or equal to 65 years with regard to quality-of-life outcomes (e.g., symptoms, cardiac functional class, activities of daily living, and emotional and social functioning).[153] This study also found a direct relationship between clinical severity and quality-of-life indicators because patients with fewer comorbid

conditions and better preoperative functional status had better quality-of-life indicators 6 months after operation. Rumsfeld and colleagues found that improvement in the self-reported quality of life [from the Short-Form Health Survey (SF-36)] was more likely in patients who had relatively poor health status before CABG compared with those who had relatively good preoperative health status.[154] Interestingly, these same authors found that poor preoperative self-reported quality-of-life indicators as measured by the SF-36 questionnaire was an independent predictor of operative mortality following CABG.[155] These findings suggest that the risks of patient dissatisfaction after CABG depend on preoperative comorbid factors, as well as on the indications for and technical complexities of the operation itself. At present, no risk-stratification scheme has been devised to identify patients who are likely to report dissatisfaction with operative intervention following CABG.

There are several difficulties with measurement of patient-reported outcomes, and consequently, cardiothoracic surgeons have not been deeply involved with systematic measurements of patient satisfaction after operation. One problem is that patient-reported outcomes may depend on the type of patient who is reporting them and not on the type of care received. For example, younger Caucasian patients with better education and higher income are more likely to give less favorable ratings of physician care.[156] However, considerable research has been done dealing with instruments to measure patient satisfaction. At least two of these measures, the SF-36[157] and the San Jose Medical Group's Patient Satisfaction Measure,[158] are used to monitor patient satisfaction over time. The current status of these and other measures of patient satisfaction does not allow comparisons among providers because the quality of the data generated by these measures is poor. These instruments are characterized by low response rates, inadequate sampling, infrequent use, and unavailability of satisfactory benchmarks. Nonetheless, available evidence indicates that patient-reported outcomes can be measured reliably[159,160] and that feedback on patient satisfaction data to physicians can improve physician practices significantly.[161] It is likely that managed-care organizations and hospitals will use patient-reported outcome measures to make comparisons between institutions and between individual providers. Risk-adjustment methods for patient-reported outcomes will be required to provide valid comparisons of this type.

Process and Structural Domains of Outcomes Assessment

In 1966, Donabedian suggested that quality in health care was defined as improvement in patient status obtained after accounting for the patient's severity of illness, presence of comorbidity, and the medical services received.[32,162] He further proposed that quality could best be measured by considering three domains: structure, process, and outcome. The notion of measuring quality in this framework is well accepted in most quality-improvement initiatives in place today.

While this general approach has become a modern mainstay in quality programs, the choice of specific measures of structure, process, or outcome can be controversial. *Procedural volume*, for example, is a structural measure that has been used as a surrogate for competent surgical quality. While it may be true that quality and volume are linked for some procedures, it is certainly not the case for all (see "Volume/Outcome Relationship and Targeted Regionalization" below). The practical implications of this structural measure are quite broad and call into play not only clinical considerations but also potentially volatile political ones as well. Likewise, *specialty certification* is a structural measure used often in quality improvement programs. Whereas it is generally true that board-certified individuals usually provide optimal care, it is not invariably true that those not boarded will provide inferior care. One may see readily how inflexible and arbitrary reliance on these structural measures could lead to inappropriate partitioning of care, particularly in small hospitals or underserved regions. Accordingly, it should be emphasized that clinical judgment and perhaps even political judgment should be an integral feature of programs using the Donebedian paradigm.

Birkmeyer pointed out distinct advantages and disadvantages associated with performance measures.[163] For example, the fact that *structural measures* can be tabulated readily in an inexpensive manner using administrative data is a distinct advantage. On the other hand, many structural measures do not lend themselves to alteration. Particularly in smaller hospitals, there simply may be no way to increase procedural volume or to introduce costly design changes in an attempt to create more favorable comparisons with structural measures. *Process measures* often are strongly linked to quality improvement, and they are usually actionable on a practical level. Their major disadvantage lies in the fact that they may not be generally applicable to all patients undergoing a given procedure. To ensure that the right population is examined requires individual clinical assessment and an appreciation for proper exclusionary criteria. This process can be time-intensive and can require sophisticated data-collection systems.

Some practical guidelines have been proposed for using performance measures to assess quality. The major considerations in using performance measures are *volume* and *operative risk*. In general, low-volume, low-risk procedures do lend themselves to a Donebedian-type analysis. Low-volume, high-risk procedures probably should focus primarily on structural measures. High-volume procedures, regardless of risk, can best be assessed with a combination of process and outcome measures.

TOTAL QUALITY MANAGEMENT (TQM) AND OUTCOME ANALYSIS: CASE STUDIES

American health care made almost unbelievable strides in the twentieth century. We are at the brink of being able to treat disease at the molecular level. Cardiac surgeons treat patients who were considered inoperable as recently as a decade ago. Yet almost no one is happy with the health care

Table 7–13.

Principles of Total Quality Management (TQM) Applied to Health Care

Principle	Explanation
Health care delivery is a process.	The purpose of a process is to add value to the input of the process. Each person in an organization is part of one or more processes.
Quality defects arise from problems with the process.	Former reliance on quotas, numerical goals, and discipline of workers is unlikely to improve quality, since these measures imply that workers are at fault and that quality will get better if workers do better. The problem is with the process not with the worker. Quality improvement involves ``driving out fear'' on the part of the worker and breaking down barriers between departments so that everyone may work effectively as a team for the organization.
Customer-supplier relationships are the most important aspect of quality.	A customer is anyone who depends on the organization. The goal of quality improvement is to improve constantly and to establish a long-term relationship of loyalty and trust between customer (patient) and supplier (health care organization) and thereby meet the needs of the patient. The competitive advantage for an organization that can better meet the needs of the customer is obvious. The organization will gain market share, reduce costs, and waste less effort in activities that do not add value for patients.
Understand the causes of variability.	Failure to understand variation in critical processes within the organization is the cause of many serious quality problems. Unpredictable processes are flawed and are difficult to study and assess. Managers must understand the difference between random (or common-cause) variation and special variation in a given outcome.
Develop new organizational structures.	Managers are leaders, not enforcers. Eliminate management by objective numerical goals. Remove barriers that rob workers of their right to pride of workmanship. Empower everybody in the organization to achieve the transformation to a quality product.
Focus on the most "vital few" processes.	This is known as the *Pareto principle* (first devised by Juran) and states that whenever a number of individual factors contribute to an outcome, relatively few of those items account for the bulk of the effect. By focusing on the "vital few," the greatest reward for effort will occur.
Quality reduces cost.	Poor quality is costly. Malpractice suits, excessive use of costly laboratory tests, and unnecessarily long hospital stays are examples of costly poor quality. The premise that it is too costly to implement quality control is incorrect.
Statistics and scientific thinking are the foundation of quality.	Managers must make decisions based on accurate data using scientific methods. Not only managers but all members of the organization use the scientific method for improving processes as part of their normal daily activity.

system. It costs too much, excludes many, is inefficient, and is ignorant about its own effectiveness. This state of confusion has been likened to the conditions that existed with Japanese industry after World War II. Out of the confusion and crisis of post–World War II, Japan has become a monolith of efficiency. Two major architects of this transformation were an American statistician, W. Edwards Deming, and a Romanian-American theoretician, J. M. Juran. They led the way in establishing and implementing certain principles of management and efficiency based on quality. Their efforts are recognized in Japan by the annual awarding of the Deming Prizes in recognition of achievements in attaining high quality. Deming's and Juran's books are some of the "bibles" of quality management in industry.[164,165]

Deming's and Juran's principles are given the acronym of *TQM,* for *total quality management.* The amazing turn-around

Table 7–14.

Steps in a TQM Project

Step	Goal	Tools
1. Definition of problem	List and prioritize problems that affect quality. Define project and identify team to solve problem.	Flow process diagram Pareto chart Customer surveys Risk stratification to identify high-risk subsets
2. Diagnosis of problem	Formulate and test hypotheses about the cause of problem.	Process flow diagram Experimental design methods Statistics to test hypotheses
3. Remedy for problem	Managers and workers participate in training and implementing new or revised process.	Managerial skills in initiating training, implementing solutions, designing controls, and dealing with resistance
4. Check performance of new process	Monitoring process for effectiveness and developing new TQM projects based on results of modifications to the old process.	Sampling methods to get representative sample of outcome Control charts used at every level of the organization—graphs, histograms, stem-and-leaf displays, CUSUM methods, regression analysis, etc.

in Japanese industry led many organizations to embrace the principles of TQM, including organizations involved in the delivery and assessment of health care.[166] Using this approach, health care is viewed as a process requiring raw materials (e.g., sick patients), manufacturing steps (e.g., delivery of care to the sick), and finished products (e.g., outcomes of care). Managerial interventions are important at each step of the process to ensure high-quality product. Table 7-13 outlines the key features of TQM.

An example of application of the principles of TQM to health care delivery is described in the book by Berwick and colleagues.[166] These authors describe the experiences of the National Demonstration Project on Quality Improvement in Health Care in applying the principles of TQM to solve a broad spectrum of health care problems. Twenty-one health care organizations throughout the United States participated in an experiment in the application of TQM to health care. Each organization selected a problem at its institution and, with the aid of an industrial consultant, applied the principles of TQM to attempt to solve the problem. Each institution involved in the project reported that the initiation of TQM practices at that institution was far more valuable than the actual solving of a particular problem in the short term. In the jargon of TQM, the implementation and understanding of TQM principles at every level within an institution produced significant improvement in customer-supplier throughput—i.e., improvement in patient care.

An important component of the TQM process is the use and availability of statistical methods to provide the necessary information to managers and workers who must make decisions about the health care process.[167] While the statistical methods of TQM have a slightly different focus from those outlined earlier for risk adjustment, the goal is the same—i.e., improving the quality of health care. Hence it is reasonable to include a description of the methods of TQM because inevitably they will come up in discussions about health care outcomes and assessing risks for those patient outcomes.

Table 7-14 provides an outline of the sequential steps involved in solving a problem using TQM. Risk stratification plays an important role in the TQM process. One of the most important applications of risk stratification in TQM is in the early stages of the project when definition of the problems that affect quality is being considered. Usually a problem is identified from critical observations—e.g., excessive blood transfusions after operation may result in increased morbidity, including disease transmission, increased infection risk, and increased cost . Tools such as flow diagrams that document all the steps in the process (e.g., steps involved in the blood transfusion process after CABG) are helpful in this phase of the analysis. A logical starting point for efforts to improve the quality of the blood transfusion process would be to focus on a high-risk subset of patients who consume a disproportionate amount of resources. An Italian economist named Pareto made the observation that a few factors account for most of the outcomes of a complex process, and this has been termed the *Pareto principle.* Juran was one of the first to apply this principle to manufacturing in the United States and Japan.[165] The Pareto principle is a valuable tool in improving quality. A graphic method of identifying the spectrum of outcomes in a process is included in most statistics programs and is termed a *Pareto diagram.* Figure 7-5 is an example of a Pareto diagram for blood product transfusion. The data are arranged in histogram format, and the population distribution of patients receiving transfusions is plotted

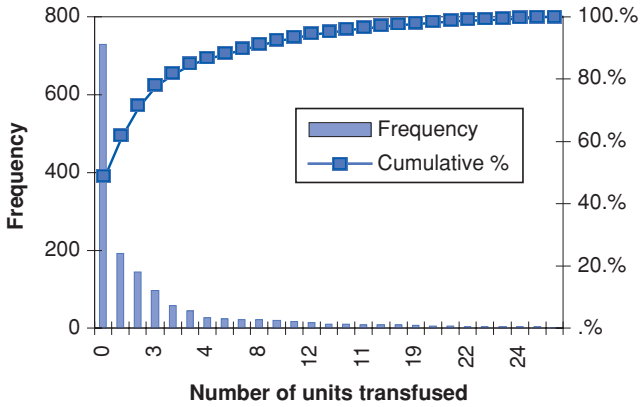


Figure 7-5. Pareto diagram of blood transfusion in 1489 patients undergoing cardiac procedures at Albany Medical Center Hospital during 1994.

simultaneously. The Pareto diagram is an example of a graphic method of risk identification. There are at least three remarkable features of the Pareto diagram in Fig. 7-5. First, over 50% of patients undergoing cardiac procedures receive no homologous blood transfusion. Second, patients who receive more than 10 donor units of blood products are in the 90th percentile of the patient transfusion profile. Third, by looking at the diagram, it is possible to identify a subset of patients who consume more than a certain threshold of blood products. For example, it can be estimated that 20% of the patients consume 80% of the blood products transfused. Substantial savings in cost and possibly other morbidity will result by decreasing the amount of blood transfusion in these 20% of "high-end" users. Strategies can be devised and tested to decrease blood product consumption in the high-risk subset, and ultimately, monitors must be set up to test the effectiveness of the new strategies. Application of the Pareto principle is a valuable tool in risk stratification and TQM, but some of the risk-stratification analytic tools discussed previously can be equally useful in the TQM process. For example, linear regression analysis might be used to identify which of several factors are most important in predicting improved blood transfusion profiles after CABG, or Cox analysis might be used to identify risk factors for increased hospital length of stay in patients at high risk for excessive blood transfusion. Other tools of TQM such as data-sampling strategies and use of control charts play an important role in the process (see below).

Tracking trends using visual aids such as Pareto diagrams and other charts are an important part of quality-improvement interventions. Another type of control-chart technique, *cumulative sum* (CUSUM), has become increasingly popular over the past decade and may help to address some of the problems associated with traditional outcome monitoring. When preparing a performance report, or "report card,"[53] the usual data-collection period is 1 year for hospitals and 2 to 3 years for individual surgeons. Add to this 1 to 1½ years for audit, validation, and analysis, and there may be a several-year delay between the early patients in a series and the ultimate publication of a report. This is clearly an ineffective way to document and address deteriorating trends in performance objectively, particularly if a new procedure is being introduced or if there are subjective concerns regarding outcomes.[168–171]

The CUSUM chart and its various modifications [e.g., sequential probability ratio test (SPRT), cumulative risk-adjusted mortality (CRAM), and variable life-adjusted display (VLAD)] are ideally suited to detecting such trends, particularly when they are small and subtle.[168,169,172,173] In its simplest form, the CUSUM chart is a plot of cumulative failures (e.g., deaths) on the vertical axis against procedure number or date on the horizontal axis. For each failure, the graph advances one unit vertically. For each case not a failure, the graph advances horizontally by one unit. Through visual interpretation of the slope, this simple graphic indicates whether the failure rate is increasing over time. Statistical control limits (e.g., alert and alarm) can be placed around the cumulative failure lines, just as they are in other types of control charts.[168,170,173] One of the earliest and still most widely cited examples of such a CUSUM graph was from de Leval and associates,[171] who described their initial experience with neonatal arterial switch operations. Having experienced only 1 death in their first 52 patients, 7 of the next 16 patients died, resulting in a marked and statistically significant rise in the CUSUM line. After technique modifications, the CUSUM plot again became nearly horizontal.

An important modification of CUSUM charts for surgical cases is the incorporation of individual patient risk, obtained through any of the standard techniques described elsewhere in this chapter. For example, the vertical axis might plot cumulative lives saved (expected minus observed deaths) rather than surgical failures,[173] in which case a gradually rising line indicates good performance, and a line descending below the baseline may indicate poor performance. For each case, a value between –1 and + 1 is added. For example, a patient with a predicted mortality of 20% who survives would have 0.2 added to the cumulative sum, and the line would rise. Conversely, a patient with an expected mortality of 10% who dies would have negative 0.9 added to the cumulative sum line, and the line would go down.[173]

CUSUM charts and their various modifications are used extensively, especially in the United Kingdom, to monitor medical and surgical outcomes. It appears that they may provide earlier detection of performance issues, as well as their remediation, than more traditional report cards. Novick and colleagues used a CUSUM chart to analyze the effect of changing from on-pump CABG to off-pump CABG as a primary means of operative coronary revascularization.[174] These authors found that the CUSUM methodology was more sensitive than standard statistical techniques in detecting a cluster of surgical failures or successes.

Northern New England TQM Project

The paradigm for a TQM-based approach to improving cardiac surgery quality is the Northern New England Cardiovascular Study Group (NNECVDSG). Founded in 1987, this

voluntary consortium of clinicians, scientists, and administrators represents cardiac surgery programs in northern New England. Its mission is to study and improve the quality of cardiovascular care provided to patients through the use of systematic data collection and feedback. Shortly after its formation, this group developed and validated a logistic risk model to account for case-mix differences across its member institutions.[175] Using this model, the group analyzed CABG outcomes for 3055 patients operated on at five medical centers in Maine, New Hampshire, and Vermont between July 1987 and April 1989.[176] Overall unadjusted CABG mortality was 4.3%, but this was found to vary substantially among centers (3.1 to 6.3%). Even after case-mix adjustment, significant variability persisted among medical centers ($p = .021$) and surgeons ($p = .025$). In 1990, the NNECVDSG initiated a regional intervention aimed at reducing both absolute CABG mortality and interinstitutional variability.[177] The three major components of this TQM approach included feedback of outcomes data, training in continuous quality-improvement techniques, and site visits to each program. During the latter, visitors from each discipline focused on the practice of their counterparts at the host institutions. Numerous changes were implemented as a result of these site visits, including technical aspects and processes of care, personnel organization and training, decision making, and methods of evaluating care. Following these interventions, observed mortality declined to less than expected in all categories of patient acuity.

Subsequent to these landmark papers, the consortium has continued to grow in size, now consisting of eight institutions in northern New England. The database currently contains entries for over 150,000 procedures, and data reports and proposed studies are discussed at meetings held three times annually. Over 60 peer-reviewed articles have been published in numerous areas pertaining to cardiac surgical care, ranging from the impact of preoperative variables on hospital and long-term mortality, the optimal conduct of cardiopulmonary perfusion, prevention of specific postoperative complications, on-pump versus off pump CABG surgery, and modes of death following CABG.[178–180] Models also have been developed for valve replacement surgery,[181] and a simplified risk-scoring method for bedside use has been developed[182] and incorporated into the 2004 ACC/AHA guidelines update for CABG. Nineteen years after its formation, the NNECVDSG remains at the forefront of global efforts to improve cardiac surgery quality through voluntary, confidential, and collaborative TQM.

STS Database and Quality Improvement

In the early 1980s, CABG operations were characterized by operative mortality rates typically in the range of 1 to 2%. A few years later, however, the severity of illness of CABG patients began a progressive rise that is still being seen today. Predictably, CABG operative mortality rates reached the 5 to 6% range.[183]

This rise in operative mortality was understood by cardiovascular specialists, but others were unaware of the changes that had produced these higher mortality rates, and surgeons were challenged to justify the increase in CABG mortality. It soon became apparent that databases would be essential for proper investigation of these issues. To truly analyze patient risk factors in a meaningful way required statistical risk models designed to generate a predicted operative mortality based on preoperative clinically significant factors. Clearly, this type of analysis was well beyond the capabilities of the great majority of surgical groups.

In addition, this scrutiny exposed the fact that true national benchmarks did not exist in cardiac surgery. The Society of Thoracic Surgeons (STS) recognized this compelling need for a national standard in cardiac surgery. In 1986, a formal STS committee was formed under the leadership of Dr. Richard E. Clark to develop a national database of cardiac surgery. This committee began to gather and to analyze perioperative patient data in a manner that would establish a national standard of care in cardiac surgery.

The STS Database is a voluntary registry that currently collects data from 70 to 80% of cardiac centers in the United States. Individual participant sites enter extensive clinical data on each patient undergoing cardiac surgery. This information is harvested every 6 months and aggregated at the Duke Clinical Research Institute (DCRI). The data are analyzed, and reports that include benchmark data and risk-adjusted outcomes are provided to each site. This reporting process allows sites to pinpoint areas in need of improvement so that tailored quality-assessment and -improvement programs can be developed.

The STS maintains an active Workforce on National Databases that provides leadership and oversight of database activities. Risk models are developed at periodic intervals using the biostatistical expertise and resources of DCRI in conjunction with STS leadership. Currently, risk models are based on logistic regression techniques and are designed to predict operative mortality for CABG, for mitral and aortic valve replacement, and for CABG combined with mitral and aortic valve replacement. As mentioned earlier, there are also risk models of five common postoperative complications.

The STS data allow one to monitor trends in the patient profiles of cardiac surgery patients over the years. As shown in Fig. 7-6, one can appreciate the progressive

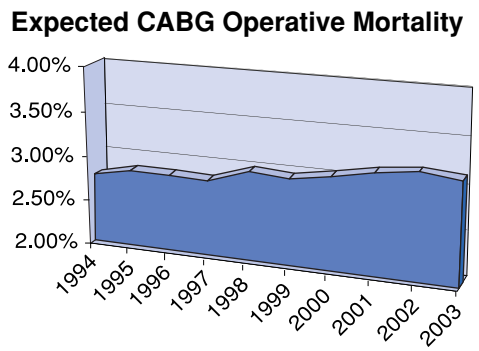


Figure 7-6. Predicted operative mortality from the Society of Thoracic Surgeons risk models between 1994 and 2003.

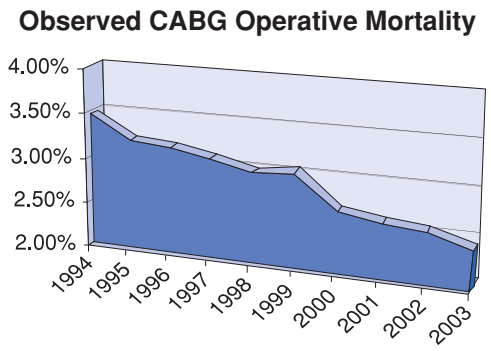


Figure 7-7. Observed operative mortality from the Society of Thoracic Surgeons Database between 1994 and 2003.

increase in operative risk in the 1994–2003 time frame. Information of this sort helps on a clinical level and has an impact on various administrative and regulatory fronts. Negotiations, with the relative value scale update committee for example, traditionally have been based on small surveys, but the use of STS data has allowed a more accurate presentation of objective information that provides a truly fair and meaningful workload analysis.

The reporting and feedback process to individual sites produced impressive improvements in surgical outcomes. As shown in Fig. 7-7, despite the increase in patient risk, there was a progressive drop in operative mortality from 1994 to 2003.

The database plays a central role in the current national quality initiatives. Information from the database allows one to monitor and analyze all but three of the NQF measures specified in Table 7-11. In future revisions, these three missing parameters will be captured in the database entry process. Specific NQF-based reports are being developed to allow users to focus directly on the measures that have been chosen to reflect surgical quality in cardiac surgery.

Third-party payors are expressing renewed interest in developing quality-improvement programs. The STS Database is being proposed as the single source of data for these programs so that surgeons will not be burdened with numerous diverse reporting requirements.

There is a groundswell of public demand for report cards and other hospital/surgeon-ranking systems. The advantages and disadvantages of such reporting systems are addressed elsewhere in this chapter, but it should be mentioned that numerous third-party payors are in the process of developing these scorecard protocols. In order to preempt the development of ill-advised and simplistic scorecards, STS experts are developing a fair and meaningful quality-rating system based on objective information from the STS Database.

The STS Database presently contains records of approximately 3 million patients, thereby making it the largest cardiac surgery database in the world. This clinical database has come to be regarded as an exceptionally valuable resource for cardiac surgeons, and its risk-assessment algorithms generally are accepted as standard quality-assessment tools in cardiac surgery. The database has numerous important practical applications that serve to promote quality improvement and ensure that the specialty is well represented in national regulatory programs.

Massachusetts Cardiac Care Quality Advisory Commission

The Massachusetts experience provides an excellent example of a successfully implemented quality-monitoring effort[65,184] in which cardiac surgeons played an active leadership role. In 2000, the Massachusetts legislature established the Cardiac Care Quality Advisory Commission, one of whose mandates was to implement a transparent, comprehensive report card for invasive cardiac services [CABG and percutaneous intervention (PCI)]. This commission consisted of representatives from the cardiac surgery and PCI communities, statisticians with particular expertise in provider profiling, and regulators from the Department of Public Health. Working together toward their common goal of assessing and improving cardiac care, this group established a collegial and mutually respectful relationship that greatly facilitated subsequent implementation of the program. The STS Database, a unique resource available to our specialty, was mandated as the data-collection instrument for all Massachusetts cardiac programs, and provider performance was analyzed using generalized hierarchical models. Data collection, cleansing, audit, validation, adjudication, and statistical analysis were performed at the Massachusetts Data Analysis Center (Mass-DAC) based at the Harvard Medical School Department of Health Care Policy. Hospital-level reports are released to the public on a yearly basis, whereas 3-year aggregate data on individual surgeons are reviewed confidentially by the commission. It was hoped that this would mitigate the potential for high-risk case avoidance, which is primarily at the discretion of surgeons.

To facilitate information flow, to provide reassurance that monitoring was being conducted in a fair manner, to provide experts for data adjudication and clinical issues, and to coordinate ongoing TQM activities, Massachusetts cardiac surgeons found it useful to form a state STS organization. They also had extensive input from the national STS and the Duke Clinical Research Institute.

Review of CABG data from 2003 revealed that 1 of 14 Massachusetts cardiac programs was a statistical outlier. Because of their close working relationship with the Department of Public Health, Massachusetts STS leaders were asked to conduct a comprehensive evaluation of this program. Because this evaluation was thus a true peer-review process, the results were readily accepted by the surgical community and the involved hospitals, and numerous constructive recommendations were made and implemented. Thus the goals of both public accountability and continuous quality improvement were achieved with little media fanfare.[53]

VALIDITY AND RELIABILITY OF OUTCOME ASSESSMENT METHODS

There is little or no consensus about how to assess the validity of outcome assessment methodology. As pointed out by Daley, the concept of validity is something that everyone understands but for which no single meaning exists.[146] The concept of validity is made up of many parts. According to Daley, five of these parts are as follows: (1) face validity (Will whoever uses the risk model accept it as valid?), (2) content validity (Does the model include risk factors that should have been included based on known risks?), (3) construct validity (How well does the model compare with other measures of the same outcome?), (4) predictive validity (How well does the model predict outcome in patients not used to construct the model?), and (5) attributional validity (Does the model measure the attribute of effectiveness of care, not patient variability?). Of these components, face and content validity are arguably the most important. Clinicians can readily accept the results of risk-stratification efforts if the model uses variables that are familiar and includes risk factors that the clinician recognizes as important in determining outcome. All the risk models shown in Table 7-9 satisfy some or all of these criteria of validity. There is no objective measure that defines validity, but most clinicians would agree that the risk models have relevance to clinical practice and contain many of the features that one would expect to be predictive of morbidity and mortality for CABG.

The issue of reliability of a risk-stratification model is measured more easily than validity. *Reliability* of a risk-adjustment method refers to the statistical term *precision,* or the ability to repeat the observations using similar input variables and similar statistical techniques with resulting similar outcome findings. There are literally hundreds of sources of variability in any risk-stratification model. Some of these include errors in data input, inconsistencies in coding or physician diagnosis, variations in the use of therapeutic intervention, data fragility (i.e., the final model may be very dependent on a few influential outliers), and the type of rater (e.g., physician, nurse, or coding technician), to name a few.[185] The most common measure of reliability is Cohen's kappa coefficient, which measures the level of agreement between two or more observations compared with agreement owing to chance alone.[186] The kappa coefficient is defined as

$$\kappa = P_o - P_c / 1 - P_c$$

where P_c is the fraction representing the agreement that would have occurred by chance, and P_o is the observed agreement between two observers. If two observations agree 70% of the time on an observation where agreement by chance alone would occur 54% of the time (i.e., $P_o = 0.7$ and $P_c = 0.54$), then $\kappa = 0.35$. Landis and Koch have offered a performance estimate of kappa as follows: $\kappa = 0$ to 0.2 signifies slight agreement; $\kappa = 0.2$ to 0.4 signifies fair agreement; $\kappa = 0.4$ to 0.6 signifies good agreement; $\kappa = 0.6$ to 0.8 signifies substantial agreement; and $\kappa = 0.8$ to 1.0 signifies near-perfect agreement.[187] Other methods of measuring the agreement between two models include weighted kappa, the interclass correlation coefficient, the tau statistic, and the gamma statistic. These methods are discussed in the work of Hughes and Ash, and any of these offer an objective means of assessing the reliability of a risk-adjustment model.[185]

Surprisingly little work has been done in assessing the reliability and validity of the risk-adjustment methods used with large cardiac surgical databases. It is absolutely essential that validity and reliability are tested in these models both in order for clinicians to feel comfortable with the comparisons generated by the risk-stratification models and for policymakers (either government or managed-care organizations) to feel confident in making decisions based on risk-adjusted outcomes.

Risk Stratification to Measure the Effectiveness of Care

The biggest single shortcoming of risk-adjustment methodology is its lack of proven effectiveness in delineating quality of care. Even though it may seem obvious that differences in risk-adjusted outcomes reflect differences in quality of care, this is far from proven. What little information there is available on this subject is inconsistent. Hartz and colleagues compared hospital mortality rates for patients undergoing CABG.[188] They found that differences in hospital mortality rates were correlated with differences in quality of care between hospitals. Hannan and colleagues attempted to evaluate the quality of care in outlier hospitals in the New York State risk-adjusted mortality cohort.[189] They concluded, as did Hartz and colleagues, that risk-adjusted mortality rates for CABG were a reflection of quality of care. The measures of quality used in these studies were somewhat arbitrary and did not reflect a complete array of factors that might be expected to influence outcomes after CABG. In TQM jargon, the entire clinical process of surgical intervention for coronary revascularization was not assessed. Other studies have not found a correlation between global hospital mortality rates and quality-of-care indicators.[57,190–192] Indeed, one study suggested that nearly all the variation in mortality among hospitals reflects variation in patient characteristics rather than hospital characteristics,[192] whereas another study found that identifying poor-quality hospitals on the basis of mortality-rate performance, even with perfect risk adjustment, resulted in less than 20% sensitivity and greater than 50% predictive error.[57] These two studies suggest that reports that measure quality using risk-adjusted mortality rates misinform the public about hospital (or physician) performance. At least three ongoing quality-improvement studies are using risk-adjusted outcome measurements to assess and influence the clinical process of CABG: the Northern New England Cardiovascular Disease Study,[193] the Massachusetts Quality Assurance Program,[65] and the Veterans Administration Cardiac Surgery Risk Assessment Program.[194] Results from these studies suggest

that using risk-adjusted outcomes (e.g., mortality and cost) as internal reference levels tracked over time (similar to the control charts of TQM described earlier) can produce meaningful improvements in outcomes. Whether these risk-adjusted outcomes can be used to indicate quality of care or cost-effectiveness of providers across all institutions is another question that remains unanswered. At present, it is not justified to equate risk-adjusted outcome measurements with effective care.[195–199]

Controversy exists as to whether changes in a physician's report card over time reflect changes in care or whether these changes are due to other factors not related to individual provider's care delivery. Hannan and colleagues suggested that the public release of surgeon-specific risk-adjusted mortality rates led to a decline in overall mortality in New York State from 4.17% in 1989 to 2.45% in 1992 and hence improvement in the quality of care.[200] The cause of this decline in operative mortality is uncertain but probably represents a combination of improvement in the process of care (especially in the outlier hospitals), low-volume surgeons retiring, and an overall national trend toward decreased CABG mortality. Ghali and colleagues found that states adjacent to New York that did not have report cards had comparable decreased CABG operative mortality during the same time period.[201] Without any formal quality-improvement initiative or report card, the operative mortality rate in Massachusetts decreased from 4.7% in 1990 to 3.3% in 1994. This occurred while the expected operative mortality of patients increased from 4.7 to 5.7%. The decline in New York State operative mortality over time associated with the publication of surgeon-specific mortality rates was greater than the overall national decrease in CABG death rates. Peterson and colleagues found that the reduction in observed CABG mortality was 22% in New York versus 9% in the rest of the nation, a highly significant difference.[202] An interesting finding in the study of Peterson and colleagues is that the only other area in the United States with a comparable decline in CABG mortality to that of New York was northern New England. The Northern New England Cooperative Group established a confidential TQM approach to improve CABG outcomes[203] at about the same time that New York State report cards were published in the lay press. These two approaches to improving outcomes for CABG represent opposite ends of the spectrum, the New York State approach representing the "stick" and the northern New England approach representing the "carrot." This suggests that the institution of a formal quality-improvement process is the key to improving outcomes and that either the carrot or the stick approach may be effective.[204]

Ethical Implications of Risk Stratification: The Dilemma of Managed Care

An important component of new proposals for health care reform is mandated reports on quality of care.[205] While reporting on quality of care sounds appealing, there are many problems associated with this effort, some of which present the clinician with an ethical dilemma.[206,207] There is general agreement that quality indicators should be risk-adjusted to allow fair comparisons among providers. Risk adjustment in this setting is extremely difficult, may be misleading, and what is worse, may not reflect quality of care at all. The release of risk-adjusted data may alienate providers and result in the sickest patients having less accessibility to care. This may have happened already in New York State[61,208,209] and in other regions where risk-adjusted mortality and cost data have been released to the public. Of even more concern is the selection bias that seems to exist in managed-care health maintenance organization (HMO) enrollment. Morgan and colleagues suggest that Medicare HMOs benefit from the selective enrollment of healthier Medicare recipients and the disenrollment or outright rejection of sicker beneficiaries.[210] This form of separation of patients into unfavorable or favorable risk categories undermines the effectiveness of the Medicare managed-care system and highlights the subtle selection bias that can result when financial incentives overcome medical standards. Careful population-based studies that employ risk adjustment are needed to study this phenomenon.

A major concern of the current move toward market-oriented health care delivery is that health plans will select only the best health risk participants—termed *cream skimming* by van de Ven and colleagues.[211] The result of cream skimming may be to widen the gap between impoverished, underserved patients and affluent patients. In an effort to address these concerns, plans have been proposed that would reward health plans for serving people with disabilities and residents of low-income areas.[212,213] At the heart of these plans is some form of risk adjustment to allocate payments to health care organizations based on overall health risk and expected need for health care expenditures. The use of risk stratification in this setting is new and unproved but offers great promise.

A related problem is that physicians are being rewarded by hospitals and managed-care organizations for limiting costs. Incentives are evolving that threaten our professionalism.[80] On the surface of it, this may seem like a strong statement, but one only has to read some of the "compromise" positions that have been advocated in order to deal with the changing health care climate. "Advice" such as hiring lawyers to optimize care (managed or capitated contracts), recruiting younger patients and discouraging Medicare-age patients away from a managed-care practice, forbidding physicians from disclosing the existence of more costly services not covered by their managed-care plan, and using accounting services to track and limit frequency of office visits have been offered to physicians.[80,214–216] A particular telling indictment is the finding by Himmelstein and colleagues that investor-owned HMOs deliver lower-quality care than not-for-profit plans.[217] Physicians who own managed-care organizations live by a dual standard—the professional standard of providing high-quality patient care and the financial standard of making a profit from this care delivery. Strategies must be devised that allow physicians both to

maintain a professional approach to patients and to participate in the marketplace without compromising patient care.

The Costs of Gathering Data

Collecting risk-adjusted data adds to the administrative costs of the health care system. It is estimated that 20% of health care costs ($150 to $180 billion per year) are spent on the administration of health care.[218] The logistical costs of implementing a risk-adjustment system are substantial. Additional costs are incurred in implementing quality measures that are suggested by risk-stratification methodology. A disturbing notion is that the costs of quality care may outweigh the payors' willingness to pay for those benefits. For example, Iowa hospitals estimated that they spent $2.5 million annually to gather MedisGroups severity data that were mandated by the state. Because of the cost, the state abandoned this mandate and concluded that neither consumers nor purchasers used the data anyway.[219] It is possible that quality improvement may cost rather than save money; although one of the principles of TQM (often quoted by Deming) is that the least expensive means to accomplish a task (e.g., deliver health care) is the means that employs the highest quality in the process. Ultimately, improved quality will be cost-efficient, but startup costs may be daunting, and several organizations already have expressed concerns about the logistical costs of data gathering and risk adjustment.[219,220] It is imperative that part of any cost savings realized by improved quality be factored into the total costs of gathering risk-adjusted data.

Inherent Dangers with Outcome Assessment

It is nearly impossible to assess the accuracy of risk-adjusted outcomes to measure provider quality of care. In a perfect world, differences in observed-to-expected (*O:E*) mortality rates are due to either random variation or to quality of care. The problem is that risk-adjustment methodologies are less than perfect.[221] What if there were perfect risk-adjustment models? Would hospital risk-adjusted mortality rates then reflect quality of care? To answer this question is impossible if currently available clinical databases are used. This is true because there is no valid measure of quality that allows identification of poor- or good-quality providers. No single outcome, process, or structural measure or combination of these measures meets the validity criteria for a quality indicator.

Nonetheless, several researchers investigated the hypothesis that high-quality risk-adjusted outcomes reflect quality of care.[57,190,199,208,222,223] Several authors attempted to circumvent the less than adequate risk-adjustment models and the lack of a recognized quality indicator by simulating mortality experience for a hypothetical set of hospitals with perfect risk adjustment and with prior perfect knowledge of poor-quality providers. These authors used various simulation models, including Monte Carlo simulation,[223] and obtained similar results. Each of the simulations found that under all reasonable assumptions, sensitivity for determining poor quality was less than 20%, and the predictive error for determining high outliers was greater than 50%.[57,222,223] Stated another way, it is likely that 50 to 80% of observed mortality-rate differences between high outliers and nonoutliers are attributable to random variation. Park and colleagues suggest that providers identified as high outliers using conventional risk-adjustment methods do not provide lower-quality care than do nonoutliers.[190] There are two concerns with outcome assessment that must be addressed before clinicians and the public can embrace such assessment: (1) high-quality risk-adjustment models are imperative, and (2) well-defined and well-validated measures of quality of care are needed. Without these two ingredients, there will be natural skepticism and apparent inequalities in the outcome assessment process.

WHAT DOES THE FUTURE HOLD?

Decision Analysis: The Infancy of Risk Stratification and Outcomes Assessment

A great deal of effort has gone into the development of risk models to predict outcomes from cardiac surgical interventions (e.g., Tables 7-1 and 7-9). For populations of patients undergoing operations, the models are fairly effective at predicting outcomes (with certain caveats, as mentioned earlier). The biggest drawback of these risk models is that they exhibit dismal performance at predicting outcomes for an individual patient. Consequently, risk adjustment to predict individual outcomes is extremely difficult to apply at the bedside. For patient-specific needs, risk stratification and outcomes assessment are in their infancy.

What are needed are patient-specific predictors for clinical decision making. On the surface, it would seem that a decision about whether to operate on a patient with coronary artery disease is straightforward. But a decision of this sort is an extremely complex synthesis of diverse pieces of evidence. As mentioned earlier, there are enormous variations in the way that surgeons practice. These variations can increase cost, cause harm, and confuse patients. The tools of decision analysis, similar to how airline pilots make decisions about complicated flight problems, have been applied to the area of physician decision making in an effort to eliminate these variations and to provide accurate and effective decisions at the patient bedside.[17,224] In the decision analytic jargon, the decision to operate for coronary artery diseases is extremely complex because there are more than two alternative treatments, more than two outcomes, and many intervening events that may occur to alter outcomes. Decision models generated to address surgical outcomes typically employ the familiar decision tree. They are commonly perceived as complex and difficult to understand by those unfamiliar with the methods, especially in the context of clinical decision making. Attempts have been made to simplify the methods and to apply them to the medical decision-making process.[224] An important part of creating the decision tree is to estimate the probabilities of each of the various outcomes

for a given set of interventions. This part of the decision analysis tree relies heavily on the results of risk stratification and regression modeling, especially computer-intensive methods such as Bayesian models,[225] to arrive at a probability of risk for a particular outcome. All the diverse pieces of evidence used to form consensus guidelines, including meta-analyses, expert opinions, unpublished sources, randomized trials, and observational studies, are employed to arrive at probabilities of outcome and intervening events. For example, Gage and colleagues performed a cost-effectiveness analysis of aspirin and warfarin for stroke prophylaxis in patients with nonvalvular atrial fibrillation.[226] They used data from published meta-analyses of individual-level data from five randomized trials of antithrombotic therapy in atrial fibrillation to estimate the rates of stroke without therapy, the percentage reduction in the risk of stroke in users of warfarin, and the percentage of intracranial hemorrhages following anticoagulation that were mild, moderate, or severe. Their decision tree suggests that in 65-year-old patients with nonvalvular atrial fibrillation (NVAF) but no other risk factors for stroke, prescribing warfarin instead of aspirin would affect quality-adjusted survival minimally but increase costs significantly. Application of decision analysis methods to clinical decision making can standardize care and decrease risks of therapy, but these methods are in the early developmental phase, and much more work needs to be done before ready acceptance by surgeons.

Volume/Outcome Relationship and Targeted Regionalization

At least 10 large studies addressed the notion that hospitals performing small numbers of CABG operations have higher operative mortality. Seven of these 10 studies found increased operative mortality in low-volume providers.[227–233] In 3 other large studies, there was no such association.[140,234,235] Interestingly, in the 3 studies done more recently (since 1996), there was no clear relationship between outcome and volume. In 2 separate studies done on some of the same patients in the New York State Cardiac Surgery Database, completely opposite results were obtained.[233,235] The Institute of Medicine summarized the relationship between higher volume and better outcome (www.nap.edu/catalog/10005.html) and concluded that procedure or patient volume is an imprecise indicator of quality even though a majority of the studies reviewed showed some association of higher volume and better outcome.[236] Significantly, the largest clinical database dealing with CABG patients, the STS Database, did not find a significant relationship between outcome and provider volume.[237] Many other risk factors are more important determinants of outcome than provider volume in this large clinical database.[147,237,238] The dilemma is that some low-volume providers have excellent outcomes, whereas some high-volume providers have poor outcomes. These observations on operator volume and outcome prompted some authorities to suggest "regionalization" to refer nonemergent CABG patients to large-volume centers.[232,239,240] A role for "selective regionalization" was advocated by Nallamothu and colleagues because they found that low-risk patients did equally well in high-volume or low-volume hospitals.[140,241] They suggest regional referral for elective high-risk patients to high-volume institutions.[140] Other authors pointed out that a policy of regionalized referrals for CABG might have several adverse effects on health care, including increased cost, decreased patient satisfaction, and reduced availability of surgical services in remote or rural locations.[241,242] Furthermore, there is no clearcut proof that a policy of regionalization will have the desired effects. Several published studies reveal the inadequacy of the volume-outcome relationship. Peterson and colleagues reviewed the STS Database to evaluate the relationship of CABG volume to outcome.[237] They found almost no potential benefit in closing low-volume centers. The wide variability in risk-adjusted mortality among hospitals with similar volume precluded the ability of hospital volume to discriminate those centers with significantly better or worse mortality. Hospital procedural volume was only modestly associated with CABG outcomes. They suggested that procedural volume is not an adequate marker of quality for CABG surgery.[237] Similar results were obtained by Rathore and colleagues, who reviewed the Medicare CABG database.[243] Other more important process variables are principal determinants of outcomes in CABG patients. Hannan suggests that regionalization of CABG patients in the New York State system would have detrimental effects on quality of care.[244] It is entirely possible that overcrowding of high-volume centers in a regionalization model would impair outcomes. It is simplistic to suggest that hospital volume is a principal surrogate of outcome, and much more sophistication is required to sort out this relationship. Nonetheless, decisions about utilization of health care resources undoubtedly will be made based on the presumed association between high volume and good outcome.

Medical Errors and Outcomes

The Institute of Medicine (IOM) released a startling report on medical errors that occur in the U.S. health system (http://books.nap.edu/catalog/9728.html). Based mainly on two large studies, one using 1984 data in New York State and the other using 1992 data in Colorado and Utah,[245,246] this report suggested that at least 44,000 Americans die each year from preventable hospital errors.[31] This estimate was not much different from ones obtained from similar analyses on patients in Australia,[247] England,[248] and Israel.[249] This IOM report caused a storm of controversy, with many experts fearing that the report could harm quality-improvement initiatives.[246,250] Some had doubts about the methodology used to derive estimates of medical errors,[251,252] whereas others made an emotional plea for drastic measures to reduce errors.[253]

The airline industry had success in limiting errors by instituting multiple quality-improvement interventions. This industry is used as a model of successful implementation

of error-avoidance behavior and process improvement.[250] These same principles were applied to pediatric cardiac surgery by de Leval and colleagues with some success.[171] These workers evaluated patient and procedural variables that resulted in adverse outcomes. In addition, they employed self-assessment questionnaires and human factors researchers who observed behavior in the operating room, an approach similar to the quality-improvement steps used in the airline industry. Their study highlighted the important role of human factors in adverse surgical outcomes, but more important, they found that appropriate behavioral responses in the operating room can retrieve potential harmful events that occur in the operating room. Studies of this sort that emphasize behavior modification and process improvement hold great promise for future error reduction in cardiac surgery.

Computer applications were applied to the electronic medical record in hopes of minimizing physician errors in ordering. Computerized physician order entry (CPOE) is one of these applications that monitors and offers suggestions when physicians' orders do not meet a predesigned computer algorithm. CPOE is viewed as a quality indicator, and private employer-based organizations used the presence of CPOE to judge whether hospitals should be part of their preferred network (www.leapfroggroup.org/). One of these private groups is the Leapfrog Group, and an initial survey by this group in 2001 found that only 3.3% of responding hospitals currently had CPOE systems in place (www.ctsnet.org/reuters/reutersarticle.cfm?article=19325). In New York State, several large corporations and health care insurers agreed to pay hospitals that meet the CPOE standards a discount bonus on all health care billings submitted. Other computer-based safety initiatives that involve the electronic medical record are likely to surface in the future. The impact of these innovations on the quality of health care is untested, and any benefit remains to be proven.

Information technology used to reduce medical errors has met with mixed success. Innovations that employ monitoring of electronic medical records may reduce errors.[254,255] However, one study that tried to implement guidelines for treating congestive heart failure into a network of physicians' interactive microcomputer workstations found it difficult.[256] The task proved difficult because the guidelines often lack explicit definitions (e.g., for symptom severity and adverse events) that are necessary to navigate the computer algorithm. Another study attempted to implement prophylactic care measures (e.g., update of tetanus immunization in trauma patients) using reminders in the electronic in-patient medical record.[93,257] These investigators were unable to increase the use of prophylactic measures in hospitalized patients with this computer-based approach. Much work needs to be done before computer-aided methods lead to medical error reduction, but the future will see more efforts of this type.

Since the IOM report on medical errors that appeared in 2000,[31] significant energy was expended on reducing medical errors by both physicians and hospitals. Several authors recently expressed dismay that little progress has been made in changing the culture of safety in our hospitals.[258,259] Brennan and colleagues point out that the IOM distinguishes safety from effectiveness. *Effectiveness* is defined as an intervention based on available evidence that improves quality, whereas *safety* encompasses a much narrower definition of limiting accidental injury.[258] These authors suggest a redirection of health care goals toward effectiveness interventions and away from accident-reduction interventions. An important advantage of a focus on effectiveness is the ease with which effectiveness outcomes can be measured compared with safety outcomes. There is some evidence that focus on evidence-based interventions such as providing aspirin to cardiac patients when they leave the hospital has improved the effectiveness of treatment with a secondary benefit of reducing errors.[260] There is still a reluctance to deal transparently with medical mistakes. Health care providers have not spent significantly increased resources on safety and error management largely because the return on this type of investment is very hard to measure. On the other hand, quality-improvement efforts based on evidence of effectiveness are likely to be embraced more readily and may save more lives than will safety-related interventions that lack an evidence base.[258]

Public Access and Provider Accountability

Multiple factors bring surgical results to the public attention. Such things as publication of individual surgeon risk-adjusted mortality rates, limitation of referrals to high-mortality surgeons by insurers, legislative initiatives to reduce medical errors, and abundant proliferation of the Internet as an information resource lead to increased public awareness of surgical outcomes. Like it or not, thoracic surgeons must be prepared to accept this scrutiny and, perhaps, even to benefit from it because the trend of public scrutiny of surgical results is an increasing one.

The World Wide Web provides ready access to medical facts of all sorts, particularly information about thoracic surgery. Everything from access to the thoracic literature, to outcomes of randomized trials, to surgeon-specific risk-adjusted mortality rates, to comparison of hospital outcomes can be obtained by the lay public with rather simple searches on the Internet. This ready public access undoubtedly will increase. Examples of available information sources for the public are listed in Table 7-15. There is very little external scrutiny attached to most of the information sources listed in this table. Almost all information available on these sites is accepted at face value by the public, and quality control of the information sources is limited to self-imposed efforts on the part of the authors of the various information sources. The Agency for Healthcare Research and Quality (AHRQ) attempted to empower the public to critically evaluate the various Web-based sources of health care information in order to limit the spread of misinformation that may creep into various Web sites. The success of these efforts is uncertain but becomes extremely critical as the amount of health care information available on the Web skyrockets.

Table 7–15.

Partial Listing of Publicly Available Information Sources Related to Cardiothoracic Surgery

Source	Targeted audience	Communication media	Information available
American College of Cardiology/ American Heart Association	Patients needing CABG (nationwide)	Internet (www.acc.org/clinical/guidelines/bypass/bypass7.htm)	Literature-based indications for CABG
Agency for Health Care Research and Quality	Broad base of health care consumers and providers	Internet (www.ahcpr.gov/)	Large knowledge base focusing on empowering consumers to judge health care quality
California Office of Statewide Health Planning and Development	Patients who purchase health care insurance in California	Internet (www.oshpd.cahwnet. gov/hpp/ccmrp/ccmrp_summary.pdf)	In-hospital CABG mortality data from 1998
Canadian Health Care System	Provide consumers with hospital outcomes for various procedures that might indicate quality at a given hospital	Internet (www.hcsc.gc.ca/ohihbsi/available/conference/presentations/guerriere_e.pdf)	Risk-adjusted hospital mortality rates for Canadian hospitals
Cochrane Collaboration	All interested consumers	Internet (www.cochraneconsumer.com/)	Summarizes available published evidence about a wide variety of health care interventions, including cardiac surgery
Dartmouth University	Use large health care databases to inform the public of nationwide trends in health care delivery	Internet (www.dartmouthatlas.org/99US/chap_5_sec_12.php)	CABG mortality rates across the United States based primarily on claims databases
Health Care Choices	New York not-for-profit corporation dedicated to educating the public about the nation's health care system	Internet (www.healthcarechoices.org/cardiacsurgery.htm)	Select state CABG mortality rates; primitive attempt to collate all publicly available data about physicians; not nearly complete enough but evolving
HealthFinder	NIH government-sponsored information Web site about a wide variety of medical problems	Internet (www.healthfinder.gov/healthcare/)	General information in fairly specific detail about cardiac procedures (with drawings and diagrams)
Healthoutcomes.com	Patients requiring operation or catheter-based intervention nationwide	Internet (www.healthoutcomes.com)	In-hospital outcome for Medicare patients having selected procedures (e.g., CABG)
Hospital Quality Initiative sponsored by the Center for Medicare and	Provide consumers with a list of performance measures achieved by any hospital in the Medicare and	Internet (www.cms.hhs.gov/quality/hospital)	Hospital rankings for most of the NQF measures; searchable by hospital with comparisons within

Table 7–15.

Partial Listing of Publicly Available Information Sources (Continued)

Source	Targeted audience	Communication media	Information available
Medicaid Services (CMS)	Medicaid system		states and regions
The Leapfrog Group (consortium of Fortune 500 companies and health care insurers)	Provide consumers with list of hospitals that employ Leapfrog-defined quality measures	Internet (www.leapfroggroup.org/index.html)	List of hospitals that use quality measures; hospitals that use these quality measures will be financially rewarded by Leapfrog Group
Medscape, Inc.	Consumer information source for all types of medical conditions and for preventive medicine	Internet (www.medscape.com/px/urlinfo)	Comprehensive, searchable Web site with multiple links to external sites capable of finding comprehensive information about details of cardiac surgery
New Jersey State Department of Health	Health care consumers in the state of New Jersey	By mail (New Jersey Department of Health and Senior Services, Office of Research and Development, P.O. Box 360, Trenton, NJ 08625)	Risk-adjusted hospital mortality rates for CABG
New York State Department of Health	Patients having cardiac procedures in New York State	Internet (www.health. state.ny.us/nysdoh/consumer/heart/1996–98cabg.pdf)	Surgeon- and hospital-specific in-hospital mortality rates for CABG
Pennsylvania Health Care Cost Containment Council	Patients who require CABG in the state of Pennsylvania	Internet (www.phc4.org/reports/cardiaccare.htm)	Hospital- and surgeon-specific CABG mortality rates
Rand Corporation	Provide the public with summary data about health care outcomes for cardiac surgery	Internet (www.rand.org/publications/MR/MR1255/MR1255.app4.pdf)	Summary of publicly available CABG mortality rates with critical appraisal of methods and some estimation of appropriateness of care
Society of Thoracic Surgeons	Provide the public with results of cardiac surgery over as broad of a population as possible (including VA, Northern New England Consortium, and Great Britain)	Internet (www.ctsnet.org/section/outcomes/)	Mortality and other outcomes data for a variety of thoracic procedures; some of the data are presented as raw mortality data without risk adjustment; one of the only databases that includes noncardiac surgery

Table 7–15.

Partial Listing of Publicly Available Information Sources (Continued)

Source	Targeted audience	Communication media	Information available
Solucient Corp., Inc. (top 100 heart hospitals)	Provide the public with rather arbitrary rating of overall quality of cardiac care at hospitals	Internet (www.100tophospitals.com/Media/releases/nr010702_cardio.htm)	Rates all hospitals in the United States that do cardiac surgery and lists the top 100 heart hospitals
Washington Post Medical Web Site	Provider of medical information reports to consumers in North America	Internet (www.medifocus.com/)	General information about cardiac disease
WebMD, Inc.	Provide information to consumers and physicians about a broad spectrum of health care issues	Internet (http://my.webmd.com/content/dmk/dmk_article_53203)	Information about CABG and expected outcomes
Women's Heart Foundation	Provide health-related information for women	Internet (www.womensheartfoundation.org/content/HeartSurgery/state_report_cards_on_ohs.asp)	Links to Internet-available report cards on cardiac surgery

New Risk Stratification Methods: Machine Learning and Other Computer-Intensive Methods

The goal of risk adjustment is to account for the contribution of patient-related risk factors to the outcome of interest. This allows patient outcomes to be used as an indicator of the care rendered by physicians or administered by hospitals. This chapter has outlined some of the risk adjustment methods commonly used for this purpose, including use of multivariate analyses to predict patient outcomes based on patient risk factors. Inevitably, refinements and use of newer techniques will be brought to bear on the problem of risk adjustment. Statistical models are used often in cardiothoracic surgery to describe the relationship between a set of preexisting demographic features or conditions (referred to as *independent variables, input variables, predictor variables,* or *covariates*) and an operative outcome such as morbidity or mortality. Such models usually combine either the original or transformed predictor variables in a linear fashion, along with their associated coefficients, to estimate a continuous (multivariable linear regression) or a binary (multivariable logistic regression) response variable. The use of such linear parametric equations for this purpose is convenient, and the relevant models may be developed and run on any personal computer. In the case of binary logistic regression, the interpretation of coefficients is particularly appealing because they translate readily into odds ratios for each predictor variable.

Notwithstanding their widespread use and easy interpretability, there is no logical reason to believe that simple linear statistical models would be the best way to represent a complex biologic process such as cardiac surgery. Often, many of the assumptions necessary to use traditional regression models are neither fulfilled nor even tested.[44,261] Furthermore, there are significant constraints on the number of predictor variables used in standard logistic regression,[44] especially when the endpoint occurs infrequently, as in cardiac surgery mortality. This results in loss of both valuable information and accuracy.[262] Finally, despite the apparent mathematical precision with which the results of such analyses are often presented, the development and application of these models can be surprisingly subjective. It is a troubling fact that different groups of investigators using the same data likely will derive different statistical models and results. This occurs for a variety of reasons, including choice of statistical technique, variable selection, data management, and clinical interpretation.[98,103,262] Based on standard goodness-of-fit testing, the relationship between predictor and outcome variables often may be described equally well by any number of models, each of which employs a somewhat different subset of the overall available predictors.[98,262] Each of these statistically plausible models, composed of different combinations of variables and their coefficients, tells a somewhat different story of how nature works.[98,262]

With the quantum increases in computational power that have become available over the past decade, many of the practical constraints previously imposed on researchers are no longer relevant. This has led to an entirely new "culture" of modeling called *machine learning* or *algorithmic models*.[98,262] Rather than using classical statistical models with their specific assumptions and limitations, algorithmic modeling is focused more on predictive accuracy and less on trying to constrain nature to a particular parametric equation.

Examples of such algorithmic techniques include neural networks, decision and regression trees, and support-vector machines.[262] Because these models often do not provide an easily understood relationship between predictor and outcome variables, some have referred to them pejoratively as *black boxes*.[262] However, despite this criticism, such models in many instances may provide superior predictive accuracy, even though the mechanism behind the relationship may be less transparent. Furthermore, in machine learning techniques, the number of predictors that can enter the model is not limited as they are in standard regression.[262]

It was postulated over a decade ago that machine learning or artificial intelligence methods such as neural networks would provide the next major advance in predictive modeling for cardiac surgery.[263] However, three studies using relatively small numbers of patients did not reveal substantial differences between the results obtained from these techniques and those from standard logistic regression.[264–266] A much larger study was conducted by Lippmann and Shahian at the MIT Lincoln Laboratory using data from the 1993 STS Database of 80,606 patients who underwent CABG.[267] A two-layer neural network with a single hidden layer, random weight initialization, and backpropagation training did not provide any substantial improvement over standard logistic regression, and this neural network also underestimated risk in the highest-risk groups. Somewhat improved performance was obtained by combining the results of the neural network with those of logistic regression, which overestimated risk in the highest-risk groups, to produce an aggregate "committee classifier." However, the absolute improvement in ROC curve area was relatively small.

Although it was expected that neural networks would improve predictive accuracy because of their ability to use nonlinear parallel processing and to elicit complex patterns and relationships, the results thus far have been disappointing. However, this is more likely a reflection of the imperfect and limited information presented to these models, which is the same information used to develop and evaluate traditional statistical models. No modeling technique is better than the information presented to it for training, and neural networks are no exception. It may well be that if presented with a more comprehensive set of predictor variables, some of which are not even recognized today as being significant, these machine learning techniques ultimately may prove to be more accurate.

INFORMATION MANAGEMENT: ELECTRONIC MEDICAL RECORDS

As mentioned earlier, accurate patient data are essential in order to apply the principles of risk stratification and quality improvement outlined in this chapter. The quality and accuracy of administrative (or claims) databases have been questioned.[26,35,36,38,39,158] Therefore, risk-adjustment methodology has placed greater reliance on data extracted from the medical record. The American College of Surgeons was among the earliest advocates of the utility of medical records for quality review.[268] In the 1960s, Weed advocated standardization and computerization of medical records.[269] Little substantive progress had been made as far as the computerization of medical records until the need arose for management of large amounts of data of the sort required for risk adjustment and outcomes assessment. Medical records are an invaluable source of information about patient risk factors and outcomes. With these facts in mind, more and more pilot studies are being undertaken to computerize and standardize the medical record in a variety of clinical situations.[257,270–276] Iezzoni has pointed out the difficulties with computerized medical records and suggests that they may not adequately reflect the importance of chronic disability and decreased functional status.[277] Nevertheless, it is apparent that the need for data about large groups of patients exists, especially for managed-care and capitation initiatives. It is reasonable to expect that efforts to computerize medical records will expand. Applications of electronic medical records that may be available in the future for cardiothoracic surgeons include monitoring of patient outcomes,[270] supporting clinical decision making with real-time analysis of the electronic medical record[271,273,274] and real-time tracking of resource utilization using computerized hospital records.[257]

CONCLUSION

Risk stratification and outcomes analysis are here to stay. The methods of risk analysis are straightforward but are in their infantile stages. The goal of risk adjustment in the analysis of outcomes is to account for the contribution of patient-related risk factors so that patient outcomes can be used as an indicator of the quality of care rendered by physicians and hospitals. The future undoubtedly will see refinements in risk-adjustment methods and increasing use of these techniques at all levels of health care delivery, including the distribution of health care dollars. Thoracic surgeons have been at the forefront of these methodologies (sometimes unwillingly), but much work remains to be done in the area of education about the use of risk stratification and application of risk-adjusted outcomes analysis toward improving quality of care. We are obliged to have an understanding of the techniques, with the ultimate goal being to improve patient outcomes and maintain high professional quality.

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CHAPTER 8

Statistical Treatment of Surgical Outcome Data

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The results (outcome) of cardiac surgery can be measured in several ways. The type of variable used as the measure of a particular outcome determines the statistical methods that should be used for its analysis. For example, some administrative outcomes are captured by continuous variables, such as hospital charges (in dollars) or length of stay (in days). Other outcomes are collected as categorical variables, such as discharge destination (e.g., acute-care facility, specialized nursing facility, or home). Health-related quality of life is another kind of outcome, which is often measured by the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36),[1] the Sickness Impact Profile,[2] or disease-specific quality-of-life measures, and can be transferred to quality-adjusted life years (QALYs).[3] Economic endpoints have been used increasingly, such as cost-effective ratio.[4]

However, the major outcomes of interest to clinicians are described by variables that indicate the occurrence of (usually adverse) events, such as death, stroke, infection, or reoperation. Statistically, we must differentiate between two fundamentally different types of events based on their timing: *early (one-time) events* and *late (time-related) events*. Different types of analyses are used for these two types of events. We somewhat arbitrarily divide the areas of statistical inquiry into three major categories based on the goals of the analysis: s*ummarize*, *compare*, and *model*. This chapter will describe and illustrate the statistical methods used most often in each situation.

EVENT TYPES

Early, One-Time Events

In cardiac surgery, early events are those occurring within 30 days of surgery or before hospital discharge, whichever is later. By the time of the analysis, the early outcome of every patient presumably is known. Thus, every patient has a "yes" or "no" value for the event being studied, and an estimate of the probability of the event can be determined by the ratio of patients with the event to total patients, usually multiplied by 100 and expressed as a percentage.

Late, Time-Related Events

Late events are those that occur after discharge and after 30 days. The analysis of these events is complicated by two considerations. First, the time of occurrence must be taken into account because, for example, a death at 6 months will have a different effect on the analysis than a death at 6 years. Second, in the usual ongoing analysis, some patients will have experienced a late event, whereas others will not have experienced an event but are still alive and at risk for the event and may have it in the future. Their event status is termed *censored*, which means that it is known not to have occurred by the time of the latest follow-up. For example, a patient in the study who had surgery 5 years ago and is still alive has a time of death that is not yet known. But we have partial information about his or her survival time, namely, that it exceeds, or is *censored* at, 5 years. When dealing with censored data, it is necessary to use special statistical methods. It is not appropriate, for example, to summarize late mortality by a simple percentage such as the number of late deaths divided by the number of patients. Mortality varies over, and must be related to, postoperative time. The simple "late mortality" percentage in any series of patients will be 100% if the investigator waits long enough.

ANALYSIS GOALS

Statistics are derived for many purposes of varying complexity. The most common ones used for evaluating cardiac surgery are (1) to *summarize* the results from a single series, (2) to *compare* the results between two or more series or subgroups of the same series based on a single discriminating

variable or risk factor, and (3) to construct a multivariable *model* that provides the simultaneous effect of many risk factors.

Summarize

A study usually includes series of patients, and rather than enumerating a particular variable of interest for each individual, the first use of statistics is to summarize the variable for the entire group with a single, representative number (statistic). The *sample average,* or *mean value,* and the *median* (50th percentile) provide a measure of central tendency, and the *standard deviation,* or *interquartile range,* measures the dispersion of the individual values. A single-valued estimate such as this is called a *point estimate,* but acknowledging the imprecision of a single estimated value, a range of values also should be given. The *standard error* (SE) is a measure of the precision of an estimate, and a *confidence interval* (CI), a range of values for the estimate that is consistent with the observed data, can be constructed using its SE or in other, often better ways.

Compare

A study often consists of evaluating subgroups of patients who received different treatments. Thus, in addition to summarizing the outcomes from the subgroups, we are interested in comparing their summary statistics. To do so, we typically compute another statistic that combines data from both groups and that approximately follows some known statistical reference distribution, such as a *normal* (bell-shaped) or other (*chi-square*, *t*, etc.) distribution. We then see how extreme or improbable the value computed from our data would be in that reference distribution if there were in fact no difference between the two groups we are comparing. This probability is called the *p-value*, and when it is smaller than .05 (5%), the difference we have observed is said to be *statistically significant.* This value (.05) is a completely arbitrary number, although in practice it is applied almost universally.

A different paradigm for making comparisons and constructing CIs that has gained much prominence with the availability of computing power and specific software is the *bootstrapping* technique.[5] Instead of using an assumed statistical distribution, it generates many repeated random samples from the data themselves to produce this reference distribution.

Model: Multivariable Regression

Comparing the outcomes between two groups based on a single factor, as described in the preceding section, is called *univariable* (or sometimes *bivariable*) *analysis,* to distinguish it from *multivariable analysis,* in which several characteristics of each subgroup are considered simultaneously. Most clinical studies are based on observational data collected in the normal delivery of care, and the patient subgroups may differ with regard to several influential characteristics. A multiple regression analysis can determine the influence of the treatment under study on the outcome variable after simultaneously adjusting for these potential patient differences. The result is a statistical model that consists of the group of factors that significantly affects the outcome and which may or may not ultimately include the treatment being studied. Each factor is assigned a coefficient that indicates the amount of weight given to that factor in the model. The model hopefully gives us a fuller understanding of the interrelationship among the treatment being studied, the outcome variable, and other important risk factors. One can compute the expected outcome for any patient using these weights applied to the values of that patient's particular set of risk factors.

MATERIALS AND METHODS

Clinical Materials

To describe and illustrate the statistical methods used most frequently in the cardiac surgical literature, we will use a mature data set of isolated mitral valve replacements with Starr-Edwards heart valves. Dr. Albert Starr and his group at the Oregon Health Sciences University and Providence St. Vincent Medical Center in Portland, Oregon, implanted 1255 Starr-Edwards mitral valves in adult patients (age $>$ 20 years old) from 1965 to 1994.[6] A prospective lifetime follow-up service was implemented for every patient. The total follow-up through 2002 was 11,621 patient-years, with a maximum of 37 years. (*Note:* In all figures in this chapter, we have plotted the curves only up the time where more than 20 patients were at risk because the estimates beyond that time are imprecisely determined.) Table 8-1 contains a summary of selected variables used herein to illustrate the statistical methods (*Note:* More variables ordinarily would be considered in a real study than in this simple expository exercise.) Several valve models are represented in this group: "Current valve model" refers to the Model 6120 valve, which is still available; "Previous valve model" refers to all the other models, mostly cloth-covered, which have been discontinued. Patients with the current valve model have a higher mean age, more valve re-replacement surgery, and more concomitant coronary artery bypass grafting (CABG).

Statistical Software

Most of the statistical methods described in this chapter are available in the commonly used statistical software package. The statistical analyses and graphics in this chapter were done using SPSS 11.0 (SPSS, Inc., Chicago, IL), Stata 9.1 (Stata Corp., College Station, TX), S-PLUS 6.1 (Insightful Corp., Seattle, WA), and the open-source program R 2.2.0 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

The only functionality not found in standard statistical packages is cumulative incidence ("Actual") analysis. Cumulative incidence in the presence of competing events is

Table 8–1.

Mitral Valve Clinical Material and Univariate Comparison of Early Mortality by Valve Model

	Previous model	Current model
Clinical material		
Number of patients	543	712
Mean age ± S.D. (y)	53.0 ± 10.8	60.3 ± 11.3
Female (%)	60.6	61.8
Re-replacement (%)	4.6	6.9
Concomitant CABG (%)	10.1	20.2
Early mortality		
Number of deaths	25	58
Point estimate (%)	4.6	8.1
Standard error (%)	0.9	1.0
95% confidence interval (%)		
Normal approximation	(2.8, 6.4)	(6.4, 10.2)
Exact binomial	(3.0, 6.7)	(6.2, 10.4)
Comparison statistics	*p*-value (2-sided)	
Pearson chi-square	0.012	
With continuity correction	0.017	
Fisher's exact test	0.016	

implemented in the Stata ado file *stcompet*, available at http://econpapers.repec.org/software/bocbocode/s431301.htm (last access at 3/20/2006). Cumulative incidence is also available for S-PLUS and R with the package *cmprsk*, available at http://biowww.dfci.harvard.edu/~gray/ (last access at 3/20/2006). Finally, the NCSS Statistical Analysis System (NCSS, Kaysville, UT) does implement this function directly.

EARLY EVENTS

We will use operative deaths to illustrate the statistical treatment of early events.

Summarize

The *mean* (point estimate) operative mortality is computed as the number of operative deaths divided by the number of patients. Multiplying by 100 converts this decimal to a percentage (P). The SE of a proportion P based on N patients equals the square root of $P(1-P)/N$. Thus, as shown in Table 8-1, the percentages of patients with early death are 4.6% (SE = 0.9%) and 8.1% (SE = 1.0%) for the previous and current valve models, respectively. Table 8-1 also contains the 95% CI, computed by two popular methods. The first method is the simple (asymptotic) method based on the fact that the *binomial* distribution, which governs proportions, can be approximated by the normal (bell-shaped) distribution as the sample size increases.[7] This CI is computed easily as the point estimate plus and minus twice the SE. A second method uses the (exact) binomial distribution directly.[8] Although the "exact" method sounds like it obviously would be the most desirable, there are other methods that actually have better statistical properties.[9]

Compare

To demonstrate a *univariable* comparison, operative mortality between the two valve models was used. This does not seem very interesting clinically because valve model should have little to do with operative mortality; nevertheless, many valve comparison papers attempt to draw clinical conclusions from just such questionable comparisons. Comparing two proportions gives rise to a matrix with two rows and two columns called a *two-by-two contingency table.* Several

Table 8–2.

Univariate and Multivariable (Logistic Regression) Modeling of Early Mortality

	Univariate		Multivariate			
Variable	*p*-Value	Odds ratio	Coefficient	SE	*p*-Value	Odds ratio (95% CI)
Age	<0.001	1.05	0.045	0.012	<0.001	1.04 (1.02, 1.07)
Concomitant CABG	<0.001	3.78	1.016	0.251	<0.001	2.76 (1.69, 4.52)
Current valve model	0.014	1.84			(0.515)	
Female gender	0.361	0.81				
Re-replacement	0.314	1.52				

methods have been used to assess the significance of such tables.[10] The most common method for extracting a *p*-value from such a matrix is the *(Pearson) chi-square test.* This test has an alternative, more conservative form using a *continuity correction.* Validity of the chi-square test depends on having an adequate sample size (technically, each cell of the table should have an expected size of at least 5), and when this is not the case, then *Fisher's exact test* often is used. All three tests find that the current valve model has significantly higher operative mortality because the *p*-values are smaller than the required .05 (see Table 8-1).

Model

Logistic regression

The simple comparison above showed that operative mortality with the current valve model was significantly higher than with the previous valve model. But patients with the current valve model were older and had more concomitant CABG and re-replacement operations (see Table 8-1). Could the apparent difference in operative mortality between valve models be due to these patient characteristics? We explore this possibility using a multivariable analysis.

For binary (dichotomous) outcomes such as operative mortality, the most common method for developing a multivariable model is *logistic regression.*[11] In this model, operative death is the outcome (*dependent variable*), and patient characteristics, plus valve model, are the potential risk factors (*independent variables*). For technical reasons, logistic regression does not use the probability (*P*) of death directly as the dependent variable in the model. Instead, it uses the logarithm of the *odds*, $P/(1 - P)$, of death. To facilitate interpretation of a regression coefficient (*B*) from such a model, it is converted into an *odds ratio* (OR) by using the exponential function. Most statistical programs do this automatically, and the ORs are sometimes labeled exp(*B*). The 95% CI for the OR is computed as the exponential of the normal approximation CI (mean plus and minus twice the SE) for the coefficient itself.

A stepwise regression program begins with a univariable test of each potential risk factor,[11] using a model with a single variable to get the OR and *p*-value associated with that variable. If the OR is greater than 1, that variable is a risk factor (meaning that it adds to the risk). If the OR is less than 1, it is a protective factor. For the heart valve example (Table 8-2), age, concomitant CABG, and valve model are statistically significant (their *p*-values are less than .05). These variables, plus any others showing a trend toward association with operative mortality (usually $p < .2$), would be included in the next step of the stepwise logistic regression. In the final regression model, only age and concomitant CABG were still significant (see Table 8-2). After those effects are accounted for, the effect of valve model is no longer significant ($p = .515$). Thus, by this analysis, the apparent increase in operative mortality with the current valve model is an artifact; current valve model is a surrogate for older age and more bypass surgery, which themselves are primarily responsible for the increased mortality. There are no doubt other clinical variables to consider in this model, but since we used the data only for demonstration purposes, not all possible variables were included. As a rule of thumb, 10 events can support one risk factor considered in a risk model.[12] In our data set, there are 83 operative deaths, so we would have been justified in considering about 8 risk factors. In practice, researchers would reference the published models and study their own data to select more variables for consideration.

The OR of a binary variable such as concomitant CABG (2.76 in Table 8-2) means that the odds of mortality for a patient having concomitant CABG are 2.76 times that of a patient not undergoing concomitant CABG. This is the point estimate; the interval estimate (see Table 8-2) ranges from 1.69 to 4.52. When the lower limit of the 95% CI is greater than 1 (as it is for concomitant CABG, i.e., 1.69), the

OR will be significantly greater than 1. For a continuous variable such as age, the OR of 1.04 means that for each year of age, the odds of dying are multiplied by 1.04.

Evaluating the risk model

HOSMER-LEMESHOW STATISTIC AND ROC CURVE: The performance of a logistic regression risk model needs to be evaluated. Traditionally, the *discrimination* is evaluated by the *c-index*, which is the area under the *receiver operating characteristic* (ROC) curve,[13] and the *calibration* is evaluated by the *Hosmer-Lemeshow (H-L)* statistic.[14] Generally, a *c*-index between 0.7 and 0.8 is considered acceptable discrimination, and a *c*-index between 0.8 and 0.9 is considered excellent discrimination.[15] If the H-L statistic is significant ($p < .5$), it may be a sign of poor calibration. For our final model in Table 8-2, the H-L statistic is $p = .365$, and the *c*-index is 0.710 (95% CI 0.653–0.767). These values can be considered optimistic, however, because the data used to generate the model also were used to test it. Ideally, one would use a different data set, or *bootstrap* resamples of the original data, to test the model.[16]

CUSUM TECHNIQUES: *Cumulative sum* (Cusum) analysis methods also can be used to examine the fit of a model and to examine the influence of variables not in the model.[17] Figure 8-1 shows the cumulative sum of observed minus predicted deaths plotted as a function of predicted mortality. For a model whose observed mortality exactly fit the expected, the line would lie along the horizontal axis. Figure 8-1 shows that patients with predicted mortality of less than about 6% (the lowest point of the curve) have observed mortality of less than predicted and that patients with predicted mortality of greater than about 6% have observed mortality of greater than predicted. When the predicted mortality is greater than about 15%, the risk is underestimated by the model. As a measure of model calibration, the Cusum could be thought of as a continuous version of the H-L test, which is based on the differences in observed minus expected deaths in each of the 10 deciles of risk, shown by shaded vertical bars in Fig. 8-1. Adding more suitable risk factors to our simplistic model hopefully would improve it and make the Cusum curve closer to the horizontal axis throughout the range of observed mortality.

When the dependent (outcome) variable is dichotomous (death), it is difficult to appreciate its relationship to a continuous risk factor, e.g., age, graphically. The Cusum[18] can be used to overcome this difficulty by plotting the Cusum against age. If the continuous factor selected for the horizontal axis is surgery date, the Cusum can be used to detect a learning curve.[19]

O/E RATIO: The predicted (expected) mortality from logistic regression can be used to compare the risk-adjusted performance between groups of patients, e.g., to compare different surgical techniques or different providers. If the ratio of observed (*O*) to expected (*E*) mortality, the *O/E ratio*, is greater than 1, then there are more deaths than expected by the model, and if the *O*/*E* ratio is less than 1, there are fewer deaths than expected. The CI of the *O*/*E* ratio can be calculated by using a normal approximation method, which, as usual, gives a symmetric interval around the point estimate, or by using a logarithmic transformation, which provides a more appropriate asymmetric interval.[20,21] Table 8-3 contains these values for our heart valve example. The CIs for the *O*/*E* ratios for both groups include 1, which means that their risk-adjusted mortalities are not different from those predicted by the model.

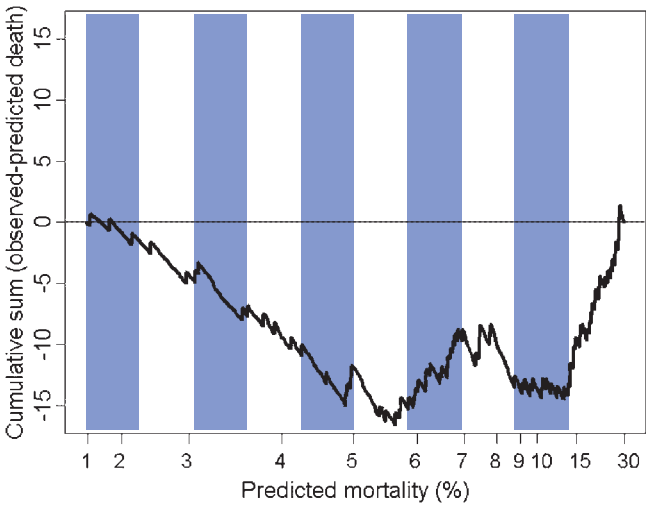

Figure 8-1. Cusum plot of operative death. Vertical axis is the cumulative sum of observed deaths minus predicted deaths by the logistic regression model in Table 8-3. Horizontal axis is scaled in number of patients (ordered by the predicted risk), so it is nonlinear in predicted risk of death. The gray/white bars each contain 10% of the patients.

TIME-RELATED EVENTS

We use both death and thromboembolism (TE) to illustrate methods for the analysis of time-related events.

Summarize

Survival curve

A single percentage is adequate to summarize mortality at a single point in time, such as the operative period (above). To express the pattern of late survival, however, requires a different estimate at virtually every postoperative time, i.e., a survivorship function, whose plot is the familiar survival curve. The most common way to estimate a survival curve is the *Kaplan-Meier* (KM) *method*,[22] called *nonparametric* or *distribution-free* because it does not presuppose any particular underlying statistical distribution. If all the patients in a given series were dead, the survival curve would be very simple to construct, as the percentage that had lived until each point in time. The KM method allows these percentages to

Table 8–3.

Ratio of Observed to Expected Early Mortality (*O*/*E* ratio)

Valve model	Previous	Current
Observed mortality	25/543 = 4.6%	58/712 = 8.1%
Predicted mortality	27.5/543 = 5.1%	55.5/712 = 7.8%
***O*/*E* ratio**	0.91	1.05
95% confidence interval		
Normal approximation	(0.55, 1.27)	(0.80, 1.29)
Log transformation	(0.61, 1.35)	(0.83, 1.32)

be estimated before all the patients have died in an ongoing series, using the assumption that patients who are still alive (whose survival time is censored) will have the same risk of future death as those who have already died. Figure 8-2 shows the KM survival curve for the mitral valve patients. The median survival time can be calculated as the survival time at which the survival curve crosses 0.5 (50%). The mean survival time can be calculated as the area under the completed survival curve. If the observation is not completed, the survival curve could be fitted with a suitable distribution, such as a Gompertz distribution, that could be extrapolated to estimate the uncompleted part.

Hazard function

Besides survival curves, there are several other statistical functions that can characterize the distribution of a time-related event. Survival curves are the easiest to interpret and apply to a patient or a population because they integrate the possibly varying risks over time and produce the probability of being alive at each point in time. The *hazard function* can be considered the fundamental building block of the other functions. The instantaneous hazard measures the risk of the event at each moment for an individual who is so far event-free. For technical reasons, the *instantaneous hazard* is difficult to measure directly, but its integral, the *cumulative hazard function,* is easy to produce either by taking the negative logarithm of the KM estimate[23] or by computing it directly using the *Nelson-Aalen method.*[24] This latter estimate can be derived from the two basic curves in the upper panel of Fig. 8-3. In the modern *counting process* formulation of survival analysis,[25,26] these two curves are the fundamental survival processes. The

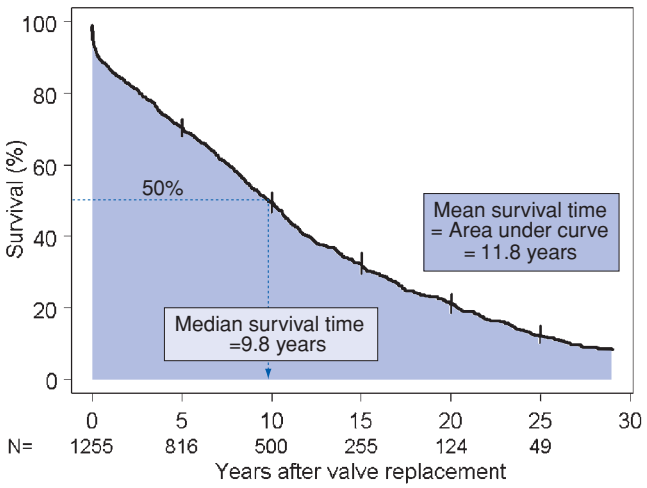

Figure 8-2. Kaplan-Meier survival curve. Vertical lines at 5-year intervals indicate the 95% CIs of the event-free percentages. Numbers below the horizontal axis indicate the number of patients remaining at risk.

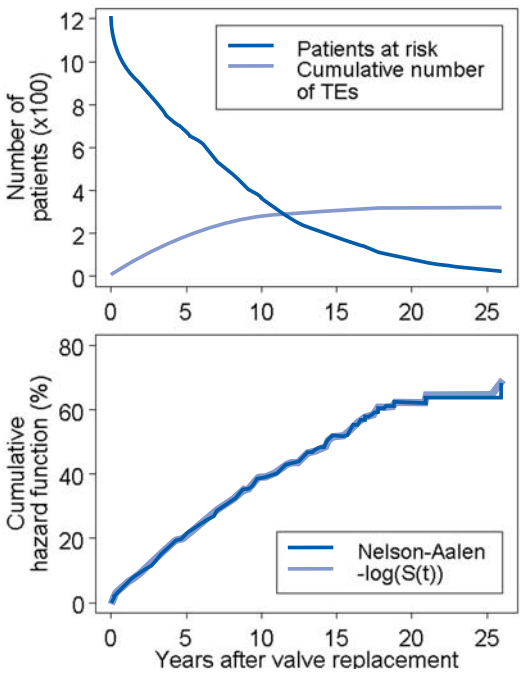

Figure 8-3. Cumulative hazard function of late thromboembolism (TE). The upper panel shows the two basic curves used to create the cumulative hazard function by the Nelson-Aalen method. The lower panel shows that the cumulative hazard function created by two methods are matched very well.

blue curve counts the number of patients still at risk at time t and is called the *at-risk process* $Y(t)$. The gray curve counts the number of events that have happened by time t and is called the *event counting process.* The gray curve rises 1 unit when each event occurs. The cumulative hazard function is similar to the gray curve, except that it rises $1/Y(t)$ each time an event occurs. The lower panel of Fig. 8-3 shows the cumulative hazard function estimated this way and also as the negative logarithm of the KM curve, $-\log[S(t)]$.

Linearized rate

One property of the cumulative hazard function is that it will be a straight line when the event hazard is constant. It is this property that gave rise to the name used in the cardiac literature to measure event rates that are presumed to be constant over time.

If the (instantaneous) hazard is a constant λ, then the cumulative hazard function $H(t)$ is a linear function of postoperative time t with slope λ: $H(t) = \lambda t$. In the cardiac literature, this constant risk parameter is called a *linearized rate.* For a given event in a series of patients, the maximum-likelihood estimate of this rate is the number of events (E) divided by the total follow-up time (T) in patient-years: E/T. Multiplying this by 100 converts it to "events per 100 patient-years," often abbreviated as *percent per patient-year* or *percent per year.* The SE is $\text{sqrt}(E)/T$, where sqrt = square root. Early events usually are not included in the calculation because the risk of most events is higher after operation, so the assumption of a constant hazard would not hold. Figure 8-4 shows that the cumulative hazard functions for two valve groups fit the constant hazard assumption fairly well.

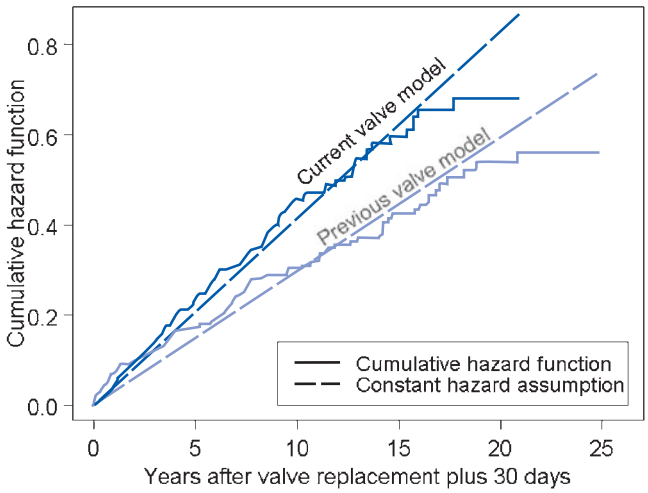

Figure 8-4. Cumulative hazard functions of late thromboembolism (TE) by valve model. The dashed lines depict the constant-hazard assumption. The total follow-up time is 4604 years and 4341 years for current and previous valve models, respectively.

Table 8-4 shows the linearized late TE rates by valve model based on the number of late TEs and late follow-up

Table 8–4.

Summary and Univariable Comparison of Linearized Rates of Late Thromboembolisms by Valve Model

Valve model	Previous	Current
Summarize		
Number of late thromboembolisms	129	191
Late follow-up (patient-years)	4,341	4,604
Linearized rate		
Point estimate (%/year)	2.97	4.15
Standard error (%/year)	0.26	0.29
95% confidence interval (%/year)		
Normal approximation	(2.47, 3.48)	(3.57, 4.72)
Cox's method	(2.49, 3.52)	(3.59, 4.77)
Likelihood ratio	(2.49, 3.50)	(3.58, 4.78)
Compare	*p*-Value (two-sided)	
Normal approximation	0.003	
Cox's method	0.003	
Likelihood ratio	0.003	

(patient-years beyond 30 days). The normal approximation (the mean plus and minus two times of SE) yields approximate 95% CIs. A preferred approximation is based on a suggestion owing to Cox,[27] which was recommended after a comparison of several methods.[28] In this method, the upper and lower 95% confidence limits are given by the 0.025 and 0.975 quantiles, respectively, of the chi-square distribution with $2E + 1$ degrees of freedom divided by $2T$. Another general technique for producing CI that usually is found to have very good properties is the *likelihood-ratio method*.[29] In our example, the CIs given by these three methods agree well, differing from each other only in the second decimal place. Note that the Cox limits and the likelihood-ratio limits are not symmetric around the point estimate, as the normal approximation limits are. (Cox's method also coincides with the probability interval produced by *Bayesian analysis*[30] using a noninformative prior.)

"Actual" analysis

The KM method is used often for events other than death. Figure 8-5 contains a KM TE-free curve for the mitral valve patients. When used for events such as TE that are not necessarily fatal, KM estimates the probability of being event-free given the unrealistic condition that death does not occur. But patients do, in fact, die before such an event has happened to them, so the KM event-free estimate is lower than the real ("actual") event-free percentage. Another method, called *cumulative incidence* in the statistical literature[31] and "*actual*" *analysis* in the cardiac literature, provides a mortality-adjusted event-free percentage.[32–35] The CI of the "actual" curve can be calculated by *Gray's method*.[36,37] The "actual" TE-free curve for this mitral valve series is much higher than the KM TE-free curve (see Fig. 8-5).

Besides providing an unrealistic estimate of the probability of TE, there is another, more technical problem with

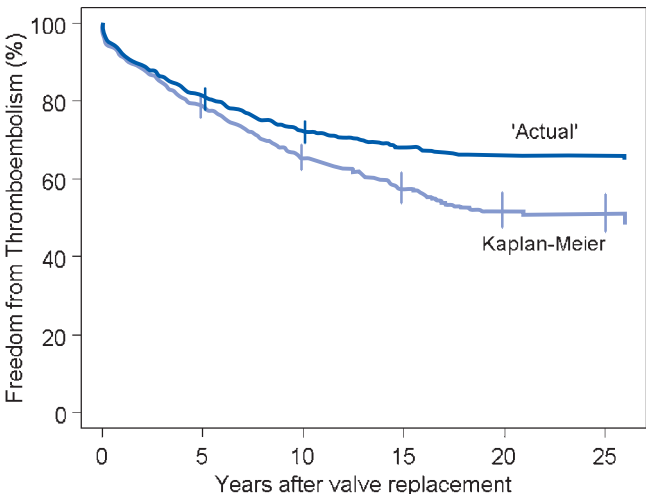

Figure 8-5. Thromboembolism-free curves constructed by the Kaplan-Meier method and the "actual" (one minus the cumulative incidence) method. Vertical lines at selected intervals indicate the 95% CIs of the event-free percentages.

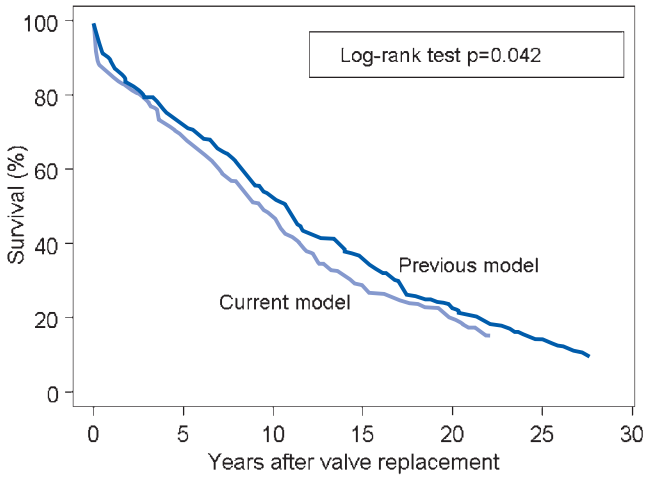

Figure 8-6. Survival by valve model. Overall survival significantly favors the previous valve model based on this univariate analysis that includes the higher mortality risk of the patients with the current valve model.

using the KM method in this situation. Its use is justified only if the risk of future TE for patients who died TE-free would have been the same as for those who actually had a TE. But this assumption cannot be proven from the data, so that the resulting TE estimate generally is regarded as statistically inappropriate.

Compare

The log-rank statistic is chosen most often to compare event-free curves.[38] Figure 8-6 shows the survival curves for the previous and current valve models, including all deaths, early and late. The previous model has significantly better survival according to this univariable comparison (log-rank test $p = .042$). But the difference mostly is due to early deaths; if we only consider late deaths, there is no significant difference between the two groups (log-rank test $p = .172$).

Comparing late TEs using linearized rates (see Fig. 8-4) also shows identical levels of statistical signficance using three different methods of testing: a normal-approximation method, a method recommended by Cox,[27] and a likelihood-ratio method[39] (see Table 8-4).

Model

Cox regression

Analogous to logistic regression, which provides multivariable analysis of the simple percentages associated with operative mortality, there is a widely used method for assessing multivariable influences on late survival: *Cox proportional hazards regression*.[12] This method assumes that the *hazard ratio* (HR) for all risk factors is constant over time. Table 8-5 shows the result of this regression as applied to the valve data for late survival. The univariable comparisons show three variables (i.e., age, concomitant CABG, and female gender)

Table 8–5.

Multivariable Modeling of Late Survival by Cox Regression and Gompertz Regression

	Univariate		Multivariate Cox regression		Multivariate Gompertz regression*	
Variable	***p*-Value**	**Hazard ratio**	***p*-Value**	**Hazard ratio (95% CI)**	***p*-Value**	**Hazard ratio (95% CI)**
Age	<0.001	1.04	<0.001	1.05 (1.04, 1.05)	<0.001	1.05 (1.04, 1.05)
Concomitant CABG	<0.001	1.65	0.052	1.23 (1.00, 1.50)	0.049	1.23 (1.00, 1.50)
Current valve model	<0.172	1.1	0.03	0.85 (0.73, 0.98)	0.03	0.85 (0.73, 0.98)
Female gender	0.005	0.82	0.005	0.81 (0.70, 0.94)	0.004	0.81 (0.70, 0.94)
Re-replacement	0.135	1.25	0.036	1.37 (1.02, 1.83)	0.036	1.37 (1.02, 1.83)

**Additional parameters in the Compertz regression: scale constant = −5.412, shape = 0.055.*

to be significant. The final Cox model includes all five variables, although current valve model and re-replacement were not significant by univariable analysis. This latter finding demonstrates that the practice of allowing only significant (by univariable analysis) variables to enter a stepwise regression may eliminate important risk factors.

The HRs for female and current valve model are less than 1; this means that they are protective factors rather than risk factors. For all the significant factors ($p < .05$) in the model, whether a risk or protective factor, the 95% CI does not include 1. *Note:* The univariable log-rank test shows no significant difference between the survival of previous and current valve models ($p = .172$); the multivariable Cox regression shows that current valve model has a lower risk of death (HR = 0.85, $p = .030$). Thus, the univariable log-rank test and multivariable Cox regression give opposite results. This tells us that if the groups are not compatible, as in this example, a multivariable comparison should be preferred. When the groups are compatible, such as in a randomized clinical trial, univariable comparisons may be appropriate.

Parametric regression

The preceding sections discussed nonparametric methods and nonparametric or semiparametric regression models to describe the survival data, such as KM curves and Cox regression, that do not make any assumptions about the underlying distribution of the survival or hazard functions. Another way

Table 8–6.

Formulas for the Hazard, Cumulative Hazard, and Survival Functions for Three Commonly Used Statistical Distributions

	Exponential	Weibull	Gompertz
h(t)	λ	$\alpha\lambda t^{\alpha-1}$	$\lambda e^{\alpha t}$
H(t)	λt	λt^{α}	$\lambda(e^{\alpha t-1})/\alpha$
S(t)	$\exp(-\lambda t)$	$\exp(-\lambda t^{\alpha})$	$\exp[-\lambda(1\text{-}e^{\alpha t})/\alpha]$
Mean time to event	$1/\lambda$	$\Gamma(1+1/\alpha)/\lambda^{1/\alpha}$	$\int S(t)dt$
Median time to event	$\log(2)/\lambda$	$[\log(2)/\lambda]^{1/\alpha}$	$\mathrm{Log}[1+\log(2)\alpha/\lambda]/\alpha$

Note: $\Gamma()$ is the gamma function. There is not a simple formula for the mean time to event of the Gompertz distribution.

to deal with survival data is to use a *parametric method.* A family of distributions is chosen, and the data are used to select the best-fitting member of that family by estimating the parameters that define the distribution. Three popular distributions used in cardiac surgery research are the *exponential, Weibull,* and *Gompertz distributions.* There are several functions that can be used to characterize a survival distribution. We have already discussed three of them: the *hazard function* $h(t)$, the *cumulative hazard function* $H(t)$, and the *survival function* $S(t)$. The hazard function can be considered the fundamental quantity from which the others are derived. It is the risk of the event at each instant of time t for a patient who is so far event-free. The cumulative hazard is the mathematical integral of the (instantaneous) hazard function. And the survival function is the exponential of the negative cumulative hazard: $S(t) = \exp[-H(t)]$.

Figure 8-7 shows typical plots of these three functions for the *exponential, Weibull,* and *Gompertz distributions,* with a selection of values for their parameters. The upper row of plots contains the hazard functions, the second row is the cumulative hazard functions, and the third row is the survival functions. Table 8-6 contains the formulas used for these functions. The exponential is the simplest lifetime distribution, having only a single parameter λ called the *scale parameter,* which is the (constant) hazard ("linearized") rate. The Weibull distribution is a natural generalization of the exponential distribution that adds a second parameter α called the *shape parameter* to accommodate an increasing ($\alpha > 1$) or decreasing ($\alpha < 1$) risk. The cumulative hazard reduces to the exponential distribution (constant risk) when $\alpha = 1$. The Weibull distribution is used commonly for time to failure and is employed in the cardiac literature to model structural deterioration of prosthetic heart valves. A Gompertz distribution[40] has a scale parameter λ and a shape parameter α. Its hazard function is an exponential function of time. The Gompertz distribution is widely used to model survival, especially in older age groups. Figure 8-8 uses the late death information from the heart valve data to show the fits derived from these 3 distributions. The data fits the Gompertz distribution very well.

Some of the advantages of the parametric method (over nonparametric or semiparametric methods) are

- The hazard function itself can be portrayed easily, which otherwise requires many data points and a complicated smoothing technique.

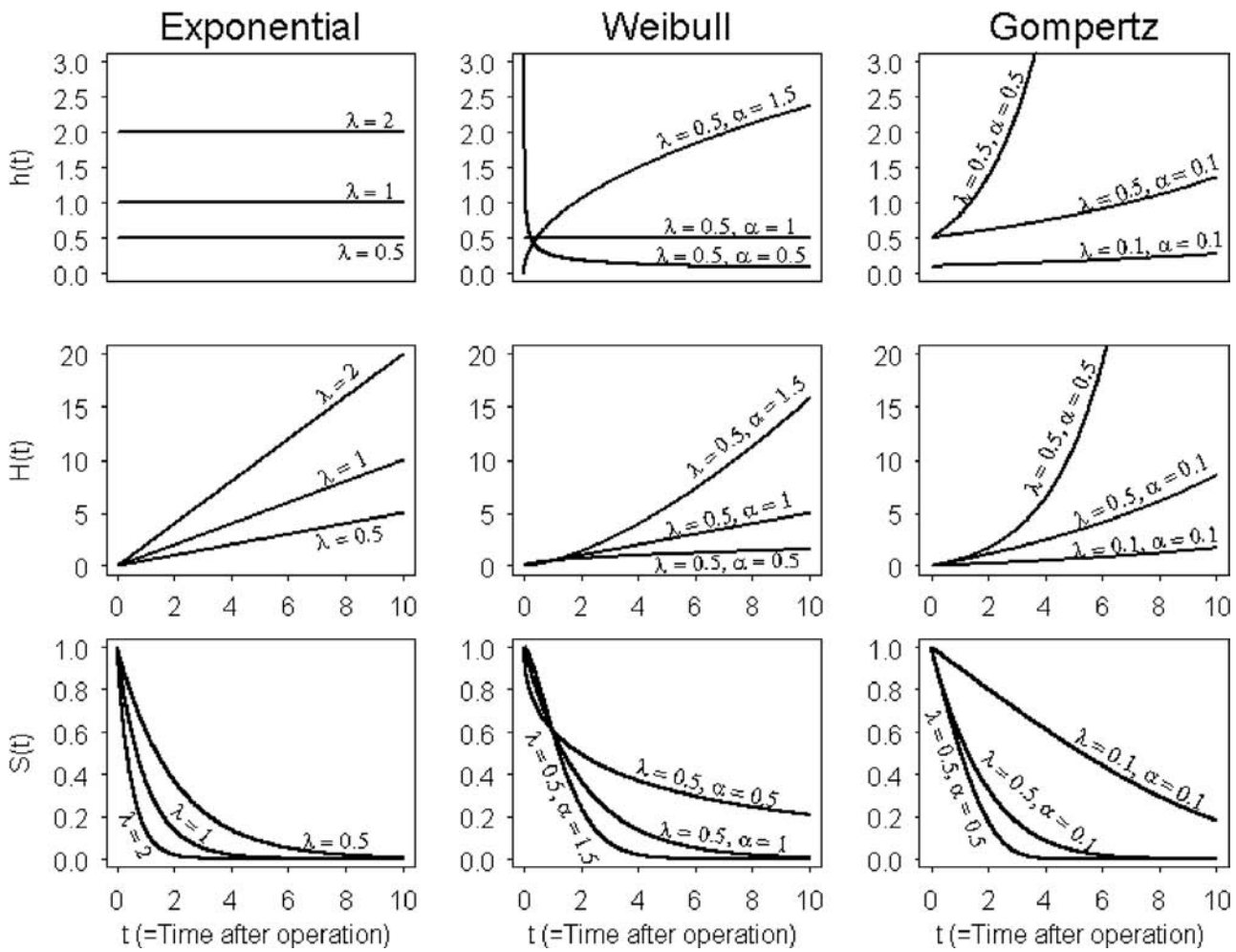

Figure 8-7. Hazard (*top row*), cumulative hazard (*middle row*), and survival function (*bottom row*) for the exponential, Weibull, and Gompertz distributions with different parameters.

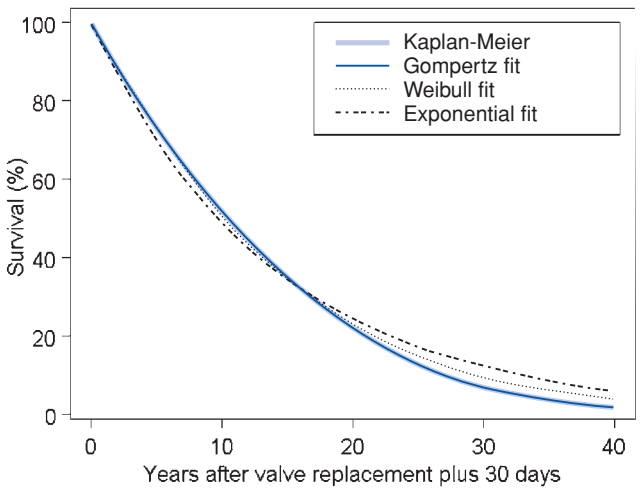

Figure 8-8. Three distributions used to fit late death. The best fit is the Gompertz model.

- The survival curve can be extrapolated into the future (beyond the maximum follow-up time).
- The median time to failure can be given, which otherwise cannot be estimated until the event-free curve reaches 50%.
- The mean time to failure can be given, which otherwise cannot be estimated until the event-free curve reaches 0%.
- The resulting curves may reproduce the underlying mortality process faithfully, which is no doubt smooth over time, unlike the random roughness of the original observed data points, which results in graphic peculiarities.
- The entire survival experience can be summarized with a small number of parameters.

A final and important advantage of fitting parametric models is that there may be a theoretical basis for the model that helps us understand the physical process rather than just describe it. The Weibull distribution has such a theoretical interpretation as the time to failure of a physical system that depends on very many parts (sites) for integrity. Thus, the Weibull distribution is a commonly used distribution for failure analysis and is employed in the cardiac literature to model the structural deterioration of prosthetic heart valves. The Gompertz distribution is used widely to model for human mortality, especially for older populations, based on the assumption that the "average exhaustion of a man's power to avoid death [is] such that at the end of equal infinitely small intervals of time he [loses] equal portions of his remaining power to oppose destruction which he had at the commencement of these intervals."[41]

These parametric distributions also can be used as the basis for regression models; usually the scale parameter is expanded to contain the risk factors. For the mitral valve data, a Gompertz regression produced hazard ratios identical to those of the Cox regression (see Table 8-5).

CONCLUSIONS

1. Different analytical methods must be used for outcome events after surgery depending on whether they are one-time (operative) or time-related (late) events.
2. Factors found significant on univariate analysis often are overturned by multivariate analysis because they are surrogates for other more clinically fundamental variables. This was the case with valve model in both the early and overall analysis of mortality. The converse also can happen; re-replacement was not significant for overall mortality by itself but became so in concert with other risk factors. Multivariable analysis, adjusting with the other risk factor, always should be the first choice.
3. The hazard and cumulative hazard functions measure the instantaneous and cumulative risks of an event, respectively. The cumulative hazard is easier to obtain. The survival curve converts their risks into probabilities of experiencing the events.
4. Linearized rates provide a convenient single-parameter summary of late-event rates but should not be used unless the hazard function is approximately constant.
5. Kaplan-Meier analysis estimates survival probabilities as a function of time after surgery. When used for events that are not necessarily fatal, KM estimates probabilities as if death were eliminated, whereas "actual" analysis gives a true mortality-adjusted estimate of the event probabilities.
6. Parametric regression is a useful tool to analyze long-term outcome. Usually, the Gompertz distribution is good for survival, and the Weibull distribution fits tissue and structural valve deterioration very well.

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PART

II

Perioperative/ Intraoperative Care

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CHAPTER 9

Preoperative Evaluation for Cardiac Surgery

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Improved operative outcomes and advances in surgical techniques have resulted in longer life expectancy for cardiac surgery patients. However, the higher risk profile of patients, including persons who are older, sicker, have multiple comorbidities, and have either failed or do not qualify for advanced percutaneous therapies, has led to increased morbidity and hospital length of stay.[1–3] Furthermore, advances in cardiac surgery using novel approaches (Table 9-1) such as robotically assisted surgery, off-pump coronary artery bypass grafting (OP-CABG), transmyocardial laser revascularization, and minimally invasive valve surgery with robotics extend the operative options for patients.[2–6] As a result, preoperative risk assessment is critical to ensuring safe performance of cardiac surgical procedures. While coronary artery bypass grafting (CABG) is cost-effective and moreover has known benefit in appropriately selected patients such as those with left main disease, three-vessel disease, and severe angina, preoperative risk assessment is nonetheless of critical importance in minimizing perioperative and long-term morbidity and mortality. Additionally, preoperative evaluation can influence hospital quality improvement, hospital/surgeon report cards, and reimbursement. Thus accurate preoperative appraisal can translate into the implementation of proper quality surveillance mechanisms and improve risk-adjusted mortality for CABG to less than 2% for the general population and 3 to 4% for the Medicare population.[7–10] This chapter reviews the information essential to the cardiologist and surgeon in the evaluation and management of patients prior to cardiac surgery.

THE PHYSICAL EXAMINATION AND LABORATORY EVALUATION

The preoperative physical examination is a critical part of a patient's evaluation for CABG because the findings can greatly influence perioperative management. During the physical examination, particular attention should be paid to the patient's risk for endocarditis, the presence of aortic insufficiency, the presence of vascular disease, and the neurologic status. Identification of an aortic regurgitation murmur is important because during cardiopulmonary bypass, regurgitation can worsen, and acute left ventricular distension may develop.

The physical examination also helps to identify potential contraindications to the use of an intra-aortic balloon pump. Also, attention should be paid to the patency of the venous system in the lower extremities because extensive varicosities may necessitate the use of arm veins as conduits; if the latter are needed, then avoidance of intravenous line placement in the arm from which veins will be harvested is necessary. In the event of reoperation, noninvasive imaging of the lower extremities may be desirable, as well as imaging of the left internal mammary artery during cardiac catheterization, to assess patency of potential conduits.

Carotid ultrasound should be performed on all patients to assess the need for timing of carotid revascularization, particularly in individuals with a history of prior stroke, severe bilateral stenoses, or contralateral occlusion and in patients with a history of neurologic symptoms.[11,12]

In women who have had a left radical mastectomy, patency of the left internal mammary artery can be compromised because of alterations in thoracic blood flow. As a result, the left anterior descending artery then becomes ineffective as a conduit.[13]

Basic laboratory testing prior to cardiac surgery is outlined in Table 9-2.

SPECIAL LABORATORY CONSIDERATIONS

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT), or "white clot syndrome," is an immune-mediated, potentially life-threatening thrombotic complication of heparin therapy that

Table 9–1.

Novel Cardiac Surgical Techniques

Technique	Reason/advantage	Mortality (%)	Preoperative considerations
MIDA-AVR	Reduce chest trauma, minimize blood loss, accelerate patient recovery	1.6–2.0*	Body habitus, elderly patients, CXR, defibrillator pads, TEE guidance
MIDA-MVR	Reduce chest trauma, minimize blood loss, accelerate patient recovery	0.8–1.1*	Same as above
MIDA-CABG	Reduce chest trauma, accelerate patient recovery	1.0†	Same as above
Robotic-assisted CABG	Can perform on beating heart	Experimental	–
Off-pump CABG	Elderly patients, COPD, reduces oxidative stress and inflammation, comorbidities, less need for blood transfusions, shorter hospital stay, decrease in deep sternal wound infections, less cerebral dysfunction, less renal dysfunction	1.3‡	Same as above, fewer diseased vessels, absence of LM disease
TMR	Refractory angina despite maximal medical therapy ± revascularization procedures	1–5§	Anginal class III/IV, left ventricular free wall ischemia

MIDA = minimally invasive direct access; AVR = aortic valve replacement; MVR = mitral valve replacement; TMR = transmyocardial laser revascularization.
**Byrne JG, et al: Minimally invasive direct access heart surgery.* J Cardiovasc Surg (Torino) *2000; 15:21.*
†*Cremer JT, et al: Minimally invasive coronary artery revascularization on the beating heart.* Ann Thorac Surg *2000; 69:1787.*
‡*Cartier R, et al: Systematic off-pump coronary artery revascularization in multivessel disease.* J Thorac Cardiovasc Surg *2000; 119:221.*
§*Nathan M, Aranki S: Transmyocardial laser revascularization. Review.* Curr Opin Cardiol *2001; 16:310.*
Source: Adapted from refs. 5, 96, 104, 162, and 164–166.

occurs in 3 to 5% of individuals approximately 5 to 14 days after heparin exposure.[14,15] HIT should be suspected in any patient who experiences a 50% or greater decrease in platelet count from baseline or 30% or greater decrease in platelet count and associated thrombotic complication while on unfractionated heparin for at least 5 days. HIT can occur earlier in patients who are within 3 months of previous exposure to heparin. When testing for platelet factor 4 (PF4)/heparin antibodies in a patient with suspected HIT, it is recommended that the test be repeated on several successive days.[16] Thrombocytopenia usually resolves within 1 week of heparin discontinuation, but thrombotic tendency can persist for up to 1 month. Although HIT can occur with the use of low-molecular-weight heparin (LMWH), the incidence and development of thrombosis are much less frequent.[17] One study demonstrated a higher incidence of saphenous vein graft occlusion among post-CABG patients with HIT compared with non-HIT patients within 2 weeks of surgery (68% versus 20%, $p < .001$). However, the incidence of internal mammary artery graft occlusion was not significantly different between the two groups [HIT patients = 6% (1 patient) and non-HIT patients = 11% (2 patients)].[18]

Antibodies to heparin/PF4 cause platelet activation and aggregation, as well as thrombin formation, resulting most commonly in deep venous thrombosis, pulmonary embolism, or cerebral sinus thrombosis.[19] Following CABG, HIT may present as graft occlusion, left atrial thrombus, valvular thrombosis, or pulmonary embolism.[20] On average, 25 to 50% of cardiopulmonary bypass patients who receive heparin acquire HIT immunoglobulin G (IgG), but only approximately 7% develop HIT.[21,22]

Many surgeons still prefer to use unfractionated heparin (UFH) during cardiopulmonary bypass because of familiarity, the need to employ specialized monitoring when using alternative agents, and the lack of antidotes for alternative agents. Besides the use of lepirudin, an irreversible antithrombin, or argatroban, a reversible direct thrombin inhibitor, reduction of thrombosis during cardiopulmonary bypass in patients with known HIT can be achieved by limiting UFH exposure time or by delaying surgery until 3 months after the patient's UFH exposure.[23] Otherwise, after receiving UFH, platelet counts should be monitored every 3 days from day 3 to day 14 of heparin exposure. In patients with HIT, warfarin initiation should be done in the presence

Table 9–2.

Preoperative Tests for Cardiac Surgery

Preoperative laboratory test	Abnormal finding	Comment
Complete blood count	1. Anemia, especially Hct <35%	1. Anticipate that hemodilution will occur on cardiopulmonary bypass and blood loss will occur intraoperatively. In stable patients, preoperative iron supplementation (weeks) or erythropoietin therapy (days) should be considered. Patients with unstable angina, congestive heart failure, aortic stenosis, and left main coronary artery disease should be advised against autologous donation of blood in the preoperative period.
	2. WBC > 10,000	2. Search for possible infection.
Coagulation screen	1. Prolonged bleeding time 2. Elevated PT and/or PTT 3. Thrombocytopenia	All these laboratory abnormalities suggest that the patient is at risk for bleeding postoperatively and may have excessive chest tube drainage. Corrective measures (e.g., vitamin K, fresh frozen plasma, platelet transfusions) should be considered preoperatively, and surgery may need to be postponed. Hematological consultation may be required if an inherited defect in coagulation (e.g., von Willebrand factor deficiency) is suspected.
Chemistry profile	1. Elevated BUN/creatinine	1. Abnormal renal function that may worsen in the perioperative period (caused by nonpulsatile flow on cardiopulmonary bypass and potential low flow postoperatively); may necessitate temporary or even permanent hemodialysis.
	2. Potassium <4.0 mEq/L and/or magnesium <2.0 mEq/L	2. Electrolyte deficits may place the patient at risk of arrhythmias perioperatively and should be corrected before induction of anesthesia.
	3. Abnormal liver function tests	3. Patient may clear anesthetic agents as well as other cardioactive drugs more slowly. Low albumin level may indicate a state of relative malnutrition that may need to be corrected with nutritional support perioperatively.
	4. Fasting plasma glucose ≥ 126 mg/dL	4. Patients with previously diagnosed or undiagnosed diabetes are at increased risk for postoperative mortality.
Stool hematest	Positive for occult blood	Because heparinization will take place while on the cardiopulmonary bypass apparatus, the patient may be at risk for GI bleeding perioperatively. The source of GI heme loss should be investigated preoperatively if clinical circumstances permit. The potential for bleeding in the future may influence the choice of prosthetic valve inserted.
Pulmonary function	Reduced VC or prolonged FEV_1	Anticipate longer than usual process of weaning from ventilator postoperatively if FEV_1 <65% of VC or FEV_1 <1.5–2.0 L. Obtain baseline arterial blood gas analysis on room air to help guide respiratory management postoperatively.
Thyroid function	These tests are not ordered routinely but should be performed in cases of suspected hypothyroidism or hyperthyroidism, known thyroid dysfunction during replacement therapy, and atrial fibrillation in patients who have not undergone evaluation of thyroid function	Hypothyroid patients require prolonged period of ventilatory support postoperatively because of slower clearance of anesthetic agents. Hyperthyroid patients have a hypermetabolic state that places them at increased risk of myocardial ischemia, vasomotor instability, and poorly controlled ventricular rate in atrial fibrillation.

(continued)

Table 9–2.

Preoperative Tests for Cardiac Surgery *(continued)*

Preoperative laboratory test	Abnormal finding	Comment
PF4/heparin antibody screen.	Positive	In patients exposed to UFH/LMWH within 3 months prior to surgery.
Echocardiography	1. Decreased LV ejection fraction	1. Patients with decreased LV function are at higher perioperative risk for surgery. Selected patients should undergo viability assessment.
	2. Decreased RV function	2. RV dysfunction increases perioperative risk and identification may lead to preoperative assessment of reversibility of pulmonary hypertension.
	3. Aortic stenosis	3. Mild to moderate aortic stenosis (gradient <25 mm Hg) may be treated by prophylactic valve replacement in selected low-risk patients.
	4. Aortic insufficiency	4. Ventricular dimension will help guide decisions to perform valve replacement in addition to revascularization in patients with combined aortic regurgitation and coronary disease.
	5. Mitral insufficiency	5. Moderate or severe mitral regurgitation may warrant valve exploration in patients undergoing coronary revascularization.
	6. LV aneurysm	6. May alert surgeons to the need of aneurysmectomy in selected patients.
	7. Ventricular septal defect	7. Identification will suggest the need for early surgical intervention.
Cardiac catheterization	1. Elevated LV end-diastolic pressure and pulmonary capillary wedge pressure	1. May remain elevated in the early postoperative period and indicate a need for careful attention to maintenance of adequate preload postoperatively.
	2. Elevated right atrial pressure	2. May reflect tricuspid regurgitation or RV dysfunction from prior infarction. Such patients require vigorous volume expansion postoperatively to maintain adequate cardiac output.
	3. Elevated pulmonary artery pressure (and pulmonary vascular resistance)	3. Fixed pulmonary vascular resistance should be suspected when the pulmonary artery diastolic pressure exceeds the mean pulmonary capillary wedge pressure. Vigorous oxygenation and pharmacological support with a pulmonary vasodilator (isoproterenol, prostaglandin E_1) are important in such cases. Patients with a pulmonary artery diastolic pressure equal to the pulmonary capillary wedge pressure usually have more rapid resolution of pulmonary hypertension postoperatively.
	4. LV mural thrombus	4. Increased risk of stroke perioperatively.
	5. Status of internal mammary arteries	5. Highly desirable arterial conduits for planned revascularization surgery. Particular care required during reoperation if patent internal mammary artery bypass is in place from previous surgery.
	6. Status of saphenous vein grafts	6. "Pseudoextravasation" of dye outside the lumen in a patent graft with slow flow probably represents thrombus-filled atherosclerotic aneurysm of the graft.

BUN = blood urea nitrogen; FEV_1 = volume of air expired at 1 second; GI = gastrointestinal; Hct = hematocrit; LMWH; = low-molecular-weight heparin; LV = left ventricular; PT = prothrombin time; PTT = partial thromboplastin time; RV = right ventricular; UFH = unfractionated heparin; VC = vital capacity; WBC = white blood cell count.

Source: Reproduced with permission from Adams DH, Antman EM: Medical management of the patient undergoing cardiac surgery, in Braunwald E, Zipes D, Libby P (eds): *Heart Disease.* Philadelphia, WB Saunders, 2001; p 2059.

of lepirudin or argatroban owing to warfarin's association with limb gangrene when used as the sole agent.[24]

Hypercoagulable Disorders

Management of patients with hypercoagulable syndromes can be especially challenging in the setting of cardiac surgery, where the need to control bleeding postoperatively is crucial in preventing potentially life-threatening complications such as pericardial tamponade. Common (e.g., factor V_{Leiden} and *G20210A* prothrombin gene) and relatively uncommon (e.g., antithrombin deficiency and protein C and protein S deficiency) causes of thrombosis have different risk associations. For example, the relative risk of venous thrombosis in the Caucasian population can range from 2.5 for the prothrombin gene mutation to 25 in the presence of antithrombin deficiency.[25] Furthermore, approximately 50% of cases of venous thrombosis associated with these hereditary disorders are provoked by known risk factors such as surgery. Therefore, aggressive prophylaxis with subcutaneous UFH or LMWH is warranted prior to surgery for patients who are not taking long-term anticoagulation.[26] In contrast, for those on long-term anticoagulation, the decision to continue treatment for thrombosis in the cardiac surgery setting should be individualized. In general, warfarin therapy can be switched to LMWH 3 to 5 days prior to cardiac surgery. Anticoagulation using UFH as a bridge should be resumed as soon as the bleeding risks associated with cardiac surgery have been stabilized, usually within 2 to 3 days postoperatively. The patients at highest risk for venous thrombosis are those within 3 months of an episode of thrombosis and those with conditions that predispose to the highest risk of thrombosis such as antithrombin deficiency.[25]

Patients with antiphospholipid antibody syndrome (e.g., lupus anticoagulant/anticardiolipin antibodies, history of arterial or venous thrombosis, and/or recurrent fetal loss) deserve special mention because this syndrome can be associated with valvular heart disease (32 to 36% requiring replacement).[27–29] Perioperative management, including the choice of prosthetic valve, is challenging and requires a multidisciplinary approach owing to the risk of thrombophilia, abnormal prolongation in clotting times, and the presence of thrombocytopenia. During cardiopulmonary bypass, anticoagulation monitoring is difficult using standard means. Therefore, preoperative in vitro testing to identify the most reliable assay for heparin monitoring during cardiopulmonary bypass may be necessary.[30] Potential heparin assays include protamine titration, kaolin, and the anti-Xa methods that measure heparin's in vitro effects differently.[29]

Multiple Anticoagulants in the Setting of Failed Percutaneous Intervention

Advancements in cardiology have resulted in the almost standard use of glycoprotein IIb/IIIa inhibitors, aspirin, and intravenous (IV) heparin or LMWH in patients with non–ST- and ST-segment elevation myocardial infarction (MI) who undergo early percutaneous intervention (PCI).[31,32] However, prospective, randomized evidence involving patients who have received multiple anticoagulants for PCI who subsequently required urgent or semiurgent cardiac surgery is lacking. Clinical decisions therefore should be based on known bleeding risks/pharmacology associated with individual agents, available subgroup analyses, and surgical urgency.

Although some studies found that the use of aspirin preoperatively increased the need for transfusions,[33,34] others showed that the use of aspirin preoperatively is associated with significantly lower postoperative mortality compared with no aspirin use in the 5 days preceding surgery [odds ratio (OR) = 0.34, 95% confidence interval (CI) 0.15–0.75].[35] Presently, many patients are safely given aspirin in the perioperative period. However, while the use of UFH and aspirin has been the standard of care for acute coronary syndromes (ACS), LMWH has shown superior clinical benefit for ACS.[36,37] Data regarding the preoperative use of enoxaparin compared with UFH are sparse and mixed. Some data demonstrate that the rates of rehospitalization for hemorrhage are higher (7.9% versus 3.7%) for UFH,[38] while other research indicates no increase in risk for postoperative bleeding or blood transfusions.[39] Additional research is needed in this area particularly because only a small number of ACS patients proceed to CABG.

In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, patients who received the glycoprotein IIb/IIIa inhibitor eptifibatide within 30 days of CABG did not experience higher rates of bleeding, probably owing to the short half-life of the drug.[31] Similar findings were noted in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM-PLUS) study.[40] By contrast, retrospective data from the Mayo Clinic show that patients who received abciximab and needed urgent/emergency CABG within 48 hours after PCI tended to have higher rates of major bleeding (90% versus 77%, $p = .68$) and more frequently received red blood cell (RBC) and platelet transfusions than those who were not treated with abciximab.[41] Despite the latter, there were no observed differences in the rates of MI, reoperation for bleeding, mediastinal reexploration, or length of hospitalization between the two groups.

However, the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial showed that the antiplatelet agent clopidogrel was beneficial in patients with ACS undergoing PCI but was associated with a concomitant increased risk of major bleeding.[42] Although clopidogrel can decrease mortality, it potentially may pose serious problems with major perioperative bleeding. In an analysis of patients in the CURE trial who underwent CABG during the initial hospitalization (average time to procedure 12 days), there was a 19% reduction in the primary outcome of MI, stroke, or cardiovascular death among the clopidogrel-treated patients

compared with the placebo group.[43] Furthermore, the incidences of major and life-threatening bleeding were 27% and 24% higher in the clopidogrel-treated patients, but these rates were not statistically significant. Further comparison of the time to CABG after clopidogrel discontinuation (i.e., ≤5 or ≥5 days) revealed a nonsignificant bleeding excess in patients whose clopidogrel was stopped within 5 days of CABG but no excess bleeding among patients who had discontinued the medication more than 5 days prior to CABG.

By contrast, other data found that among in-hospital referrals for CABG, clopidogrel was associated with higher 48-hour in-hospital mortality, reoperation for bleeding, intubation time, transfusions, and hospital stay.[44,45] Thus data suggest that it is probably best for patients to wait at least 5 days after discontinuing these agents before undergoing cardiac surgery in order to minimize bleeding complications. Nonetheless, emerging data suggest that among patients who require surgery fewer than 5 days after exposure to clopidogrel, aprotinin, a serine protease inhibitor that has multiple effects including platelet aggregation, reduces the rate of postoperative bleeding and blood transfusions.[46,47]

Another area of interest relates to OP-CABG, where hemorrhagic events occur at a lesser frequency than in traditional CABG using cardiopulmonary bypass (CABG-CPB). Research by Kapetanakis and colleagues suggests that clopidogrel administration prior to surgery increases the need for hemostatic reoperation (OR = 5.1, 95% CI 2.47–10.47) and blood transfusions (OR = 2.6, 95% CI 1.94–3.90), thereby possibly extinguishing the advantage of OP-CABG.[48] Still, some argue that this tradeoff between the anti-ischemic benefit of clopidogrel and perioperative bleeding can be balanced by delaying surgery after discontinuing the drug.[49] One exception may be when clopidogrel is being taken in the context of new stent implantation for coronary artery restenosis. In this instance, the risk of stent thrombosis may outweigh the risk of bleeding complications.

Limited data are available regarding the use of thrombolytic agents prior to CABG. However, in a subgroup analysis of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) trial, patients who underwent PCI or CABG after receiving fibrinolytics had a lower rate (0%) of intracranial hemorrhage than those treated with repeat thrombolysis (1.3%) or medical therapy (0.5%; $p = .046$).[50] By contrast, in the Assessment of the Safety of a New Thrombolytic (ASSENT 2) study, no difference in the rate of intracranial hemorrhage was observed among the revascularization, rethrombolysis, and conservative treatment groups.[50] Moreover, an evaluation of the long-term survival in patients who received thrombolysis compared with those who were not given thrombolytic therapy within 7 days of CABG showed no difference in early outcome and increased survival [hazard ratio (HR) = 0.54, 95% CI 0.36–0.81) at 5 years of follow-up, thereby reinforcing the long-term benefit of CABG in decreasing MI and mortality.[51]

PREOPERATIVE ESTIMATION OF MORBIDITY AND MORTALITY RISK: SCORING SYSTEMS

Preoperative risk assessment has important implications for patient well-being, containment of hospital costs, and provision of objective risk stratification data aimed at assessing an accurate potential risk:benefit ratio. Several scoring systems have been developed to assess perioperative risk, particularly in the setting of isolated CABG. The major risk factors for adverse outcome during CABG include advanced age, emergency surgery, history of prior CABG, dialysis dependency, and a creatinine concentration of 2 mg/dL or higher.

Owing to the changing profile of patients undergoing cardiac surgery, accurate preoperative risk stratification has become increasingly difficult. Factors affecting outcome data include surgery type (Table 9-3), follow-up time, medical therapy after hospitalization, and geographic, cultural, social, and economic issues.[52,53] Immer and colleagues compared three different scores (Parsonnet, Higgins, and French scores) used for preoperative risk stratification of postoperative morbidity, mortality, and hospital length of stay for 1299 consecutive patients undergoing CABG and/or heart valve surgery.[54] All three scoring systems performed well, with *c*-statistics between 0.76 and 0.79. The Higgins and French scores were especially useful in predicting postoperative outcome. Both of these scoring systems showed a progressive increase in cardiac risk class with increasing cardiac risk score.

Among European centers, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) algorithm has been used to predict perioperative risk. In a single-center comparison of 19 risk scoring systems, the EuroSCORE algorithm provided the best discriminatory capability for 30-day and 1-year mortality (*c*-statistic 0.84 and 0.76, respectively), closely followed by Cleveland Clinic/Higgins (0.82 and 0.76) and Magovern (0.82 and 0.76) algorithms.[55] For CABG, the EuroSCORE and New York State risk scores best predicted outcome (Fig. 9-1). Unfortunately, risk stratification scoring systems might be somewhat hindered by differences in geographic population, the lack of information related to morbidity, and long-term information on survival.

Rumsfeld and colleagues examined a nontraditional approach to cardiac surgical risk stratification that involved assessment of a patient's self-perceived health status using the Physical Component Summary (PCS) scores from the preoperative Short-Form 36 (SF-36) health status survey.[56] After adjustment for known clinical risk factors of mortality following CABG, the PCS from the preoperative SF-36 was found to be an independent predictor of mortality such that a 10-point or 1-SD decrement in baseline PCS was associated with a 39% increase in 6-month mortality (95% CI 1.11–1.77, $p = .006$). As noted by the authors, this study may have had a selection bias toward lower-risk elective cases and did not determine the predictors of the baseline PCS. While the role of these data in the preoperative evaluation of cardiac surgery patients remains unclear, they illustrate that in addition to

Table 9–3.

Procedure-Based Cardiac Surgical Mortality in Several Large Studies

	Jamieson et al, USA[1] (1986–1995)	Roques et al, Europe[2] (1995)	Turner et al, United Kingdom[3] (1993–1994)	Nowicki et al, USA[4] (1991–2001)	Likosky et al, USA[5] (1992–2001)	Shroyer et al, USA[6] (1997–1999)
Procedure	Mortality (%)	Mortality (%)	Mortality (%)	Mortality (%)	Mortality (%)	Mortality (%)
CABG	—	3.4	2.5	—	3.43	3.05
CABG + multiple valve	18.8	—	10.1*	—	—	—
MVR	6.4	7	2.4	12.0	—	—
AVR	4.3	6	2.1	6.2¶	—	—
MVR + CABG	15.3	—	—	12.8‡	—	—
AVR + CABG	8.0	—	—	8.2§	—	—
Multiple valves	9.6	—	8.7	—	—	—
MV repair	3.0	—	—	6.4	—	—
AV repair	5.9	—	—	—	—	—
Emergency	—	—	13.9	21.9–34.5	—	—
Elective	—	—	3.0	3.8–4.2	—	—
Overall	7.5†	4.8	3.8	—	—	—

**Represents CABG and any valve surgery.*

†*Represents all listed operations plus tricuspid valve surgery and aortic aneurysm repair.*

‡*Represents CABG and any mitral valve surgery.*

§*Represents CABG and any aortic valve surgery.*

¶*Represents both aortic repair and replacement procedures.*

MVR = mitral valve replacement; AVR = aortic valve replacement; CABG = coronary artery bypass grafting.

[1]*Jamieson et al: Risk stratification for cardiac valve replacement. National Cardiac Surgery Databse.* Ann Thorac Surg *1999; 67:943.*

[2]*Roques et al: Risk factors and outcome in European cardiac surgery.* Eur J Cardiovasc Thorac Surg *1999; 15:816.*

[3]*Turner et al: Difficulties in predicting outcome in cardiac surgery patients.* Crit Care Med *1995; 23:1843.*

[4]*Nowicki et al: Multivariable predictions on in-hospital mortality associated with aortic and mitral valve surgery in northern New England.* Ann Thorac Surg *2004; 77:1966.*

[5]*Likosky et al: Comparison of three measurements of cardiac surgery mortality for the Northern New England Cardiovascular Disease Group.* Ann Thorac Surg *2006; 18:1393.*

[6]*Shroyer et al: The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models.* Ann Thorac Surg *2003; 75:1856.*

physician-determined components of risk stratification, patient self-report may provide a complementary, noninvasive, cost-effective measurement of mortality prediction.

RISK FACTORS FOR MORBIDITY AND MORTALITY

Atrial Fibrillation

Commonly encountered after cardiac surgery, atrial fibrillation occurs in as many as 10 to 40% of patients after CABG and in up to 65% of patients undergoing combined CABG and valve surgery.[57–60] Atrial fibrillation occurs most frequently within 24 to 48 hours after surgery and is associated with prolonged hospitalization (the excess length of stay that was independently attributable to postoperative atrial fibrillation was 4.9 days, with additional costs of $5000 to $6000 per patient), hemodynamic instability, and thromboembolization.[61–65] The risk of stroke increases threefold in patients with postoperative atrial fibrillation.

Risk Scores for In-Hospital Mortality for Coronary Artery Bypass Grafting

Risk Factor	Score
Age (yrs)	
<61	0
61–69	1
70–79	3
80 and older	5
Female gender	2
Hemodynamic state	
Unstable	2
Shock	5
Ejection fraction	
<20%	4
20%–29%	3
30%–39%	2
Pre-procedural MI	
MI <6 h	5
MI 6–23 h	4
MI 1–20 days	1
Chronic obstructive pulmonary disease	1
Extensively calcified ascending aorta	2
Peripheral arterial disease	2
Renal failure requiring dialysis	5
Previous open heart operations	3

* Range of total score, 0–34.

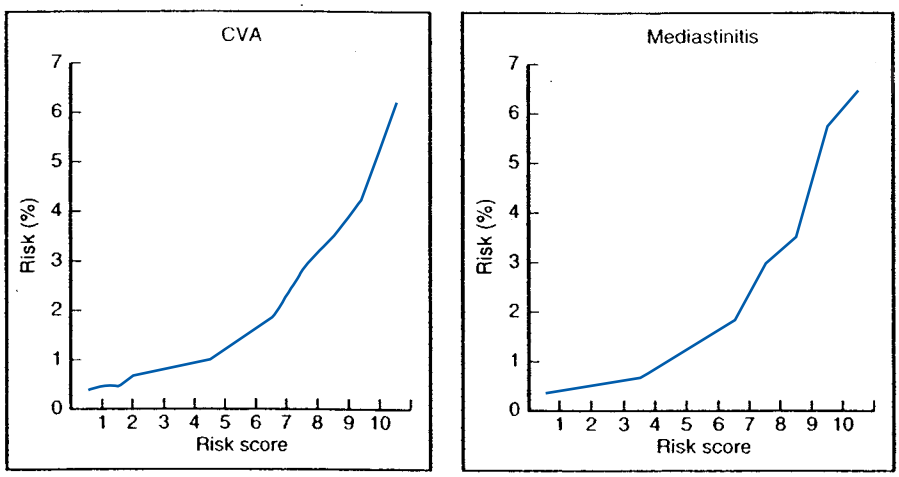
Source: Hannan et al, *JACC* 2006; 47(3):661–8.

Predicted Risk of In-Hospital Mortality Associated With Individual Risk Scores and the Distribution of Total Risk Score Among Coronary Artery Bypass Grafting Patients in New York State in 2002 (N = 16,120)

Total Risk Score	Predicted Risk (%)	Cumulative Percentage of Patients With This Risk Score or Less (%)	Total Risk Score	Predicted Risk (%)	Cumulative Percentage of Patients With This Risk Score or Less (%)
0	0.30	12.00	12	20.22	99.12
1	0.43	25.88	13	26.86	99.46
2	0.62	34.69	14	34.72	99.70
3	0.90	52.03	15	43.52	99.84
4	1.29	60.31	16	52.74	99.92
5	1.86	73.78	17	61.78	99.94
6	2.67	81.44	18	70.07	99.97
7	3.82	88.18	19	77.23	99.99
8	5.45	92.78	20	83.09	99.99 †
9	7.70	95.66	21	87.68	99.99 †
10	10.78	97.57	22+	>90	100.00
11	14.90	98.51			

† The highest observed total risk score was 22, and there were no patients who had total risk scores of 20 or 21 in 2002 data.

Source: Hannan et al, *JACC* 2006; 47(3):661–8.



Source: Eagle KA et al, *J Am Coll Cardiol* 1999; 34:1262.

Figure 9-1. Preoperative estimation of risk of mortality, cerebrovascular accident, and mediastinitis, developed by the Northern New England Cardiovascular Disease Study Group.

Atrial fibrillation also was found to be the most common reason for readmission to the hospital after cardiac surgery.[61]

Although usually considered benign and self-limited, postoperative atrial fibrillation is associated with increased early and late mortality, an association that persists after adjustment for existing comorbid conditions and advanced age.[66]

Many patients (25 to 80%) convert spontaneously to sinus rhythm within 24 hours.[67] However, the incidence of atrial fibrillation during the first year following CABG is

greater than in the general population in patients younger than 70 years of age.[68]

The mechanism of atrial fibrillation following cardiac surgery is not well understood, but possible etiologies include multiple wavelet reentry in the atria, rapid firing of an atrial focus, and less likely, atrial ischemia.[60,69] Preoperative clinical predictors of atrial fibrillation after cardiac surgery include increased age, history of hypertension, male sex, previous history of atrial fibrillation or congestive heart failure, peripheral and/or cerebral vascular disease, and severity of coronary artery disease.[58,60,62,70,71] Less well-characterized predictors of postoperative atrial fibrillation include aortic cross-clamp time, pulmonary vein venting, respiratory disease [chronic obstructive pulmonary disease (COPD)], prolonged ventilation,[60] and obesity.[71]

Current guidelines (ACC/AHA/ESC) recommend prophylactic beta-blocker therapy for all patients without contraindications. Therapy with amiodarone or sotalol is reserved for patients at increased risk for postoperative atrial fibrillation (e.g., those with a history of atrial fibrillation, left atrial enlargement, or valvular heart disease).[72] The prophylactic use of beta-blocker therapy decreases the incidence of post-CABG atrial fibrillation by as much as 70 to 80%.[73] Preoperative initiation of beta-blocker therapy probably attenuates the high sympathetic tone associated with cardiac surgery. Unless specifically contraindicated, patients who have received long-term beta blockers should continue receiving them promptly after surgery.[74,75]

Aasbo and colleagues demonstrated a reduction in atrial fibrillation, ventricular tachyarrhythmias, stroke, and length of hospital stay after cardiac surgery attributable to amiodarone prophylaxis. The decrease in atrial fibrillation was similar whether amiodarone therapy was initiated preoperatively or perioperatively. No difference was noted between oral and intravenous administration.[76] The relative merits of adding prophylactic amiodarone compared with beta blockers universally for postoperative atrial fibrillation for all patients is unknown.[75,76] Sotalol, a class III antiarrhythmic drug, also reduces the incidence of postoperative atrial fibrillation compared with placebo and half-dose beta blockade.[77,78] Sotalol may be considered for prophylactic use in high-risk patients, being mindful of potential side effects.[75] Preoperative drug therapy for atrial fibrillation has been shown to decrease hospital length of stay and cost.[79,80] Interestingly, basic science and clinical data show promise for the use of N-3 polyunsaturated fatty acids (PUFAs) in reducing the incidence of postoperative atrial fibrillation and hospital length of stay. PUFAs are believed to decrease the incidence of arrhythmias owing to their effects on rat atrial muscle in experimental models and also have a favorable safety profile.[81] Prophylactic use of calcium channel blockers and digoxin does not reduce the incidence of atrial fibrillation.[56,75] Biatrial pacing may have a role in patients at highest risk for postoperative atrial fibrillation (e.g., those with concomitant mitral valve surgery and CABG).[82,83]

For patients with persistent atrial fibrillation after cardiac surgery, priority should be given to electrolyte repletion and rate control. While beta blockers are considered first-line therapy, calcium channel blockers such as verapamil and diltiazem also are useful in controlling ventricular rate. Amiodarone is also beneficial for rate control, particularly in individuals who are unable to tolerate beta blockers or calcium channel blockers because of hypotension. Antiarrhythmic therapy usually is reserved for individuals who have persistent or recurrent atrial fibrillation. Class IA (e.g., disopyramide, quinidine, procainamide), class IC (e.g., propafenone and flecainide), and class III agents (e.g., sotalol, amiodarone, ibutilide, and dofetilide) all have varying degrees of efficacy for conversion of post-CABG atrial fibrillation.[60] While class IC and class III drugs can be used in the setting of resistant atrial fibrillation, cardiology consultation is prudent prior to their use because they are contraindicated in select patient populations, and the risk for drug-induced proarrhythmia is high. Electrical cardioversion should be performed if the patient demonstrates hemodynamic instability and in patients with persistent symptoms or rapid ventricular rate despite optimal drug therapy. Figure 9-2 outlines an algorithm for the prevention and management of atrial fibrillation after cardiac surgery.

Anticoagulation in patients with postoperative atrial fibrillation for 48 hours or more should be individualized. American College of Chest Physicians (ACCP) guidelines recommend warfarin treatment to therapeutic INR (2 to 3) in select patients with chronic atrial fibrillation or in patients in whom atrial fibrillation persists over 48 hours.[84] Heparin therapy as a bridge to a therapeutic INR with warfarin is troublesome because it is associated with higher rates of large pericardial effusion and cardiac tamponade compared with patients receiving aspirin or placebo.[60] Despite this, heparin should be considered in high-risk patients (e.g., those with a history of stroke or transient ischemic attack).[84]

Although the actual percentage of patients who remain in atrial fibrillation after surgery remains unknown, it is believed that many patients with persistent atrial fibrillation at discharge will convert spontaneously to sinus rhythm within 6 weeks.[85]

Renal Disease

Acute renal failure develops in approximately 1 to 5% patients after cardiac surgery.[86] Morbidity and mortality related to renal disease after cardiac surgery are heavily dependent on comorbid disease. Risk factors for acute renal failure include advanced age, baseline renal dysfunction, left ventricular dysfunction, peripheral vascular disease, and clinical signs of poor cardiac function such as pulmonary rales and the use of an intra-aortic balloon pump.[86–88] Other risk factors include a history of diabetes, hypertension, reoperation, urgent operation, prolonged cardiopulmonary bypass and aortic cross-clamp times, concomitant procedures, and deep sternal or systemic infections.[89]

Additionally, preoperative renal insufficiency is an independent risk factor for postoperative morbidity and mortality.[90–92] Renal insufficiency is associated with greater risk of both 30-day (OR = 3.7) and 1-year mortality

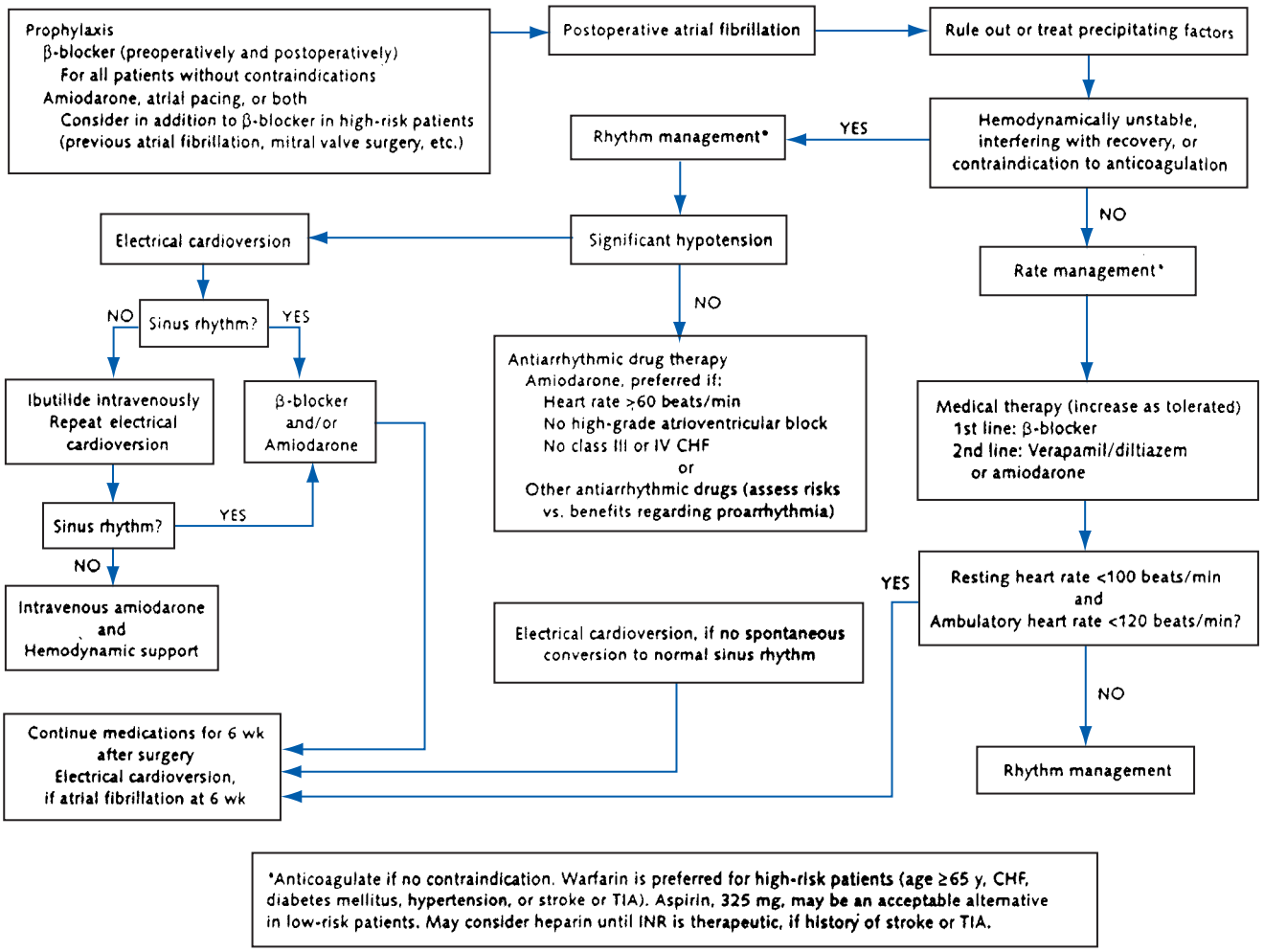


Figure 9-2. Algorithm for the prevention and management of atrial fibrillation after cardiac surgery. *(Adapted with permission from Maisel WH, Rawn JD, Stevenson WG: Atrial fibrillation after cardiac surgery. Ann Intern Med 2001; 135:1061.)*

(OR = 4.6).[90] Even mild renal dysfunction (serum creatinine 1.47 to 2.25 mg/dL) is associated with increased rates of operative and long-term mortality, need for postoperative dialysis, and postoperative stroke.[93]

Dialysis is necessary in 1% of patients who develop acute renal failure; the 30-day mortality is almost 64% for patients with acute renal failure compared with 4.3% for those without acute renal failure.[86] Renoprotective drugs, such as fenoldopam and *N*-acetylcysteine, have no effect on the deterioration of renal function in high-risk patients.[94,95] However, Bucerius and colleagues have demonstrated that OP-CABG was associated with a lower prevalence of the need for postoperative renal replacement therapy compared with CABG-CPB.[96] Thus it seems logical that OP-CABG should be considered in appropriate patients with or at risk for renal failure. Caution must be exercised because analyses that have involved OP-CABG did not include a substantial number of persons with renal dysfunction. The VA Continuous Improvement in Cardiac Surgery Program developed a recursive partitioning clinical risk algorithm that performs well across different patient populations.[94] It helps to identify individuals who are at high risk of developing acute renal failure (Fig. 9-3).

Age

The prevalence of cardiac surgical procedures in the elderly continues to increase as life expectancy improves and procedural benefits outweigh the risks. Moreover, the outcome of surgical coronary revascularization has improved progressively despite increased numbers of elderly patients and worsened preoperative risk profiles over the past several decades. Overall operative mortality in patients over 70 years of age still remains higher than in younger patients, with octogenarians having the highest operative risk.[98,99] While perioperative mortality does not vary significantly by age, 1-year mortality is greater in patients over 75 years of age.[100] Additionally, patients aged 75 years and over are more likely

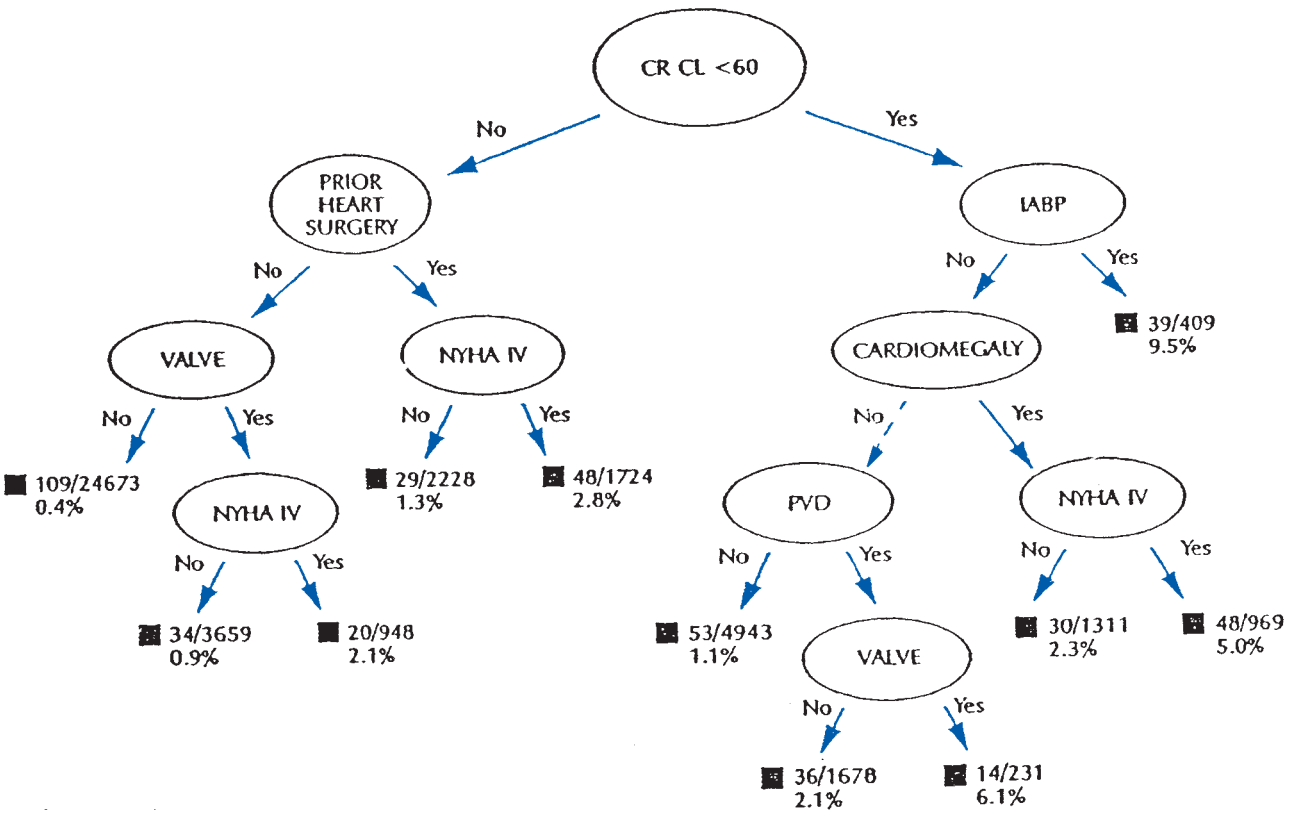


Figure 9-3. Recursive partitioning analysis of the risk of renal failure after CABG. CrCl = estimated creatinine clearance; LVEF = left ventricular ejection fraction; IABP = intra-aortic balloon pump; PVD = peripheral vascular disease. *(Adapted and modified with permission from Fortescue EB, Bates DW, Chertow GM: Predicting acute renal failure after coronary bypass surgery: Cross-validation of two risk-stratification algorithms. Kidney Int 2000; 57:294.)*

to experience perioperative neurologic and renal complications, tend to require prolonged ventilatory support, and are reoperated on more often owing to bleeding.[99,100] Table 9-4 and Fig. 9-4 demonstrate the effect of age on postoperative morbidity and mortality.

Identified risk factors for poor operative outcome are very similar across age groups[99] and include concomitant CABG and valve replacement (mitral valve in particular); emergency procedure; shock; lower body mass index (BMI); advanced New York Heart Association (NYHA) class; lower ejection fraction[101]; higher prevalence of diabetes, renal dysfunction, and peripheral vascular disease; previous CABG; recent MI; and CABG-CPB.[102] Mortality statistics also may vary based on multiple socioeconomic and demographic factors. For example, whereas a study by Zacek and colleagues reported higher mortality in the 70 years and older versus 70 years and younger age group (7.3% versus 2.3 %, $p < .005$), a Canadian study reported operative mortality declining from 7.2% in 1982–1986 to 4.4% in 1987–1991 in the elderly.[102,103] The latter study also stratified patients by risk and demonstrated that while the prevalence of high-risk elderly patients increased significantly over time, operative mortality decreased for medium- and high-risk patients. Possible reasons for better outcomes include more frequent use of OP-CABG,[102,104] improved myocardial protection and anesthetic techniques perioperatively, as well as greater use of arterial grafts. While some studies demonstrate that patients aged 75 years and over tend to have a higher incidence of mental confusion and reduced quality of life compared with their younger counterparts,[105] others show that they derive similar health status benefits from CABG (e.g., angina relief and quality-of-life improvement) but tend to have a slower rate of recovery following surgery.[100]

Race and Gender

Approximately 28% of all CABG procedures in the United States are performed on women.[106] Some but not all epidemiologic studies suggest that female gender is an independent predictor of postoperative morbidity and mortality.[107,108] Women are more likely to be older when undergoing CABG, have fewer arterial grafts during surgery, and more often undergo emergent CABG than men.[108,109] Moreover, younger women have a higher mortality after CABG compared with their male counterparts. Vaccarino and colleagues reported that despite having higher ejection fractions and fewer diseased coronary arteries, women younger than 50 years of age had in-hospital mortality rates that were three times higher than men (3.4% versus 1.1%).[110] Although reasons for this difference are uncertain, women

Table 9–4.

Outcomes for Cardiac Surgery by Age Category

	CABG only		CABG/AVR		CABG/MVR	
All patients	**Age < 80 (*N* = 60, 161)**	**Age ≥ 80 (*N* = 4306)**	**Age < 80 (*N* = 1690)**	**Age ≥ 80 (*N* = 345)**	**Age < 80 (*N* = 1170)**	**Age ≥ 80 (*N* = 92)**
In-hospital mortality	3.0%	8.1%*	7.9%	10.1%	12.2%	19.6%*
All neurologic events (stroke, TIA, coma)	4.2%	10.2%*	9.1%	15.2%*	11.2%	22.5%*
Stroke only	1.8%	3.9%*	3.2%	4.9%	4.7%	8.8%
Renal failure	2.9%	6.9%*	6.8%	12.1%*	11.4%	25.0%*
Perioperative MI	1.7%	2.5%*	2.0%	3.0%	2.7%	1.5%
PLOS days†	6 (5,8)	7 (6,11)*	7 (5,10)	9 (6,15)*	9 (6,14)	11 (7,19)
Patients w/o comorbidity‡(% of population)	*N* = 24,811 (41.2%)	*N* = 1588 (36.9%)	*N* = 571 (33.8%)	*N* = 100 (29.0%)	*N* = 196 (16.8%)	*N* = 11 (12.0%)
In-hospital mortality	1.1%	4.2%*	4.0%	7.0%	7.1%	18.2%

**p <.05 for comparison by age category.*
†Median and 25th and 75th quartiles.
‡Subset of patients without significant comorbidity: EF < 35%, prior CABG, history of CHF, COPD, vascular disease, renal insufficiency, MI within 21 days or emergency surgery.
AVR = aortic valve repair; CABG = coronary artery bypass grafting; MI = myocardial infarction; MVR = mitral valve repair; PLOS = postprocedural length of stay.
Source: Alexander et al: *J Am Coll Cardiol* 2000; 35(3):731.

had more comorbidities than men in this analysis. Additionally, after adjustment for potential confounders, women undergoing CABG had lower rates of functional gain at 6 months of follow-up (measured by the physical function and mental health scores of the SF-36) compared with their male counterparts.[106] Hospital readmission rates within the first postoperative year also were greater for women.[106,108]

Possible explanations for worse outcomes in women include smaller coronary arteries (which might enhance the difficulty of performing anastomoses and limit graft flow), differences in referral for surgery (i.e., women being referred at later disease stages), and gender differences in self-reported outcomes.[106]

Finally, although crude post-CABG mortality rates differ significantly by race, data suggest that after control for patient and hospital variables, these differences are small.[111,112] However, in the United States, self-described black race is associated with an increased risk of postoperative complications, including prolonged ventilatory support, length of stay, reoperation for bleeding, and postoperative renal failure.[113]

Ventricular Dysfunction

Viable myocardium that has not been revascularized in persons with ischemic heart disease and congestive heart failure promotes the development of further functional and myocardial disability.[114–116] Left ventricular dysfunction is associated with a fourfold increase in operative mortality.[117] Surgical revascularization improves ventricular function in individuals with "hibernating" myocardium.[114] For individuals with ejection fractions of less than 30%, low-cardiac-output syndrome and supraventricular arrhythmias are the most common complications, and in this group, mortality rates approach 10%.[118] However, CABG improves ventricular function and 3-year survival rate, making adequate assessment of myocardial viability via thallium reperfusion imaging, positron-emission tomography, or stress echocardiography necessary prior to surgery.[114,115,119]

Hepatic failure, renal failure, previous MI, reoperation, emergent procedures, female gender, congestive heart failure, and age are all independent predictors of in-hospital mortality in patients with low ejection fraction.[117] Over time, the relative influence of left ventricular dysfunction on operative outcome has declined. Therefore, CABG remains a viable option in patients with low ejection fraction and acceptable perioperative risk.[117,120,121] Despite advances in surgical techniques, 1% of cardiac surgery patients develop postoperative ventricular dysfunction.[122] In these individuals, implantation of ventricular assist

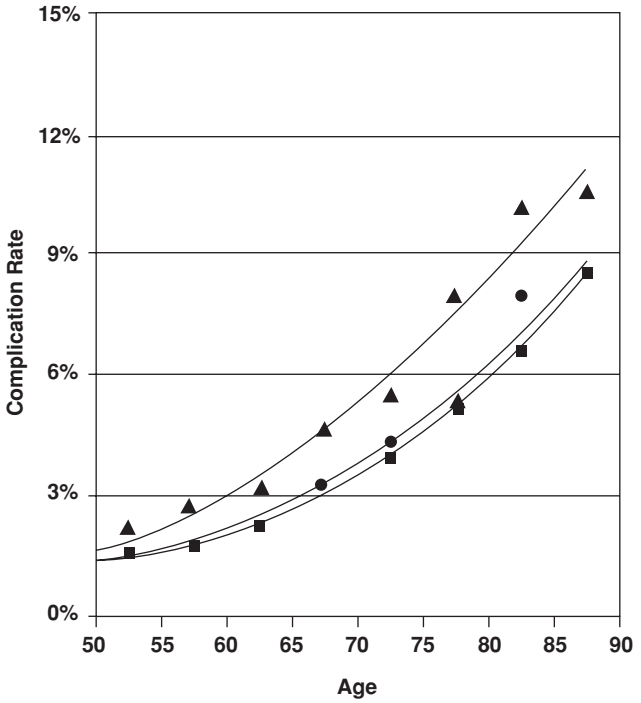


Figure 9-4. In-hospital mortality (circles), postoperative neurologic complications *(triangles)*, and postoperative renal failure (squares) after CABG by age. *(From Alexander KP, Anstrom KJ, Muhlbaier LH, et al: Outcomes of cardiac surgery in patients age ≥ 80 years: Results from the National Cardiovascular Network.* J Am Coll Cardiol *2000; 35:731.)*

devices as a bridge either to recovery or to transplantation can be beneficial, particularly in the bridge to transplant subgroup, often resulting in successful discharge from the hospital.[122]

Patients with left ventricular dysfunction and valvular disease such as mitral regurgitation or aortic stenosis require special preoperative management. Individuals with mitral regurgitation and heart failure should receive preoperative afterload reduction with angiotensin-converting enzyme (ACE) inhibitors or intravenous sodium nitroprusside to maintain systolic blood pressures in the 90 to 100 mm Hg range. While patients with aortic stenosis and hemodynamically significant cerebral or renovascular disease should not receive the latter therapies, intra-aortic balloon counterpulsation (IABP) may be useful in such subgroups. Intra-aortic balloon support also can be used in the setting of acute mitral regurgitation owing to papillary muscle rupture as well as in infarct-related ventricular septal defect. Preoperative IABP use in high-risk patients decreases mortality and shortens ICU stay owing to enhanced hemodynamic performance.[123]

Right ventricular dysfunction also increases perioperative risk, and patients should be assessed for pulmonary hypertension (pulmonary artery systolic pressure > 60 mm Hg), documentation of a history of inferior MI, or chronic tricuspid regurgitation. Right ventricular dysfunction caused by increased pulmonary vascular resistance should be treated with inotropes that have vasodilator properties such as dobutamine (5 μg/kg per minute) and milrinone (5 μg/kg per minute). Intravenous nitrates, aerosolized prostacyclin, and nitric oxide also are effective agents for lowering pulmonary vascular resistance with resulting improvement in right ventricular function.[124]

Pulmonary Disease

In patients with COPD, prolonged weaning from mechanical ventilation postoperatively is common if the forced expiratory volume at 1 second (FEV_1) is less than 65% of vital capacity or if FEV_1 less than 1.5 L. CABG patients with severe COPD are more likely to develop ventilatory failure and have higher mortality rates than those with mild to moderate or no COPD (death: 19% versus 4% versus 2%; $p = .02$).[125] Preoperative screening of arterial oxygen concentration on room air can provide guidance in respiratory management postoperatively. The roles of preoperative spirometry and perioperative bronchodilators remain unclear in stable patients, and these interventions cannot be recommended on a routine basis.

Reoperation

Approximately 3 to 20% of patients who undergo CABG will require reoperation within a decade; reoperations represent roughly 20% of CABG operations performed yearly.[126] Continued aging of the population also is expected to increase the number of reoperations. Generally, operative mortality for reintervention is almost two times higher than the associated mortality for the initial procedure, hovering between 1% and 6% in most case series.[127,128] Furthermore, emergency reoperations increase the baseline operative mortality rate fourfold.[126] Preoperative risk factors for reoperation include female sex, a history of diabetes, hypertension, renal insufficiency, hyperlipidemia, smoking, and reduced ventricular function.

Some studies suggest that improvement in operative techniques and reduced pump time exposure may affect reoperative mortality. For example, data from Sabik and colleagues show that compared with cardiac surgery patients who underwent reoperation prior to 1997, those reoperated on after this date had improved outcomes. However, higher mortality for reoperations was observed if these procedures were performed within 1 year of prior surgery.[129] Interestingly, reoperations in patients 70 years of age or older appear to have an acceptable morbidity and mortality.[130] For example, one study found that reoperative mortality was 7% and survival at 2 to 8 years was 90% in this patient subgroup.

Nutrition and BMI

The postoperative hypermetabolic state requires increased nutrition in order to facilitate wound healing and to meet corporeal metabolic demands. Consequently, patients who are malnourished preoperatively should receive at least 2 to 4

weeks of intensive nutritional bolstering prior to elective surgery, and all patients should resume an oral diet within 24 hours of uncomplicated surgery. Since perioperative stroke may limit the ability of some patients to protect their airway, a swallowing evaluation is mandatory in this subset of patients. Low BMI (<20 kg/m^2) and hypoalbuminemia (<2.5 g/dL) are associated independently with increased risk of morbidity and mortality after cardiac surgery.[131,132] Patients with decreased albumin levels are at increased risk for bleeding, renal failure, prolonged ventilatory support, and reoperation.

While obesity is not associated with increased mortality, patients with a high percent of body fat and poor aerobic capacity are at higher risk for reoperation, increased length of hospitalization, pulmonary edema, renal failure,[133,134] early hospital readmission,[135] higher total costs,[136] sternal wound infection (OR = 2.3; $p < .001$), saphenous vein harvest-site infection, and atrial arrhythmias.[131,137,138]

Diabetes

Diabetes is an important independent risk factor for atherosclerotic heart disease and a significant predictor of in-hospital mortality after CABG.[139] Although the Bypass Angioplasty Revascularization Investigation (BARI) did not evaluate stented patients, it demonstrated that diabetic patients with multivessel disease have greater survival with CABG compared with those who receive PCI.[140] Postoperative mortality does not differ significantly between nondiabetic and diabetic patients without diabetic sequelae. However, diabetic patients with vascular disease and/or renal failure have an increased risk of mortality compared with those without vascular/renal sequelae.[141]

Overall, diabetic patients who undergo CABG have more renal and neurologic complications and longer ICU stays, require more blood transfusions, and have higher reopening rates.[142] Diabetic patients who undergo valve operations have a fivefold increased risk of a major pulmonary complication.

Additionally, patients with undiagnosed diabetes undergoing CABG require more resuscitation and have higher rates of reintubation, longer periods of ventilatory support, and a higher 30-day mortality rate compared with known diabetic and nondiabetic patients.[143] This finding underscores the importance of performing diabetes screening for patients in the preoperative setting.

Neurologic Complications and Carotid Artery Disease

Approximately 1 to 6% of persons develop neurologic complications after cardiac surgery.[144–146] Stroke is the most debilitating of these complications, with an estimated 15,000 victims yearly.[146] It is believed that neurologic complications are related to the effects of cardiopulmonary bypass.[147] Carotid artery disease is responsible for as many as 30% of postoperative strokes. Cerebral microembolization from the

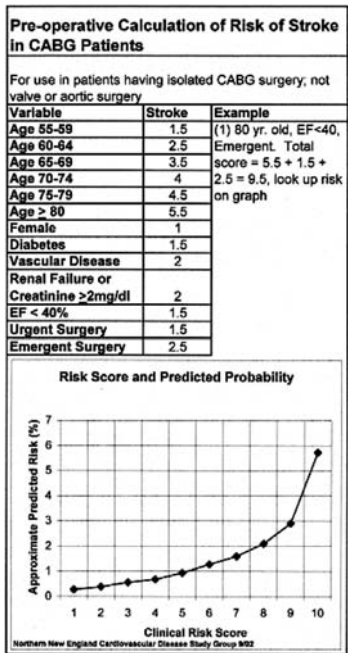


Figure 9-5. Risk prediction card for stroke. CABG = coronary artery bypass grafting; EF = ejection fraction. *(From Charlesworth DC, Likosky DS, Marrin CAS, et al: Development and validation of a prediction model for strokes after coronary artery bypass grafting.* Ann Thorac Surg *2003; 76:436.)*

arterial tree during CABG is likely the most common culprit. In fact, atherosclerosis of the ascending aorta is an independent predictor of long-term neurologic insult and mortality.[148] Moreover, an analysis from Boeken and colleagues showed that among 783 patients undergoing cardiac surgery, the predictors of central nervous system complications include symptomatic cerebrovascular disease, advanced age, type of surgery, and aortic atheroma[149,150] (Fig. 9-5 and Tables 9-5 and 9-6).

For patients undergoing CABG, the incidence of carotid artery disease can be as high as 22% depending on multiple factors, including screening method, age, diabetic status, the presence of left main disease or left ventricular dysfunction, female sex, history of smoking, or prior cerebrovascular attacks.[151] However, whether or not to screen all CABG candidates for carotid stenosis is uncertain. Some data have suggested that selective screening should be performed in patients who are identified to be at high risk, including those with age greater than 65 years, carotid bruit, prior neurologic event, peripheral vascular disease, hypertension, diabetes, and smoking, as a method of decreasing screening burden, cost, and time to surgery.[152,153] However, presently, routine screening of all cardiac surgical candidates via carotid artery ultrasound is advisable to enable detection of significant carotid stenoses prior to surgery.

Indeed, patients with concomitant carotid and coronary artery disease often present a management challenge to physicians because they have decreased long-term survival

Table 9–5.

Risk Factors for Neurologic Complications; Multivariate Logistic Regression Analysis for Pre- and Intraoperative Parameters

Predictor	Beta coefficient	Odds ratio	95% CI	*p* Value
Previous neurologic events	1.88	6.8	4.2–12.8	0.0001
Age > 70 years	1.46	4.5	1.2–7.8	0.03
Preoperative anemia	1.22	4.2	2.8–6.6	0.001
Aortic atheroma	1.45	3.7	2.0–5.8	0.001
Duration of myocardial ischemia	1.12	2.8	1.8–3.2	0.0001
Number of bypasses	1.06	2.3	1.5–2.3	0.0006
LVEF <35%	1.01	2.2	1.2–1.5	0.001
Insulin-dependent diabetes mellitus	0.9	1.5	1.3–2.5	0.0001
Duration of ECC	0.48	1.4	1.0–2.2	0.0001
Reoperation	0.48	1.4	0.9–2.4	0.01
Emergency operation	0.46	1.2	0.7–2.0	0.02

Source: Boeken et al: *Thorac Cardiovasc Surg* 2005; 53:33.

Table 9–6.

Incidence of Neurologic Complications According to Surgical Procedure

Type of procedure	Neurologic events (%)
CABG	1.7
AVR	3.6
MVR	0
TVR	0
AVR + CABG	3.3
MVR + CABG	0
AVR + MVR	6.7

Source: Boeken et al: *Thorac Cardiovasc Surg* 2005; 53:33.

compared with their counterparts who have only coronary artery disease.[151] Generally, perioperative stroke risk is believed to be highest (>5%) in patients with greater than 80% unilateral stenosis, bilateral stenoses of at least 50%, and unilateral occlusion with at least a 50% carotid artery lesion on the contralateral side.[151] Consequently, previous data suggested that all patients who fall into one of these categories should receive combined carotid endarterectomy (CEA) and CABG. Several authors reported operative mortality rates of between 0% and 5% and perioperative neurologic and myocardial events of approximately 3%.[151–157] However, a systematic review of 97 studies involving 8972 operative outcomes after staged and synchronous CEA and CABG revealed that patients who underwent combined CEA and CABG had higher mortality, stroke, and MI rates (11.5%, 95% CI 10.1–12.9) than those who underwent staged CEA and then CABG (10.2%, 95% CI 7.4–13.1)[158,159] (Table 9-7). Perioperative MI rates were lowest among those who had undergone CABG and then CEA. Overall, although the procedural comparisons did not achieve statistical significance, synchronous procedures were associated with higher rates of stroke or death. To date, randomized trials to guide treatment are lacking, and thus the correct approach remains controversial. Despite this, it presently seems reasonable to perform a staged procedure instead of combined CABG/CEA, although the timing of CEA in relation to CABG is institution-dependent.

Carotid artery stenting also can be performed in close proximity to CABG. Potential advantages of carotid artery stenting include decreasing perioperative risk, hospital cost, and patient discomfort and minimizing the need

Table 9–7.

Perioperative Outcomes for Synchronous and Staged CEA-CABG

	Operative mortality	Ipsilateal stroke	Any stroke	Myocardial infarction	Death ± ipsilateral CVA	Death ± any CVA	Death ± any CVA ± MI
Synchronous CEA+CABG							
Observed risk %	4.6	3.0	4.6	3.6	7.4	8.7	11.5
95% CI	4.1–5.2	2.4–3.5	3.9–5.4	3.0–4.2	6.5–8.3	7.7–9.8	10.1–12.9
Heterogeneity (*p*)	0.0048	0.0002	<0.0001	0.0174	0.0001	<0.0001	n/a
Staged CEA-CABG							
Observed risk %	3.9	2.5	2.7	6.5	4.8	6.1	10.2
95% CI	1.1–6.7	1.3–3.6	1.6–3.9	3.2–9.7	2.8–6.8	2.9–9.3	7.4–13.1
Heterogeneity (*p*)	<0.0001	<0.0001	<0.0001	0.9968	<0.0001	<0.0001	<0.0001
Staged CABG-CEA							
Observed risk %	2.0	5.8	6.3	0.9	3.4	7.3	5.0
95% CI	0.0–6.1	0.0–14.3	1.0–11.7	0.5–1.4	0.0–9.8	1.7–12.9	0.0–10.6
Heterogeneity (*p*)	<0.0001	0.2190	0.1784	<0.0001	0.0060	<0.0001	0.0102

Source: Naylor et al: *Eur J Vasc Endovasc Surg* 2003; 25;380.

for systemic heparinization prior to CABG. Thus carotid artery stenting might be advantageous in patients with stable carotid and coronary artery disease, in elderly patients who are at high risk for thoracotomy, and in patients who have concomitant carotid artery disease and single-vessel left anterior descending artery disease for which minimally invasive surgery is planned. Evidence-based data to support the routine use of carotid stenting among patients who are to undergo cardiac surgical procedures remains sparse, but emerging research suggests that carotid stenting should be considered as a viable alternative. For example, Babatasi and colleagues reported 97% procedural success with coronary artery stenting in a series of 36 patients treated with carotid stenting and CABG.[160] In this study, CABG was performed a mean of 24.3 days after carotid artery stenting, with no embolizations or deaths and a minor stroke rate of 3.6%; two patients developed restenosis at 23 ± 2 months. Other data from Ziada and colleagues demonstrate that in a comparison of patients who had undergone carotid stenting versus CEA and cardiac surgery, while those patients who underwent carotid stenting had a higher baseline risk profile, they suffered fewer adverse myocardial or stroke events than those who underwent CEA. However, of possible concern related to these results is the cutoff for peak MB fraction of creatine kinase of greater than 10 times normal for this study and the retrospective nature of the analysis.[161]

Bradyarrhythmias and Atrioventricular and Intraventricular Block

Preoperative temporary transvenous pacemaker wire insertion is recommended in patients with hemodynamic instability and high-grade heart block (third-degree or Mobitz II). Permanent epicardial pacing lead implantation should be done intraoperatively for patients undergoing tricuspid valve replacement with a mechanical prosthesis owing to the contraindication of passing a transvenous lead through the latter. For individuals with permanent pacemakers, information regarding patient pacemaker dependency, as well as the make, model, and settings of the device, should be clearly documented in the medical record. Previously implanted automatic cardioverter-defibrillator devices should be disabled before surgery to minimize inappropriate shocks caused by electrocautery signal sensing intraoperatively. Bedside external defibrillation equipment must be readily available.

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CHAPTER 10

Cardiac Anesthesia

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The objectives of a general anesthetic are analgesia, amnesia, and unconsciousness while supporting vital physiologic function and creating satisfactory operating conditions. An effective general anesthetic prevents patient movement and blunts the physiologic responses to surgical trauma, nociception, and hemodynamic perturbations and permits recovery at a predictable time after operation. To accomplish this, the anesthesiologist must act as the patient's medical intensivist: support life with mechanical ventilation, control the circulation, and diagnose and treat acute emergencies during surgical incision, rapid changes in body temperature, extracorporeal circulation, and acute shifts in intravascular volume. The task in cardiac surgery is unique because of the nature of the operations and the narrow tolerance for hemodynamic alterations in patients with critical cardiac disease. Furthermore, anesthetic management of the cardiac surgical patient is intimately related to the planned operative procedure and the anticipated timing of intraoperative events.

Anesthetics are chosen based on the patient's preoperative cardiovascular function, drug pharmacokinetics, and the dose-dependent pharmacologic actions. Surgical incision in the presence of inadequate concentrations of a volatile anesthetic produces hypertension, tachycardia, tachypnea, and movement. In the absence of stimulation, the same anesthetic produces cardiovascular depression, hypotension, and apnea. The anesthesiologist titrates the anesthetic to a measurable end point by monitoring cardiovascular effects. Increasing public attention on intraoperative awareness has prompted the American Society of Anesthesiologists to publish a "practice advisory" intended to assist decision making pertaining to this issue.[1] The incidence of intraoperative awareness is approximately 0.2% with general anesthesia.[2] Cardiac surgery is associated with an increased risk of intraoperative awareness.[3–7] Decisions to administer benzodiazepines prophylactically may be prudent in selected patients, such as those with a history of drug resistance or tolerance and young age. High doses of benzodiazepines may preclude early emergence. Alternatives include increasing doses of inhalational agents, propofol, and other sedative hypnotics (e.g., scopolamine). There is no direct method for assessing or monitoring adequacy of analgesia or state of awareness in a paralyzed patient, although the BIS monitor offers some insight. The BIS monitor is an integrated electroencephalographic (EEG) system that relates a bispectral index to depth of general anesthesia and should be considered for select patients.[8,9] Brain function monitors may direct therapy that conflicts with other important anesthesia goals (e.g., preservation of organ function, minimizing risks of aggravating comorbidities, or supporting circulation).

PREOPERATIVE EVALUATION

The preoperative visit by the anesthesiologist is aimed at formulation of an anesthetic plan based on the patient's surgical illness, scheduled operation, and concomitant medical problems. The anesthesiologist is responsible for informing the patient of the conduct of the planned anesthetic and associated risks and obtaining consent for the anesthesia and related procedures. The medical history is elicited by questioning the patient and reviewing the medical records. The nature and severity of the surgical illness and related cardiovascular and pulmonary disease often dictate the choice of anesthetic drugs and monitors. All anesthetic drugs have a direct effect on cardiac function, vascular tone, or the autonomic nervous system. The anesthesiologist must know the status of the cardiovascular system, related morbidity, and concurrent medications to design the anesthetic safely for a patient undergoing heart surgery.

The exchange of information between patient and physician is often a balance between providing sufficient insight regarding possible complications and producing harmful anxiety. An outline of upcoming events accompanied

Table 10–1.

American Society of Anesthesiologists, Physical Status Classification

Class 1: Normal healthy patient
Class 2: Systemic disease without end-organ dysfunction
Class 3: Systemic disease with end-organ dysfunction that is not incapacitating (e.g., diabetes mellitus with abnormal renal function)
Class 4: Systemic disease with end-organ dysfunction that is incapacitating (e.g., diabetes mellitus with renal failure and ketoacidosis)
Class 5: Moribund patient unexpected to survive beyond 24 yours (e.g., diabetes mellitus with renal failure, ketoacidosis, and infarcted bowel requiring vasopressor support)
E*: Emergency surgery

**The E is added to the classification number.*

by an informative discussion of risks and options usually leads to informed consent. Laboratory tests are ordered to complement findings of the medical history and physical examination. Routine preoperative tests for patients scheduled for a cardiac operation include a complete blood and platelet count; electrolyte battery; determination of blood glucose, serum creatinine, and blood urea nitrogen levels; prothrombin time and partial thromboplastin time; chest radiograph; electrocardiogram (ECG); and urinalysis.

The American Society of Anesthesiologists (ASA) has developed a physical status classification as a general measure of the patient's severity of illness[10] (Table 10-1). Concurrent medical illness often defines an acceptable range for monitored parameters that are controlled during cardiac surgery, contributes to postoperative morbidity, or influences the response to a specific drug. Acceptable intraoperative blood pressure is defined by the range of blood pressure before surgery. A severely hypertensive patient may perfuse vital organs inadequately if the blood pressure during surgery is maintained within a "normal" range rather than within the patient's usual range. A previous stroke with apparent recovery may become manifest after general anesthesia without evidence of a new neurologic injury. Chronic obstructive pulmonary disease and its response to bronchodilators permit guided management of perioperative bronchospasm to ensure adequate respiration. Prior surgical and anesthetic procedures are investigated by reviewing medical records. A history of a difficult intubation or adverse response to a specific drug is highly relevant to the anesthesia plan.

Concurrent medications usually are continued until the operation, although the dose may be altered or a shorter-acting preparation substituted. Statins decrease perioperative complications in patients undergoing noncardiac vascular surgery.[11] Their protective effects are less clear for cardiac surgery. Oral medications are administered according to schedule on the day of surgery with a small sip of water. Intravenous heparin given for unstable angina pectoris is not discontinued before surgical incision. For patients scheduled for late afternoon surgery and not receiving maintenance intravenous fluids, preoperative diuretics may be withheld to avoid dehydration. Sudden cessation of certain medications may provoke withdrawal physiology. Caution should be taken when stopping nicotine, benzodiazepines, narcotics, alcohol, beta blockers, alpha agonists (clonidine), and caffeine.

The physical examination includes measurement of vital signs and height and weight and a comprehensive assessment of the heart, lungs, peripheral vasculature, nervous system, and airway. Samsoon's modification of the Mallampati classification to predict a difficult airway is based on the examiner's ability to view intraoral structures[12,13]:

Class 1: Soft palate, tonsillar fauces, tonsillar pillars, and uvula
Class 2: Soft palate, tonsillar fauces, and uvula
Class 3: Soft palate and base of uvula
Class 4: Soft palate not visualized

Classes 1 and 2 represent airway anatomy associated with minimal difficulty with tracheal intubation. Classes 3 and 4 are more likely associated with an inability to intubate the trachea using conventional direct laryngoscopy. Other features associated with difficult intubations include a recessed chin, small mouth, large tongue, and inability to sublux the mandible.

Before the patient enters the operating room, the anesthesiologist formulates a plan to control the circulatory response to anesthesia, secure the airway, and maintain body homeostasis. Emergency operation frequently is incompatible with leisurely preparation but is dictated by a sense of urgency. Rarely is there no opportunity to provide reassurance or to prepare for anesthesia and operation meticulously.

MONITORING PHYSIOLOGIC FUNCTIONS DURING ANESTHESIA

Extensive physiologic monitoring is employed during cardiac operations because virtually every major physiologic system required for life is affected. The reasons for physiologic monitoring are (1) to ensure patient safety in the absence of protective reflexes made ineffective by anesthetic drugs, (2) to enable pharmacologic and mechanical control of vital function, and (3) to diagnose acute emergencies that require immediate treatment. For example, morbidity as a consequence of breathing circuit disconnects, loss of oxygen from the hospital's central supply, or unrecognized

esophageal or main stem intubations can be prevented by capnography, pulse oximetry, airway pressure monitors, oxygen analyzers, and a stethoscope.

The senses of touch, hearing, and sight are the basic monitors. Electronic monitors are vigilance aids that supplement the anesthesiologist's perceptions. In setting up a monitoring and diagnostic system, it is important to establish the sensitivity and specificity for detecting physiologic changes and disease. *Sensitivity* is a measure of the ability of a monitor to detect change in whatever is measured (*measurand*). *Specificity* is the degree that a change in the measurand is peculiar to a singular condition or disease. Sensitivity and specificity of a monitor depend on sensor calibration, accuracy, and precision. A *sensor* is an instrument that detects change in the measurand and provides a corresponding output signal. *Calibration* is the relationship between the measurand and the output signal such that the magnitude of the output signal reflects the magnitude of the parameter being measured. Pressure transducers, light detectors, flowmeters, thermistors, and gas analyzers are examples of sensors used commonly in the operating room. The ideal sensor is accurate during static and dynamic conditions, precise, reliable, safe, practical, and inexpensive. *Accuracy* is defined by how well the output signal agrees with the true value or a calibration quality standard. *Precision* is a measure of repeatability. A sensor is precise if it provides little variability between repeated measures. A pulse oximeter is an accurate monitor of percentage of oxyhemoglobin because it agrees with in vitro measures (between values of 80 to 100%). Thermodilution is an imprecise method of determining cardiac output because successive measurements vary by 20% or more. All monitors are calibrated properly prior to clinical use, and specifications for accuracy and precision must be established to maximize sensitivity and specificity for detecting change.

The selection of monitors is dictated by the utility of the data generated, expense, and risk. Routine or essential monitors that have been deemed cost-effective with low risk:benefit ratios include pulse oximetry, noninvasive blood pressure, capnography, temperature, ECG, precordial or esophageal stethoscope, and oxygen analyzers. These have been defined by the American Society of Anesthesiologists (House of Delegates, 1989) as essential monitors to be used in all surgical patients requiring anesthesia unless there are contraindications (e.g., esophageal stethoscope during esophageal surgery) (Table 10-2). Other noninvasive and invasive monitors are used only with clear indication.

The growth in monitoring technology and sophistication is paralleled by an equal growth in cost. The balance between cost and enhancement of patient safety must be considered when additional monitoring is selected. It is difficult to justify a monitor that provides data that do not influence medical or surgical management. Improved safety decreases patient morbidity and mortality, decreases the direct costs of health care providers, and reduces legal costs, insurance premiums, and possibly the risk of early retirement by physicians. However, monitors do not interpret data and therefore must be monitored by a human being.

Table 10–2.

Physiological Monitors

Organ system	ASA standard operating room monitors	Additional monitoring for cardiac Surgery
Cardiovascular	ECG Noninvasive blood pressure	Invasive blood pressure CVP PAP/PAOP Cardiac output Svo_2 TEE
Pulmonary	Capnography Pulse oximeter Airway pressure Stethoscope Oxygen analyzer	Arterial blood gases
Nervous system		EEG SSEP Transcranial Doppler CSF Pressure
Metabolic	Temperature Urine output	Serum electrolytes Acid-base Glucose Serum osmolarity Hematocrit

Measurement of Blood Pressure

Blood pressure changes abruptly during anesthesia and surgery and is the most commonly measured index of cardiovascular stability in the perioperative period. Anesthetics and surgery cause changes in blood pressure that may be great enough to cause harm unless anticipated and treated. A change in blood pressure alters perfusion pressure but may not change organ blood flow. Most vital organs have autoregulation of blood flow in response to changes in mean arterial blood pressure, permitting a constant blood flow over a range of perfusion pressures.[14] In hypertensive patients, the boundaries for autoregulation are shifted so that significant decreases in organ perfusion may occur with blood pressures in the "normal" range. Both the type and dose of anesthetic medications affect the relationship between vital organ perfusion and blood pressure. Volatile anesthetics are potent vasodilators that tend to disrupt autoregulation in a dose-dependent manner to render

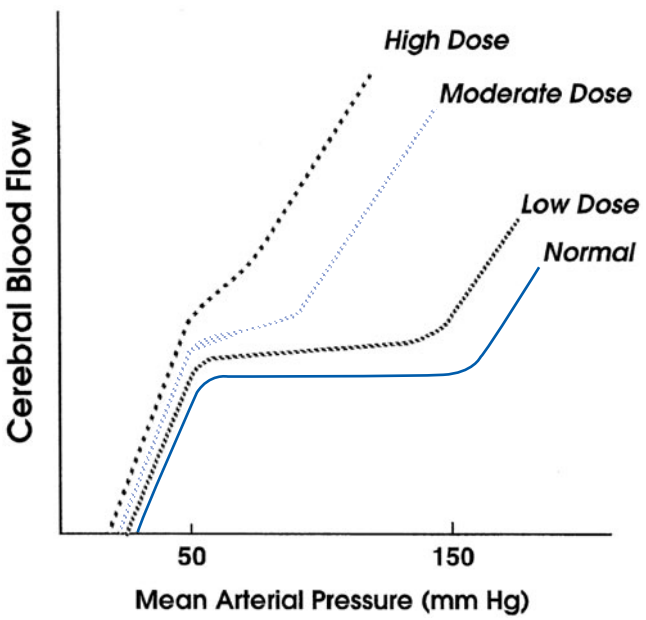


Figure 10-1. Autoregulation maintains a constant cerebral blood flow between mean arterial blood pressures of 50 to 150 mm Hg in the conscious, unanesthetized state. Increasing doses of potent inhalation anesthetics produce a dose-dependent disruption of autoregulation owing to cerebral vasodilatation. (*Modified with permission from Shapiro H: Anesthesia effects upon cerebral blood flow, cerebral metabolism, electroencephalogram and evoked potentials, in Miller RD (ed): Anesthesia, 2d ed. New York, Churchill-Livingstone, 1986; p 1249.*)

blood flow more linearly dependent on blood pressure (Fig. 10-1).

Although noninvasive blood pressure monitoring suffices for most patients during routine noncardiac surgery, direct measure of arterial blood pressure with an indwelling catheter is necessary for cardiac surgery in order to detect changes rapidly, to measure nonpulsatile blood pressure during cardiopulmonary bypass, and to facilitate blood sampling for laboratory analysis. The measuring system includes an intra-arterial catheter and low-compliance saline-filled tubing connected to a transducer with a pressure-sensing diaphragm. The transducer has a strain gauge that converts the mechanical energy (displacement of the diaphragm by a change in pressure) into an electric signal that typically is displayed as a pressure waveform with numeric outputs for systolic, diastolic, and mean pressures. The mean blood pressure is determined by calculating the area under several pulse waveforms and averaging over time. This represents a more accurate measure of mean arterial blood pressure than weighted averages of systolic and diastolic pressures.

The transducer requires a zero reference at the level of the right atrium. Any movement of the patient or the transducer that changes the vertical distance between the transducer and the right atrium affects the value of the blood pressure measured. If the transducer is lowered, the pressure diaphragm senses arterial blood pressure plus hydrostatic pressure generated from the vertical column of fluid contained in the tubing and displays a falsely high blood pressure. A transducer elevated above the zero reference level decreases the displayed blood pressure. A 1-cm column of water (blood) exerts a hydrostatic pressure equal to 0.74 mm Hg. Small changes in patient or transducer position have a relatively insignificant effect on arterial blood pressure measurements but have a more important effect on lower-amplitude pressure measurements, such as central venous, pulmonary artery, and pulmonary artery occlusion pressures.

The intra-arterial cannula, tubing, and transducer assembly are prepared prior to surgery and flushed with heparinized saline. All air bubbles must be cleared from the system to prevent damping and air embolism. The radial artery is the most common site for insertion of an intra-arterial catheter. The increased use of arterial conduits for coronary grafts limits the possible sites for monitoring. Twenty-gauge catheters are preferred because larger catheters are more likely to cause thrombosis. Thrombosis of the radial artery does not produce ischemia of the hand and fingers in the presence of intact ulnar blood flow and a patent palmar arch, although distal emboli remain a risk. The Allen test was designed to assess ulnar and palmar arch blood flow during abrupt occlusion of the radial artery, but its value to predict morbidity with radial artery cannulation is equivocal.[15] Other sites selected for the insertion of an intra-arterial catheter include the brachial, axillary, and femoral arteries.

The contour of the arterial pressure waveform is different in central and peripheral arteries. The propagating pressure waveform loses energy and momentum with a corresponding delay in transmission, loss of high-frequency components such as anacrotic and dicrotic notches, lower systolic and pulse pressures, and decreased mean pressure.[16] The changes in the pulse waveform can be attributed to damping, blood viscosity, vessel diameter, vessel elastance, and the effects of reflectance of the incident arterial waveform by the artery-arteriolar junction.[17,18] The blood pressure waveform measured in the ascending aorta is minimally affected by reflected waves in contrast to measurement of blood pressure in the dorsalis pedis or radial artery. Vasodilators decrease terminal impedance at the artery-arteriolar junction and decrease the resonant frequency of the arterial waveform.

The contour of the pressure waveform is affected by the physical construction of the monitoring system. A hyperresonant response to a change in pressure, or ringing, occurs when the frequency response of the monitoring system (i.e., extension tubing, catheter, and stopcocks) is close to the frequency of the pressure waveform.[16] The natural or resonant frequency f_n of a monitoring system is defined by

$$f_n = \frac{1}{2\pi}\sqrt{\frac{\pi D^2}{4pL \cdot C}}$$

where C is compliance of the measuring system, L is the length of the tubing, D is the diameter of the catheter extension tubing, and p is the density of the solution.

To prevent ringing, the natural frequency of the monitoring system f_n must be greater than the frequencies of the pulse waveform. Any process that decreases f_n, such as narrow, long, compliant tubing, may cause *ringing*.[19] Ringing increases the value of the systolic blood pressure and decreases the value of the diastolic blood pressure but generally does not affect the value of the mean arterial pressure.

Damping is the tendency of the measuring system, through frictional losses, to blunt the peaks and troughs in a signal.[20] Kinks in the pressure tubing or catheter, stopcocks, and air bubbles contribute to damping. Overdamped systems underestimate systolic blood pressure and overestimate diastolic blood pressure. When long lengths of tubing are necessary, deliberate damping may improve the fidelity of the arterial waveform.

Testing a measuring system for ringing and damping ensures that an arterial contour is reproduced faithfully. A simple test is the brief flush of a high-pressure heparinized saline-filled catheter extension assembly. Flush and release should produce a rapid return of the pressure waveform to baseline with minimal oscillations. A gradual return to baseline and loss of higher-frequency components of the waveform suggests overdamping. A rapid return to baseline followed by sustained oscillations suggests ringing.

Electrocardiogram

The intraoperative ECG monitor has evolved from the fading-ball oscilloscope to a sophisticated microprocessor analog display. ECG signals are filtered digitally to eliminate electrical artifact produced by high-frequency (60-Hz) electrical power lines, electrocautery, patient movement, and baseline drift. The bandwidth filter modes are diagnostic, monitor, and filter. The diagnostic mode has the widest bandwidths (least filtered signal) and is preferred for detecting ST-segment changes caused by myocardial ischemia. Monitor and filter modes have progressively narrower bandwidths that effectively eliminate high-frequency interference and baseline drift but decrease the sensitivity of detecting ST-segment changes and decrease the specificity of ST-segment change to diagnose myocardial ischemia. Abnormal ST-segment depression (>1 mV) can occur from excessive low-frequency filtering and result in the misdiagnosis of myocardial ischemia. Filter modes are useful for detecting P waves and changes in cardiac rhythm in the presence of high-frequency interference.

The ECG is the most sensitive and practical monitor for the detection and diagnosis of disorders of cardiac rhythm and conduction and myocardial ischemia and infarction. Continuous monitoring of leads II and V_5 is common (Fig. 10-2). Together these leads detect greater than 90% of ischemic episodes in patients with coronary artery disease who have noncardiac surgery.[21] The ECG leads selected for monitoring of myocardial ischemia can be guided by preoperative testing. Myocardium at risk, identified by exercise testing or coronary angiograms, can be monitored by selecting the lead with the appropriate vector. A

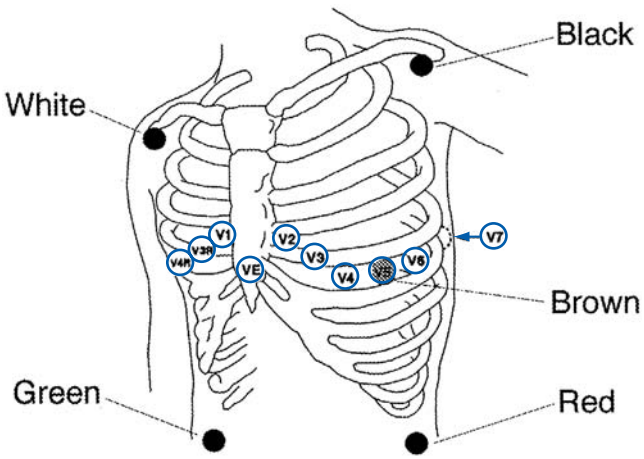


Figure 10-2. Standard intraoperative electrocardiogram (ECG) lead placement. Typically, leads II and V_5 are monitored continuously.

reversible perfusion defect of the inferior wall of the left ventricle during an exercise thallium reperfusion scan may encourage the anesthesiologist to specifically monitor leads II, III, and AVF.

Diagnostic criteria for myocardial ischemia based on the ECG are (1) acute ST-segment depression greater than 0.1 mV 60 ms beyond the J point or (2) acute ST-segment elevation greater than 0.2 mV 60 ms beyond the J point[22] (Fig. 10-3). The normal ST-segment curves smoothly into the T wave. Flat ST segments that form an acute angle with the T wave or downsloping ST segments are worrisome for subendocardial ischemia. ST-segment elevation occurs with transmural myocardial injury but also may occur after direct current (dc) cardioversion and in normal adults. The lack of specificity of ST-T-wave changes for myocardial ischemia is a major limitation of intraoperative ECG monitoring. Pericarditis, myocarditis, mitral valve prolapse, stroke, and digitalis therapy may produce changes in the ST segment that mimic myocardial ischemia.

Digital signal processing handles much larger quantities of information than the unaided eye and may increase the ability to detect ischemic episodes. ST-segment position analyzers automatically measure the displacement of the ST segment from a predetermined reference and enhance the ability to quantify changes in ST-segment position. Appropriate application requires accurate identification of the various loci in the P-QRS-T-wave complex. The operator defines the baseline and the J point of a reference QRS complex by movement of a cursor. New QRS-T-wave complexes are superimposed onto a predefined mean reference complex. Vertical ST-segment displacement is measured in millivolts and displayed graphically in 1-mV increments (see Fig. 10-3). Because the accuracy of automated ST-segment monitoring is vulnerable to baseline drift and dependent on appropriate identification of the PR and ST segments, the diagnosis of myocardial ischemia is always verified by inspecting the actual ECG tracing.

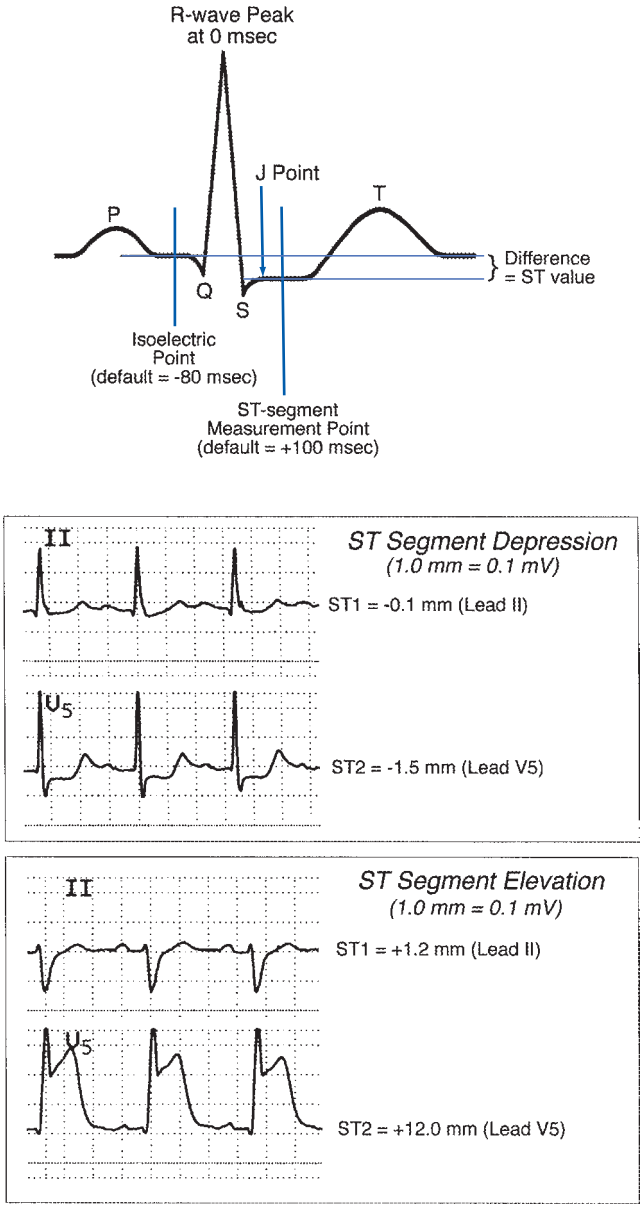


Figure 10-3. Automated ST-segment monitoring of the ECG can be used to detect intraoperative myocardial ischemia. General criteria for myocardial ischemia are ST-segment depression greater than 0.1 mV or ST-segment elevation greater than 0.4 mV that persists for longer than 1 minute. At fast heart rates, the ST-segment measurement point may occur on the upslope of the T wave, causing erroneous indication of ST-segment elevation.

Disturbances of rhythm and conduction are common during anesthesia and especially during cardiac surgery. Instrumentation of the heart, hypothermia, electrolyte abnormalities, myocardial reperfusion, myocardial ischemia, and mechanical factors such as surgical manipulation of the heart affect normal propagation of the cardiac action potential. Heart rate is measured by averaging several RR intervals of the ECG. The ECG may not sense the R wave of the selected lead if the electrical vector is isoelectric. A prominent T wave or pacemaker spike may be miscounted as an R wave by the ECG and artifactually double the rate. Usually, heart rate is best monitored by selecting the lead with an upright R wave and adjusting the sensitivity.

The QT interval can be measured only on hard copy. A normal QT interval is less than half the RR interval, but the QT interval must be corrected for heart rates higher than 90 or lower than 65 beats per minute. A prolonged QT interval increases the risk of reentrant ventricular tachydysrhythmias and may occur from hypokalemia, hypothermia, and toxic drug effect (e.g., quinidine or procainamide). The electrically dormant heart during aortic cross-clamping and perfusion with cold cardioplegia is monitored by the ECG. Hypothermia decreases action potential conduction velocity, and high-dose potassium decreases the transcell membrane potassium concentration gradient to prevent depolarization of cardiac muscle. During cardiopulmonary bypass and aortic cross-clamping, the loss and persistent absence of electromechanical activity suggest that myocardial oxygen consumption is maintained at a minimum.

Monitoring the ECG is most valuable when it begins before induction of general anesthesia. A hard copy of the pertinent leads permits comparison should a change be detected. An abnormal or marginal finding is less worrisome if it was present in the preoperative ECG and remains unchanged during the perioperative period. However, new-onset ST-T-wave changes or disturbances in rhythm and conduction suggest an ongoing active process that usually requires immediate attention.

Capnography

Capnometry is the measure of carbon dioxide (CO_2) concentration in a gas. The capnogram is the continuous graphic display of airway carbon dioxide partial pressure (Fig. 10-4). Changes in its contour reflect disorders of ventilation, carbon dioxide production, or carbon dioxide transport to the lungs. The capnogram is the single most effective monitor for detecting esophageal intubation, apnea, breathing circuit disconnects, accidental extubation of the trachea, and airway obstruction. Tracheal intubation is verified by detection of physiologic carbon dioxide concentrations in the exhaled gas. A steep increase in the phase 3 slope of the exhaled CO_2 concentration suggests partial airway obstruction, either mechanical (e.g., tube kinking) or physiologic (e.g., bronchospasm). A progressive decrease in exhaled

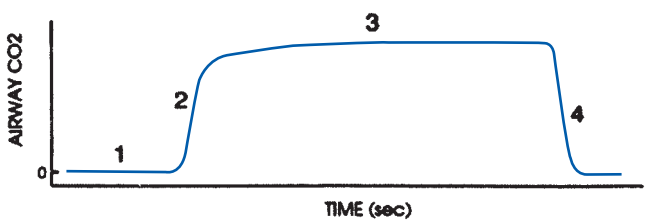


Figure 10-4. The normal capnogram: (1) inspired CO_2 concentration = zero, (2) washout of anatomic dead space, (3) plateau represents alveolar gas CO_2 content, and (4) beginning of inhalation.

carbon dioxide concentration occurs with decreased CO_2 production (e.g., hypothermia), increased minute ventilation, increase in physiologic dead space ventilation (e.g., pulmonary embolus), or low cardiac output. A progressive increase in exhaled carbon dioxide concentration occurs with hypoventilation, increased CO_2 production (e.g., malignant hyperthermia), or increased delivery of CO_2 to the lungs (e.g., during weaning off bypass). The contour of the capnogram is also affected by the expiratory flow rate, distribution of pulmonary blood flow, distribution of ventilation, and use of sidestream or mainstream CO_2 analyzers. Despite the interplay of mechanical and physiologic factors that affect the shape of the capnogram, any abrupt change in contour always signifies an acute change in the patient's cardiovascular, pulmonary, or metabolic state.

Pulse Oximetry

Pulse oximeters were adopted universally into the practice of anesthesia almost immediately after their introduction despite lack of data demonstrating improved outcome with their use. Oxyhemoglobin saturation and arterial oxygen tension are measured routinely during cardiac surgery by intermittent arterial blood sampling. Arterial blood gas analysis does not replace the pulse oximeter, which continuously measures arterial hemoglobin saturation and pulse rate. The pulse oximeter detects decreasing percentages of oxyhemoglobin before changes in the color of the patient's skin or blood are evident.[23] The pulse oximeter is reusable, inexpensive, and noninvasive and provides continuous online data. Its major limitations include electrical interference, motion artifact, high failure rate during periods of low flow or inadequate perfusion, and the need for pulsatile flow for proper operation.[24]

Pulse oximetry measures the percentage of oxyhemoglobin in arterial blood by transillumination and detection of differences in the optical absorption properties of oxy- and deoxyhemoglobin. Transmission oximetry at wavelengths of 660 and 940 nm and photoplethysmography and rapid signal processing permit reliable and rapid determination of the relative proportion of oxy- and deoxyhemoglobin. Oxyhemoglobin has a higher optical absorption in the infrared spectrum (940 nm), whereas reduced hemoglobin absorbs more light in the red band (660 nm). The ratio *R* of light absorbance at the two wavelengths is a function of the relative proportions of the two forms of hemoglobin.

Photoplethysmography permits the measure of arterial hemoglobin saturation by isolating the pulsatile component of the absorbed signal. The peaks and troughs in the blood volume of the finger or ear being transilluminated produce a corresponding pulsatile effect on light absorption, rendering the calculated oxyhemoglobin saturation independent of nonpulsatile venous blood and soft tissue. Calculation of arterial hemoglobin saturation is based on calibration algorithms derived from healthy volunteers. The *R* values were determined by in vitro measures of oxyhemoglobin saturation and are less accurate at oxyhemoglobin saturations below 70%. Motion artifact produces a high absorption of light at both wavelengths and an *R* value of approximately 1 that corresponds to an oxyhemoglobin saturation of approximately 85%.

The pulse oximeter is unable to distinguish other hemoglobin species that absorb light at the emitted wavelengths. Methemoglobin (ferric instead of ferrous hemoglobin) has similar absorption at both 660 and 940 nm with an *R* value of 1 and a corresponding displayed saturation of 85% regardless of the true value. Carbon monoxide poisoning produces carboxyhemoglobin that has significant absorption at 660 nm and is interpreted erroneously by the pulse oximeter as oxyhemoglobin.

Measurement of Temperature

Profound changes in body temperature during cardiac surgery are common, often deliberate, and affect vital organ function (Fig. 10-5). Anesthetized patients are poikilothermic. Intrinsic temperature regulation normally controlled by the hypothalamus fails during general anesthesia. Hypothermia occurs by passive and active heat loss. Passive mechanisms of cooling include radiation, evaporation, convection, and conduction. Active cooling usually occurs with extracorporeal circulation and with the use of cold or iced solutions poured into the chest cavity. Deliberate hypothermia during cardiac surgery is designed to arrest and cool the heart and decrease systemic oxygen consumption. Hyperthermia may result from preexisting fever, bacteremia, malignant hyperthermia, or overzealous rewarming during cardiopulmonary bypass.

Malignant hyperthermia is a rare inherited disorder of muscle that is potentially fatal.[25] It is an autosomal dominant trait with variable penetrance that is almost always quiescent until the patient is exposed to a triggering agent, such as volatile anesthetics or succinylcholine. Malignant hyperthermia is associated with derangements in calcium metabolism. Ineffective uptake of calcium by sarcoplasmic reticulum and abnormal release of calcium from intracellular storage sites occurs with massive skeletal muscle depolarization in response to triggering agents. Clinical manifestations of malignant hyperthermia include increased production of carbon dioxide, tachycardia, and increased cardiac output, followed by fever, metabolic and respiratory acidosis, hyperkalemia, cellular hypoxia, rhabdomyolysis, myoglobinuria, renal failure, and cardiovascular collapse. Serum creatine kinase is increased and may be of diagnostic value. The fever may reach 43°C but may be masked by deliberate hypothermia during cardiopulmonary bypass. Despite increased awareness, improved monitors, and the advent of established treatment algorithms with dantrolene, mortality rates remain high. Treatment is aimed at discontinuing the trigger agent and controlling body temperature through active cooling. Oxygen, hyperventilation, and correction of metabolic acidosis and electrolyte abnormalities are the cornerstone of therapy.

Dantrolene blocks calcium release and is administered at a dose of 2 mg/kg intravenously every 5 minutes for a total

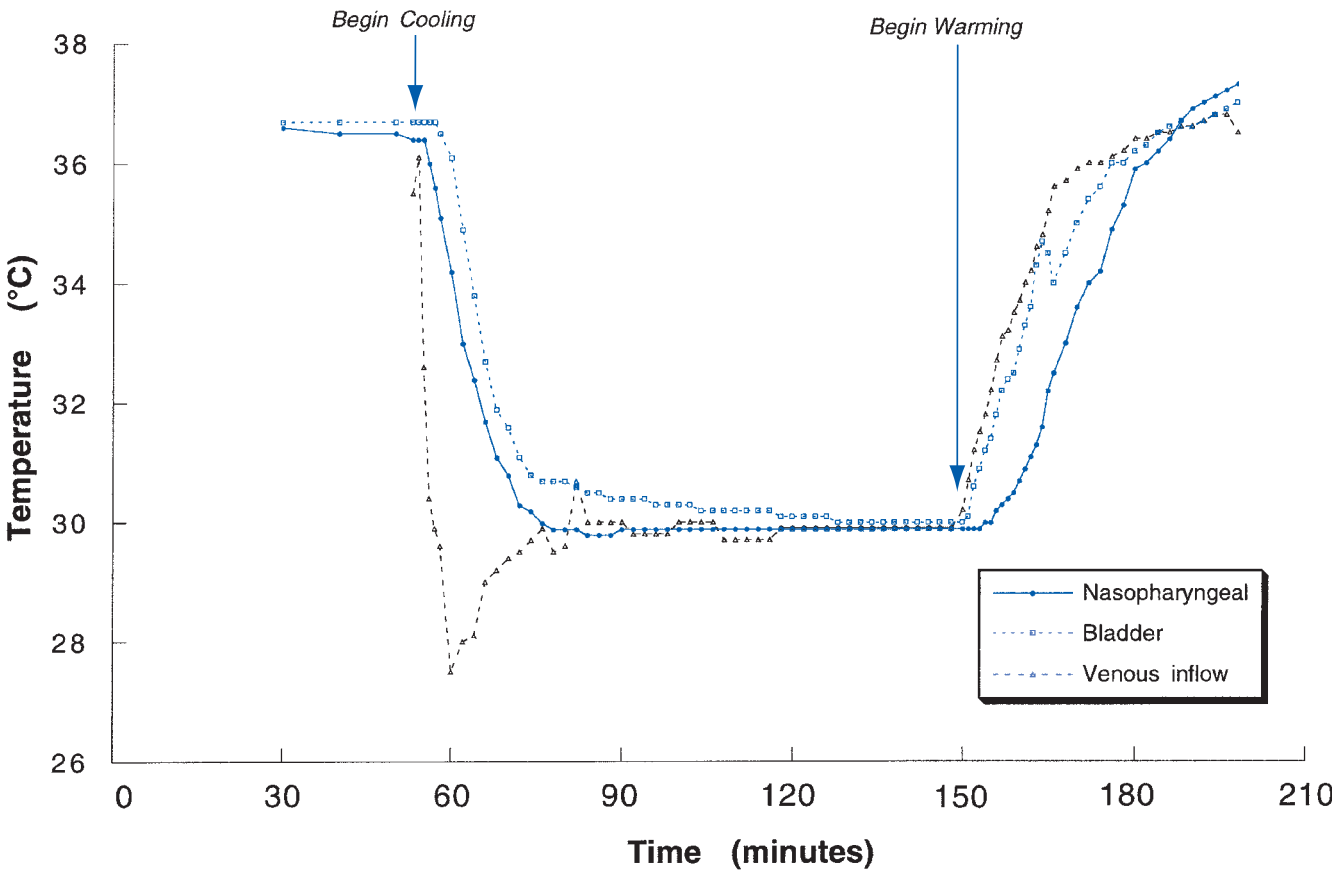


Figure 10-5. Changes in body temperature during hypothermic cardiopulmonary bypass. A brisk diuresis accompanied rewarming, rendering the urine an ultrafiltrate of blood and resulting in the urine (bladder) temperature closely tracking temperature measured in the venous blood in the cardiopulmonary bypass machine.

dose of 10 mg/kg.[26] Intravenous dantrolene generally is continued at 12-hour intervals for a minimum of 24 hours because episodes of malignant hyperthermia may recur even after the trigger agent has been discontinued. The incidence of malignant hyperthermia is approximately 1 in 62,000 anesthetics. Patients with a history of malignant hyperthermia and those with most types of muscular dystrophies are at increased risk. Not all episodes of malignant hyperthermia lead to progressive metabolic and cardiovascular collapse. Unexplained fever after an anesthetic or in the recovery room may identify a patient at increased risk. Testing by in vitro skeletal muscle responses to halothane and/or caffeine is recommended for the preoperative diagnosis of patients suspected to be at increased risk. High-risk patients can be anesthetized safely by using anesthetic drugs such as narcotics, barbiturates, nitrous oxide, local anesthetics, and nondepolarizing muscle relaxants that are not believed to trigger malignant hyperthermia.

Hypothermia after cardiopulmonary bypass is the result of ineffective rewarming; cold operating rooms; cold, wet surgical drapes; a large surgical incision; and administration of cold intravenous fluids. Hypothermia exacerbates dysrhythmias and coagulopathy, potentiates the effects of anesthetic drugs and neuromuscular blockers, increases vascular resistance, decreases the availability of oxygen, and contributes to postoperative shivering. The elderly are especially susceptible because of limited compensatory reserve. Evidence supports the efficacy of mild therapeutic hypothermia for brain protection after cardiac arrest and resuscitation.[27]

Temperature typically is monitored from several sites during cardiac surgery. Blood temperature is measured from the tip of the pulmonary artery catheter and within the cardiopulmonary bypass circuit (typically venous and arterial lines). Blood temperature is the first to change in response to deliberate hypothermia or active rewarming during cardiopulmonary bypass. Nasopharyngeal and tympanic temperatures reflect the temperature of the brain and closely track blood temperature because these sites are highly perfused. Rectal and bladder temperatures provide a measure of core temperature only at equilibrium. Esophageal temperature often underestimates core temperature because of the cooling effects of ventilation in the adjacent trachea. Axillary and inguinal temperature are shell measurements and are impractical.

The degree and site of temperature change are important indicators of an intact circulatory system. A persistent

discrepancy in temperature between two sites may be a sign of malperfusion. Rewarming during cardiopulmonary bypass normally is associated with an increase in nasopharyngeal or tympanic temperature accompanied by a more gradual increase in temperature in organs with low perfusion. A persistently cold nasopharynx with a normal rate of increase in rectal temperature may be due to aortic dissection and hypoperfusion of the head.

Measurement of Cardiac Output and Central Venous and Pulmonary Artery Pressures

Cannulation of the central venous circulation permits central administration of drugs, passage of catheters and pacing electrodes into the heart, rapid administration of fluids through short, large-bore cannulas, and the measure of central venous pressure. The most commonly used site for central venous access is the internal jugular vein because of easy, reliable insertion; easy access from the head of the table; decreased risk of pneumothorax; and decreased risk of catheter kinking during sternal retraction. The subclavian vein is the preferred site for insertion of a central venous catheter for long-term intravenous total parenteral nutrition because of a decreased risk of blood-borne infection.[28] The most important complication of internal jugular vein cannulation is inadvertent puncture or cannulation of the carotid or subclavian artery. Cannulation of the central venous circulation is confirmed by transducing the pressure waveform prior to insertion of a large-bore catheter. Ultrasound-guided cannulation of the internal jugular vein renders the procedure less dependent on anatomic landmarks and is associated with a decrease in the number of unsuccessful cannulation attempts[29] (Fig. 10-6). With the advent and wide availability of portable ultrasound imaging devices, ultrasound-guided central venous cannulation is becoming commonplace to increase the success rate and decrease the risk of complications.[30]

Central venous pressure (CVP) is an index of right ventricular preload. The pulsatile *a, c,* and *v* pulse waveforms are a function of uninterrupted return of venous blood to the right atrium, right atrial contraction and right atrial size and compliance, intrathoracic pressure, and mechanical properties of the tricuspid valve and right ventricle. The normal CVP is 6 to 10 mm Hg and is measured at end exhalation. A decrease in CVP suggests hypovolemia or vasodilation. An increased CVP with normal cardiac function occurs with hypervolemia, vasoconstriction, and increased intrathoracic pressure. CVP is increased by positive-pressure ventilation and positive end-expiratory pressure. Systemic hypotension accompanied by an increased CVP suggests cardiac dysfunction. The most common cause of venous hypertension is left-sided heart failure, although acute left ventricular dysfunction may cause an increase in left atrial and pulmonary artery occlusion pressure without significant change in CVP.

Pulmonary artery catheters are inserted via the central venous circulation through the right side of the heart with the catheter tip positioned just downstream of the pulmonic valve. The pulmonary artery catheter measures pulmonary artery pressure, pulmonary artery occlusion pressure, cardiac output, and mixed venous oxygen saturation and permits calculation of the derived values of systemic and pulmonary vascular resistance. The pulmonary artery occlusion pressure is an index of left ventricular preload in the absence of mitral stenosis. However, the use of a pressure measurement to estimate preload is limited because of variability in left ventricular size and compliance. The hemodynamic parameters derived from the pulmonary artery catheter may be used to detect myocardial ischemia if ischemia produces ventricular dysfunction that is associated with a decrease in

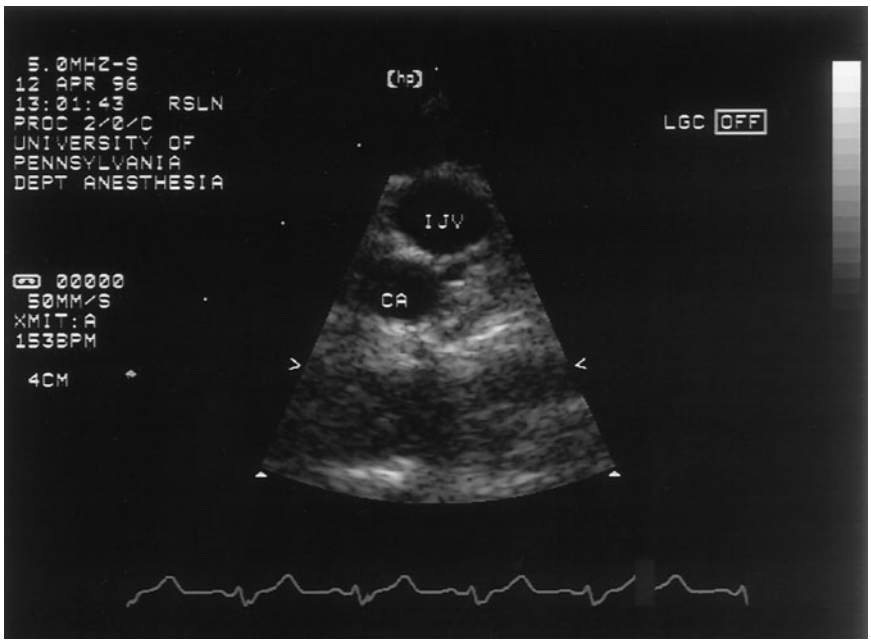


Figure 10-6. A two-dimensional short-axis image of the internal jugular vein (IJV) and carotid artery (CA) using a handheld ultrasound transducer.

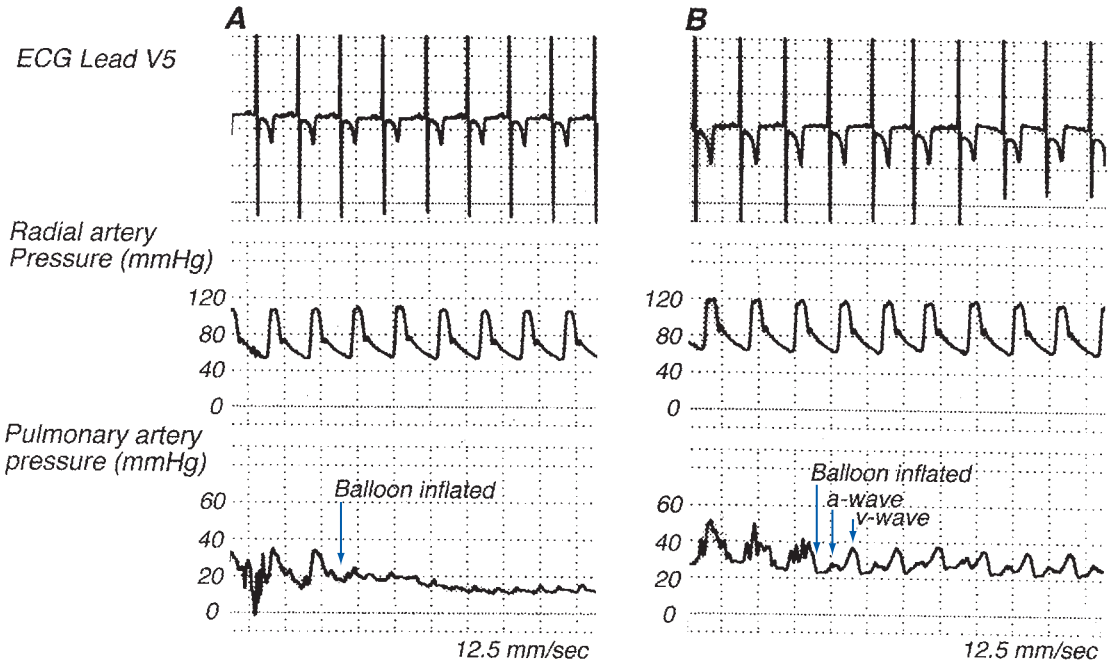


Figure 10-7. Pulmonary artery occlusion pressure tracing at two time points. The acute onset of myocardial ischemia (*B*) was associated with ST-segment depression in ECG lead V_5, increased pulmonary artery pressures, and a prominent *v* wave.

cardiac output, increase in left ventricular end-diastolic pressure, or pulmonary hypertension (Fig. 10-7). However, hemodynamic parameters derived from the pulmonary artery catheter are not as sensitive or as specific for detecting myocardial ischemia as the ECG.[31] Pulmonary artery occlusion pressure is affected by volume status, myocardial compliance, mode of ventilation, and ventricular afterload.

Complications associated with insertion of a pulmonary artery catheter include infections, dislodgment of pacemaker wires or right atrial or ventricular clot or tumor, atrial and ventricular arrhythmias, pulmonary infarction, pulmonary artery rupture, catheter entrapment, and heart block. The incidence of right bundle-branch block (RBBB) is approximately 3% and may cause complete heart block in patients with a preexisting left bundle-branch block (LBBB).[32] A mechanism to treat complete heart block (e.g., external pacer) should be available for these patients. Passage of the pulmonary artery catheter can be delayed for most patients until after sternotomy, when heart block can be treated with epicardial pacing wires. Chronic indwelling pulmonary artery catheters are associated with a progressive thrombocytopenia.[33] Heparin-bonded catheters decrease the incidence of thrombus formation,[34] but high-dose aprotinin may increase the risk of early thrombus formation.[35]

Multiport pulmonary artery catheters equipped with a tip thermistor permit the measurement of pulmonary blood flow or cardiac output by thermodilution. Thermodilution cardiac output is an indicator-dilution technique. The indicator, a known volume of cold saline, is injected rapidly into the right atrium. Cardiac output (CO) is calculated from the rate of change in blood temperature in the pulmonary artery over time using the Stewart-Hamilton equation[36,37]:

$$CO = \frac{V(T_B - T_1)K_1K_2}{\int_0^\infty \Delta T_B(t)\,dt}$$

where CO is cardiac output, V is the volume of the injectate, T_B is the blood temperature at time 0, T_I is the injectate temperature at time 0, $\Delta T_B(t)$ is the change in blood temperature at time t, K_1 is the density factor, and K_2 is the computation factor.

Thermodilution measures the degree of mixing that occurs between the cold injectate and blood. More mixing implies increased flow. Complete mixing of 10 mL of cold injectate with a circulating blood volume produces a small decrease in temperature at the catheter tip. Poor mixing, suggestive of slow, sluggish flow, produces a large decrease in temperature as the injectate bolus passes the thermistor. The derived value for cardiac output is inversely proportional to the area under the thermodilution curve. Rapid infusion of cold intravenous fluids at the time of measurement may falsely increase the derived cardiac output. Thermodilution measures right-sided cardiac output, which does not equal left-sided cardiac output in patients with intracardiac shunts. There are no outcome data to support the routine use of a pulmonary artery catheter in cardiac surgery.

Cardiac output may be monitored continuously using a specialized pulmonary artery catheter. The continuous cardiac output catheter intermittently heats blood adjacent to a proximal portion of the catheter and senses changes in blood

temperature at the catheter tip using a fast-response thermistor. The method requires no manual injections, and values are acquired, averaged, and updated automatically every several minutes. Disadvantages include increased cost and a cardiac output display that is not instantaneous but is an average value over the prior 2 to 10 minutes. Other methods of measuring cardiac output that do not depend on an indwelling pulmonary artery catheter include transthoracic bioimpedance, echocardiography, and analysis of the aortic pressure pulse contour. These have proven cumbersome, impractical, or unreliable for routine use.[38]

Mixed venous oxygen saturation ($S\bar{v}O_2$) can be measured intermittently by manual blood sampling from the pulmonary artery or continuously using a modified pulmonary artery catheter equipped with an oximeter. The $S\bar{v}O_2$ provides a continuous monitor of cardiovascular well-being. Assuming normal oxygen consumption, a normal $S\bar{v}O_2$ generally denotes adequate oxygen delivery but does not provide information about the adequacy of perfusion to specific organs. A normal $S\bar{v}O_2$ may not reflect adequate tissue perfusion in patients with intracardiac shunts, sepsis, or liver failure. A decrease in $S\bar{v}O_2$ is rarely caused by an increase in oxygen consumption during cardiac surgery but is more likely a sign of decreasing oxygen delivery owing to decreased cardiac output, anemia, or hypoxia.

$S\bar{v}O_2$ provides an alternative method to calculate cardiac output if oxygen consumption is assumed to be constant. By the Fick equation, cardiac output is equal to the rate of systemic oxygen consumption divided by the arterial-venous oxygen content difference:

$$O_2 \text{ delivery} = CO \times CaO_2$$
$$O_2 \text{ delivery} = \dot{V}O_2 + (CO \times C\bar{v}O_2)$$
$$CO \times CaO_2 = \dot{V}O_2 + (CO \times C\bar{v}O_2)$$
$$CO(CaO_2 - C\bar{v}O_2) = \dot{V}O_2$$
$$CO = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2}$$

where $\dot{V}O_2$ is oxygen consumption, CO is cardiac output, CaO_2 is the oxygen content in arterial blood, and $C\bar{v}O_2$ is the oxygen content in mixed venous blood.

Although routine use of a pulmonary artery catheter for monitoring patients during cardiac operation is debated, it does provide clinical information that is used to direct therapy in high-risk patients (Fig. 10-8). Hypotension associated with increased cardiac output with a normal pulmonary artery occlusion pressure likely is caused by vasodilation and is treated effectively with a vasoconstrictor such as phenylephrine, vasopressin, or norepinephrine. Hypotension associated with a low cardiac output and a low pulmonary artery occlusion pressure indicates hypovolemia and is treated with volume expansion (Fig. 10-9). Hypotension associated with a low cardiac output and increased pulmonary artery and pulmonary artery occlusion pressure indicates cardiac dysfunction and may require treatment with an inotropic or anti-ischemic medication. Increasing evidence suggests that pulmonary artery catheter–guided therapy is not necessary for management of acute respiratory distress syndrome, congestive heart failure, and some types of surgery.[39] The pulmonary artery catheter appears to demonstrate continued utility in the care of pulmonary hypertension and right ventricular dysfunction.[40]

An insidious decrease in $S\bar{v}O_2$ may be an early warning of impending circulatory insufficiency owing to a decrease in arterial oxygen tension, ventricular dysfunction, bleeding, or tamponade. $S\bar{v}O_2$ pulmonary artery catheters serve as diagnostic tools and vigilance monitors, especially in the intensive-care unit, where early deterioration in cardiac function can be detected and treated before an adverse event occurs.

Anesthetic Gas Monitors

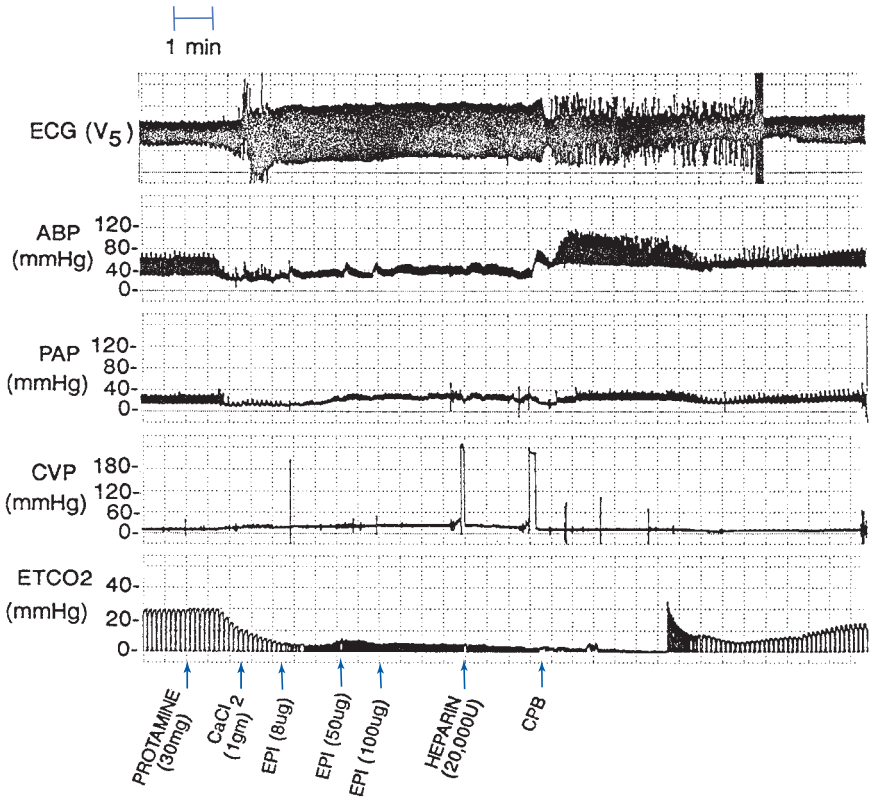
Inhaled volatile anesthetics are different from other parenteral medications. The dose of the drug administered is dictated by its concentration in the blood rather than by a set standard. The concentration of an anesthetic in the exhaled gas at end exhalation reflects the alveolar gas concentration that is in direct equilibrium with the blood. Monitoring the concentration of anesthetic in the end-tidal gas mixture adds precision to the administration of inhaled anesthetics and guards against inadvertent overdose.

The concentration of anesthetic gases is measured clinically by mass spectroscopy. A gas sample retrieved from the breathing circuit is analyzed offline by measuring the dispersion of the ionized sample as it is accelerated and deflected by a magnetic field. The site of impact on a collecting plate is specific for a gas species, and the number of impacts represents the relative concentration of the gas species in the sample. The end-tidal concentration is determined by gating the measure of the anesthetic gas to the carbon dioxide expirogram (capnogram). Other methods of measuring anesthetic and respiratory gases include infrared spectroscopy, Raman spectroscopy, electrochemical and polarographic sensors, and piezoelectric absorption.[41]

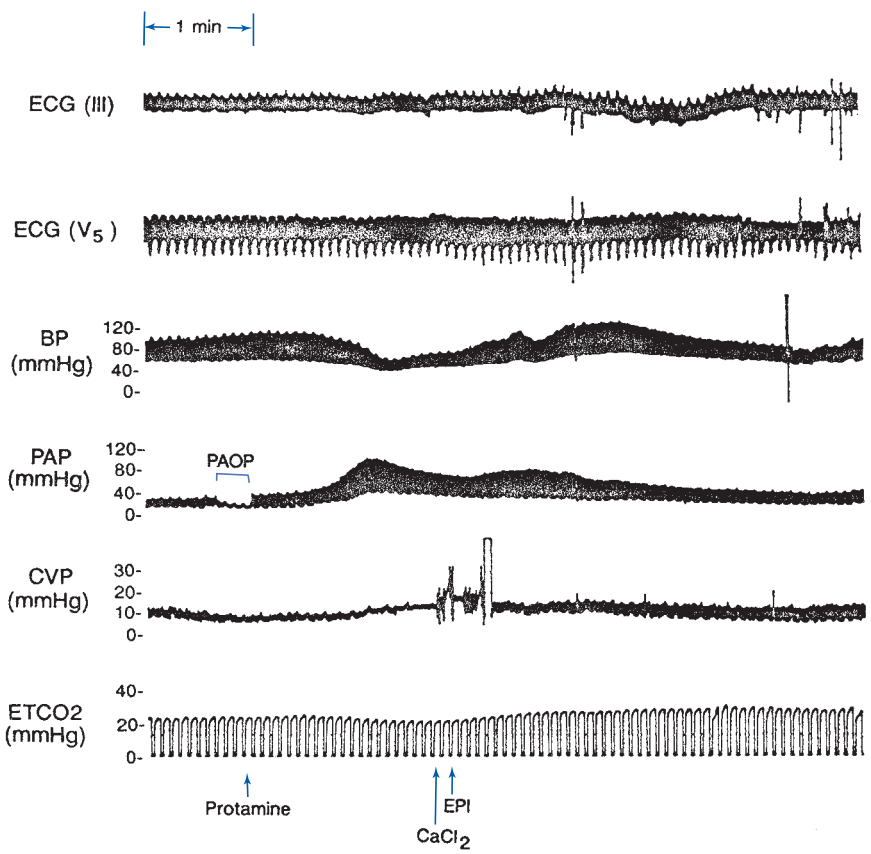
Measurement of Electrolyte Concentration

Electrolyte abnormalities occur commonly during and after cardiopulmonary bypass and are monitored intermittently using routine laboratory tests that are reported promptly to the operating room.[42] Reliable online measurements of electrolytes are not yet available. The capability to detect and correct electrolyte disturbances is an important aspect of intraoperative care.

Abnormalities in sodium and water homeostasis are caused primarily by hemodilution with solutions used to prime the cardiopulmonary bypass circuit. Nonosmotic secretion of arginine vasopressin provoked by surgical stress, pain, hypotension, or nonpulsatile perfusion contributes to the development of hyponatremia by stimulating renal retention of free water. A 2 to 5 mEq/L decrease in the plasma sodium concentration is expected after beginning cardiopulmonary bypass and does not normally require treatment. Hyperglycemia or excessive mannitol administration causes



A



B

Figure 10-8. Intraoperative hemodynamic recordings showing the time sequence of systemic severe vasodilation (*A*) and catastrophic pulmonary vasoconstriction–type (*B*) protamine reactions during the reversal of heparin anticoagulation in patients undergoing heart operation. Arterial blood pressure (ABP) and pulmonary artery pressure (PAP) decrease in parallel during systemic vasodilation. In contrast, an increase in PAP and central venous pressure (CVP) precedes the decrease in ABP during the pulmonary vasoconstriction–type reaction. The decreases in end-tidal carbon dioxide concentration ($ETCO_2$) during the protamine reactions reflect the decrease in blood flow through the lungs.

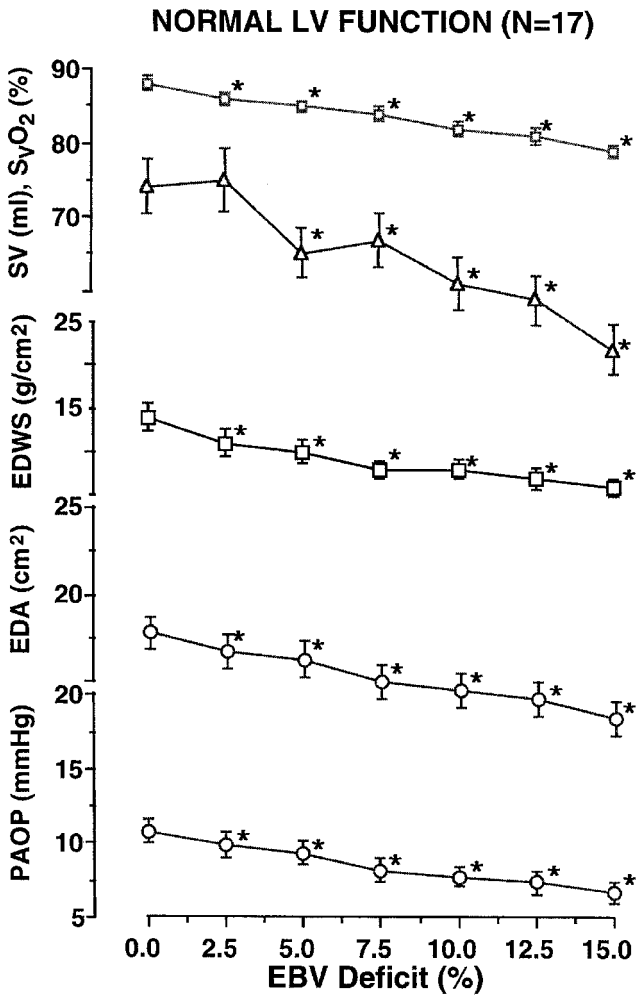


Figure 10-9. Decreased left ventricular preload produced by graded estimated blood volume deficits (EBVs) was associated with a serial decreases in the mixed venous oxygen saturation ($S\bar{v}O_2$), cardiac stroke volume (SV), left ventricular end-diastolic meridional wall stress (EDWS), left ventricular end-diastolic cavity cross-sectional area (EDA), and pulmonary artery occlusion pressure (PAOP). Patients with dilated cardiomyopathy displayed less change in SV and $S\bar{v}O_2$ in response to equivalent EBV deficits. *$p < .05$ versus baseline value (ANOVA for repeated measures). (*Modified with permission from Cheung AT, Weiss SJ, Savino JS: Protamine-induced right-to-left intracardiac shunting. Anesthesiology 1991; 75:904.*)

pseudohyponatremia by decreasing the plasma sodium concentration. Hypernatremia usually is caused by excessive diuresis without free-water repletion or by the administration of hypertonic sodium bicarbonate solutions. Hyperkalemia is common because high-potassium cardioplegic solutions are distributed into the systemic circulation. Hyperkalemia during cardiac surgery also may be caused by hemolysis, acidosis, massive depolarization of muscle, and tissue cell death. Increasing serum potassium concentration is manifested by peaked T waves, a widened QRS complex, disappearance of the P wave, heart block, and conduction abnormalities that may be life-threatening. Very high concentrations of potassium used to provide cardioplegia inhibit spontaneous depolarization and produce asystole. Patients with diabetes mellitus are at increased risk for hyperkalemia because cellular uptake of potassium is mediated by insulin. Impaired renal excretion of potassium enhances hyperkalemia in patients with renal insufficiency. The initial treatment of hyperkalemia is aimed at redistributing extracellular potassium into cells, but the elimination of potassium from the body requires excretion by the kidneys or gastrointestinal tract. Insulin and glucose administration rapidly decrease extracellular potassium by redistributing the ion into cells. Alkalosis, hyperventilation, and beta-adrenergic agonists also favor redistribution of potassium into cells, but the response is less predictable. Calcium carbonate and calcium chloride antagonize the effects of hyperkalemia at the cell membrane. A typical intravenous dose of glucose and insulin for the acute treatment of hyperkalemia is 1 g/kg of glucose and 1 unit of regular insulin per 4 g of glucose administered.

Hypokalemia is also common during cardiac surgery and may be caused by hemodilution with nonpotassium priming solutions, diuresis, or increased sympathetic tone during nonpulsatile perfusion. Intraoperative hypokalemia is exacerbated by preoperative potassium depletion owing to chronic diuretic therapy. Beta$_2$-adrenergic agonists acutely decrease the plasma potassium concentration by directly stimulating cellular uptake of potassium. Hypokalemia predisposes to atrial arrhythmias, ventricular ectopy, digitalis toxicity, and prolonged response to neuromuscular blocking drugs. Hypokalemia is treated by slow administration of KCl in increments of 10 mEq, with potassium concentrations measured between doses.

Hypocalcemia decreases myocardial contractility and peripheral vascular tone and is associated with tachycardia.[43,44] Hypocalcemia produces prolongation of the QT interval and T-wave inversions, but significant arrhythmias owing to disturbances in ionized calcium concentration are not common. Hypocalcemia occurs soon after the onset of cardiopulmonary bypass but may resolve without treatment. Increasing serum concentrations of parathyroid hormone during cardiopulmonary bypass may explain, in part, the gradual increase in ionized calcium concentration to pre–cardiopulmonary bypass levels.[45] The etiology of cardiopulmonary bypass–induced hypocalcemia probably is multifactorial, but hemodilution and decreased metabolism of citrate after rapid blood transfusion are contributing factors. The routine administration of calcium salts without prior measurement of ionized calcium concentration poses the risk of hypercalcemia. Excessive calcium administration may increase the risk of postoperative pancreatitis and myocardial reperfusion injury.[46]

Magnesium deficiency is common in cardiac surgical patients, and acute magnesium supplementation decreases the incidence of postoperative cardiac dysrhythmias and overall morbidity after cardiac operations.[47,48] However, measuring total plasma magnesium concentration has questionable clinical significance because the value primarily

reflects the concentration of protein-bound magnesium and not physiologically active, ionized magnesium.[49]

Perioperative glucose control affects outcome after heart surgery. Hyperglycemia increases the risk after myocardial infarction, stroke, and cardiac surgery.[50–52] Aggressive protocols aimed at maintaining normoglycemia with the use of insulin infusions during cardiac surgery and into the early postoperative period lead to a decrease in morbidity (e.g., sternal wound infection) and possibly mortality.[49,53] However, aggressive control of blood glucose in diabetic patients increases the incidence of hypoglycemia, which can have severe consequences if not detected early and treated.[54]

Monitoring the Nervous System

Anesthetics produce characteristic changes in the electrical activity of the brain. The cellular mechanism of general anesthetics is controversial. Unconsciousness and general anesthesia are not achieved by producing energy failure in the brain. The central nervous system cellular concentrations of ATP, ADP, phosphocreatine, glucose, and glycogen are increased and lactate concentrations are decreased during general anesthesia. Most general anesthetics, and especially the extensively studied barbiturates, decrease cerebral metabolic rate and oxygen consumption.

A myriad of neurologic complications may be associated with cardiac surgery,[55] including stroke, paralysis, cognitive dysfunction, blindness, and peripheral nerve injury.

Stroke

Stroke associated with cardiac surgery occurs in 3 to 8%[56,57] of patients, but the incidence alarmingly may approach 35 to 70% in those with multiple risk factors such as previous stroke, carotid disease, advanced age, hypertension, and diabetes mellitus.[56] The majority of strokes are not identified immediately after cardiac surgery but occur in the first several days postoperatively. The cause of these strokes and their causal relationship to cardiopulmonary bypass remain unclear.

Strokes may be related to micro- or macroemboli but also may be secondary to regional hypoperfusion. The combination of preexisting regional hypoperfusion and embolic phenomenon may be particularly deleterious.[58] The existence of a heavily calcified aorta increases the risk of stroke secondary to macroemboli.[59] Efforts to reduce the incidence of stroke in this patient group include the use of off-pump coronary artery bypass grafting, epiaortic ultrasound to identify "safe" areas for cannulation, and single clamping techniques for proximal anastamoses.[60] Previous work in animal models has demonstrated that in regions of the brain with compromised blood flow, acute anemia may not be well tolerated.[61] Acute anemia in individuals at risk for cerebrovascular disease may be exacerbated by an imbalance in oxygen supply and demand.[62]

The possibility exists to intervene to alter the course of perioperative stroke in individuals at high risk. For example, the application of intra-arterial thrombolytics in a highly selective fashion to the affected cerebral arteries can be done with acceptable morbidity even early after cardiac surgery.[63,64]

Paralysis

Paralysis, a devastating complication, is associated with dissection of the thoracic aorta, with repair of descending thoracic and thoracoabdominal aneurysm, and most recently after placement of endovascular stents.[65] The incidence in repair of a descending thoracic or thoracoabdominal aneurysm is 5 to 10%[66,67] and may exceed 25% in certain high-risk groups.[68] The likely cause is hypoperfusion of the spinal cord during aortic cross-clamping and ligation of intercostal and lumbar arteries.[69] Risk factors for paralysis include extent of the aneurysm and acuteness of disease. Patients without demonstrated flow in intercostals within the aneurysm may be at lower risk for paralysis after resection,[70] presumably because collateral blood supply to the cord in the involved region has been allowed to occur slowly, whereas subjects experiencing acute dissection, which does not permit time for collateralization, may experience a high rate of paralysis.

Intraoperative monitoring, including motor evoked potentials and somatosensory potentials, may be of some benefit to detect early spinal cord ischemia[71,72] yet may lack the sensitivity and specificity necessary to reliably guide intervention.[73] Preemptive measures to limit the degree of spinal cord ischemia have included identification and reimplantation of the artery of Adamkiewicz as well as intercostal vessels,[74,75] placement of cerebrospinal fluid (CSF) drainage catheters to increase the mean arterial pressure to CSF pressure gradient, epidural cooling of the spinal cord,[76,77] and distal perfusion techniques such as left atrial–femoral artery (LA-FA) bypass to enhance cord perfusion from below the inferior clamp site.[78,79] All these techniques have met with potentially important but limited success, and controlled studies demonstrating a difference in outcome do not exist.[80] Spinal cord ischemia is managed in a similar fashion to the management of cerebral ischemia.[81] A continuum of injury exists from infarcted to ischemic tissue. Signs of spinal cord ischemia may improve or deteriorate with time, and there may be, at the very least, an opportunity to ameliorate the extent of the injury through early intervention, such as increasing perfusion pressure and decreasing CSF pressure through drainage.[82] Most treatments are fraught with risk (e.g., the placement of CSF drainage catheters).[83]

Cognitive dysfunction

Postoperative alterations in cognitive function include disturbances of memory, attention, and intellectual function. Cognitive dysfunction occurs after cardiac operations at a rate estimated to be as high as 80% in the acute phase after surgery and may persist in 20 to 40% of patients depending on length of follow-up.[84] More than any other factor, advanced age has been identified consistently as the greatest risk factor for cognitive dysfunction after cardiac surgery

with cardiopulmonary bypass. Early and late mortality may be markedly increased, quality of life is diminished, and costs of care are increased in the short and long run.[85,86]

Etiology has focused on a myriad of potential causes[71] that predominantly include the effects of cardiopulmonary bypass such as hypotension,[87] microemboli,[88] open versus closed cardiac procedures,[89] acute anemia,[90] changes in brain water content,[91] hypoxemia, rewarming strategies,[92] cold versus warm cardiopulmonary bypass,[93] pH management strategy (alpha-stat versus pH-stat),[94] pulsatile versus nonpulsatile perfusion,[95] bypass duration,[96] flow rates,[97] hypo- and hyperglycemia,[98] presence of the apolipoprotein E ϵ-4 allele,[99] and immunologic mechanisms.[100] Lastly, although cognitive dysfunction in the general population has been associated with chronic hypotension[101] and congestive heart failure,[102] the role of left ventricular function in cognition surrounding cardiac surgery is not known.

Research outside the arena of cardiac surgery into neurologic injury in cerebrovascular disease has focused on the immune system as the generator of mediators and modulators of the cerebral endothelium[103,104] and of blood-brain barrier permeability.[105] One theory of immunologic-mediated neuronal injury postulates a cascade of events initiated by complement- and neutrophil-mediated vascular endothelial damage and disruption of the blood-brain barrier, thus allowing neutrophil access to the parenchyma with resulting neural destruction.[103,105]

Neurologic sequelae in noncardiac surgery

It would be irresponsible not to mention that stroke and cognitive dysfunction occur in patients after noncardiac surgery at a rate that is significantly less than that seen in the cardiac surgery group, yet the incidence is not negligible[106–108] and also may be associated with prolonged deficits.[109,110] There may be similar risk factors and similar pathophysiologic mechanisms in this group of patients, especially in the origins of delayed stroke in the perioperative period. Investigations ultimately even may implicate the anesthetic agents themselves,[111] irrespective of issues of intraoperative hemodynamic management.

Neurophysiologic monitoring techniques permit assessment of nervous system function during and early after operation because clinical evaluation is not possible. Techniques to monitor neurophysiologic function during general anesthesia include electroencephalography (EEG) and somatosensory evoked potentials (SSEPs). The EEG is a recording of the spontaneous electrical activity of the cerebral cortex and is defined by frequency, amplitude, and spatial distribution.[112] The amplitude of electrical activity decreases by more than 80% when the recording electrode is displaced only 2 cm from the site of maximum amplitude. This necessitates multiple electrodes and channel recordings to obtain a spatial representation of the EEG rhythm.[113] A change in EEG amplitude or frequency may be produced by cerebral ischemia, anesthetics, or hypothermia. Barbiturates produce a flat EEG, whereas enflurane may cause seizurelike activity. EEG burst suppression is not uncommon after induction of general anesthesia but does not exclude an impending neurologic catastrophe if induced by changes in cerebral blood flow. While continuous EEG monitoring may detect cerebral ischemia during carotid operations, its application during cardiac operations is problematic because the decrease in EEG frequency and amplitude owing to anesthesia and hypothermia during operation cannot be distinguished from changes caused by cerebral ischemia.[114,115] Electrical artifacts from the heart-lung machine also interfere with the ability to monitor the EEG continuously during operation. Intraoperative monitoring of SSEPs to detect cerebral ischemia overcomes some of the problems inherent in EEG monitoring because the temperature dependency of SSEPs is well established.[116] Embolic stroke and brachial plexus injury can be detected using intraoperative SSEP monitoring, but the utility, sensitivity, and specificity of this technique for detecting, preventing, and guiding the treatment of neurologic complications remain to be established[117,118] (Fig. 10-10).

Alternatively, intraoperative transesophageal echocardiography (TEE) and transcranial Doppler (TCD) may be used to detect arterial embolic events (Fig. 10-11). The embolic burden to the cerebral circulation measured by quantitative TCD correlates with the incidence of intraoperative surgical manipulation and postoperative neurologic deficits.[119] Intraoperative TEE can be applied to detect right-to-left intracardiac shunting through an atrial septal defect,[120,121] intracardiac masses,[122,123] or residual air within the cardiac chambers.[124] Routine epiaortic ultrasonography to assess the degree of aortic atherosclerosis and guide the insertion of the aortic cannula and application of the aortic cross-clamp may decrease the risk of embolic stroke, but outcome data to suggest efficacy are sparse.[125]

ANESTHESIA

Anesthetic techniques presently employed for patients undergoing cardiac operations have been selected after extensive testing and clinical experience. Current clinical practice techniques have minimal organ toxicity, predictable cardiovascular and physiologic effects, well-established pharmacokinetic behavior, and excellent safety profiles. No benchmark anesthetic technique has been defined for all patients undergoing cardiac operations.[126–129] Combining drugs that selectively provide hypnosis, amnesia, analgesia, and muscle relaxation permits control of the anesthetic state and minimizes side effects of a single anesthetic drug used in high concentrations. Achieving the desired anesthetic state while preserving or improving vital organ function during operation requires an understanding of the physiologic actions of anesthetics, individually and in combination, in patients with a wide range of medical conditions.

Anesthesia drug management is dictated, in part, by the underlying cardiovascular disorder. Coronary artery disease renders the ventricle susceptible to myocardial ischemia, and management is designed to support coronary perfusion

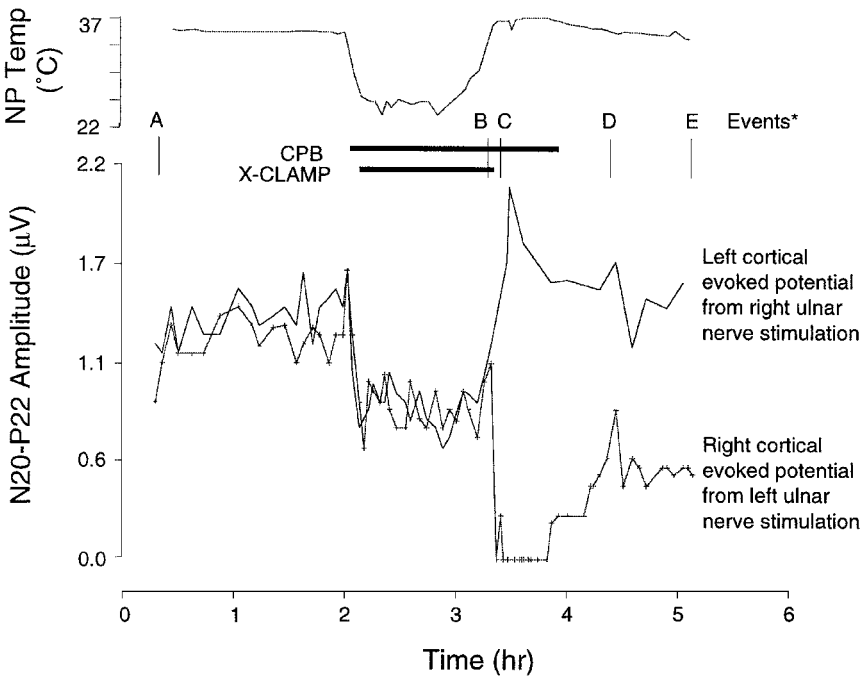


Figure 10-10. Intraoperative monitoring of somatosensory evoked potentials (SSEPs) was used for the acute detection of embolic stroke during mitral valve replacement. The symmetric changes in the peak-to-peak amplitudes of N20-P22 SSEPs before removal of the aortic cross-clamp were caused by the decrease in body temperature during deliberate hypothermia. The asymmetric decrease in the right cortical SSEPs after removal of the aortic cross-clamp was associated with an acute embolic stroke to the right thalamus or right somatosensory cortex. CPB = cardiopulmonary bypass; NP = nasopharyngeal temperature; X-clamp = ascending aorta cross-clamp. (*Reproduced with permission from Cheung AT, Savino JS, Weiss SJ, et al: Detection of acute embolic stroke during mitral valve replacement using somatosensory evoked potential monitoring. Anesthesiology 1995; 83:201.*)

pressure while decreasing myocardial oxygen demands. Tachycardia, hypertension, and increased inotropic state caused by nociception during operation are prevented by anticipating the inciting events and providing effective anesthesia. In contrast, patients with heart failure owing to valvular disease, dilated cardiomyopathy, or cardiac tamponade may depend on underlying sympathetic tone to support the circulation. In these patients, the anesthetist must be prepared to replace endogenous catecholamines pharmacologically while the patient is anesthetized.

Anesthetic-induced hemodynamic perturbations must be considered when assessing valve function intraoperatively using TEE (Fig. 10-12). Patients with regurgitant valve lesions frequently exhibit acute hemodynamic improvement during anesthesia because systemic oxygen demand and ventricular afterload decrease with anesthetic agents. Potent volatile anesthetics produce varying degrees of dose-dependent vasodilation and afterload reduction: isoflurane > enflurane > halothane. Assessment of mitral regurgitant grade during general anesthesia is not necessarily predictive of regurgitant grade in the awake state and may lead to mismanagement.[130,131] Provocative pharmacologic testing may be required to mimic circulatory conditions in the awake, exercising patient. Stress-testing the mitral valve may be achieved with incremental doses of phenylephrine to increase the transmitral systolic pressure gradient; however, the determinants of regurgitant volume are many, and it is unlikely that phenylephrine reliably reproduces the cardiovascular conditions that occur when a patient is exercising.

Maintenance of cardiovascular stability during general anesthesia for patients with aortic stenosis is based on avoiding systemic vasodilation and tachycardia and preserving sinus rhythm. Systemic vasodilation provides no significant decrease in left ventricular afterload because of the stenotic aortic valve. Tachycardia is poorly tolerated owing to shortened diastole and decreased filling of the noncompliant left ventricle. Nonsynchronous atrial contraction, a common occurrence during induction of general anesthesia, may produce significant hypotension and rapid deterioration in stroke volume. Narcotic-based anesthetics possess many desired hemodynamic attributes for patients with aortic stenosis. Synthetic narcotics are potent vagotonic drugs that decrease heart rate with minimal vasodilating effects and provide profound analgesia.

Anesthetics and Neuromuscular Blockers

Inhaled anesthetics

Inhaled anesthetics alone produce all the conditions necessary for operation.[132] All inhaled anesthetics cause circulatory depression at concentrations necessary to produce general anesthesia. When ventilation is controlled, circulatory actions of the inhaled anesthetics usually limit the anesthetic dose that can be tolerated, especially in patients with cardiovascular disease. For this reason, lower doses of inhaled anesthetics usually are combined with other anesthetics to produce general anesthesia for cardiac operations.

The decrease in blood pressure caused by volatile anesthetics is a direct result of vasodilation and depression of myocardial contractility and an indirect result of attenuation of sympathetic nervous system activity. The decrease in blood pressure is so predictable that it is often used as a sign for assessing the depth of anesthesia. Overdose with inhaled anesthetics is manifested by hypotension, arrhythmias, and bradycardia that, if unrecognized, may lead to circulatory shock.

The inhaled anesthetics decrease myocardial contractility based on both experimental and clinical studies[133–135]

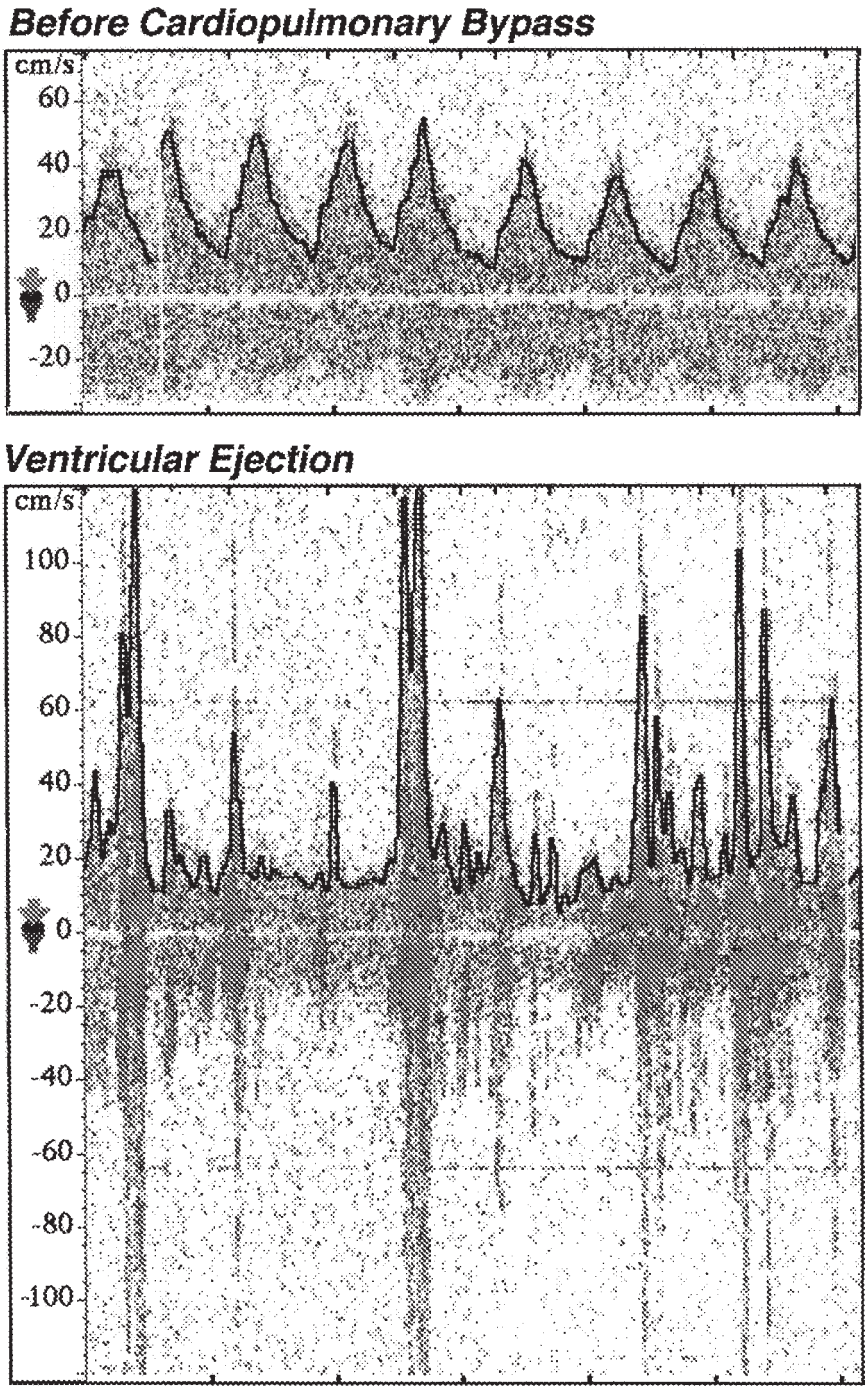


Figure 10-11. Middle cerebral artery blood flow velocity measured intraoperatively using a 2-MHz transcranial Doppler ultrasound transducer. The phasic velocity profile in the top panel was recorded before cardiopulmonary bypass. The irregular high-velocity, high-amplitude signals recorded in the lower panel indicate microemboli traveling through the middle cerebral artery immediately after ventricular ejection.

(Fig. 10-13). Inhalation anesthetics produce a dose-dependent decrease in mean maximal velocity of circumferential shortening, mean maximal developed force, and dP/dt.[136–138] The effects of each individual inhaled anesthetic on cardiovascular function depend on selective dose-dependent effects of the drug on myocyte contraction and relaxation, vascular smooth muscle tone, and sympathetic nervous system reflexes, as well as the underlying disease state, intravascular volume status, surgical stimulation, temperature, mode of ventilation, and acid-base status. The decrease in blood pressure in response to 1.0 minimum alveolar concentration (MAC) of halothane is primarily the result of decreased cardiac output caused by direct myocardial depression. Despite a decrease in myocardial contractility, cardiac output generally is unchanged at 1.0 MAC of isoflurane because of direct arterial vasodilation and preservation of baroceptor reflexes, with a resulting decrease in ventricular afterload and increase in heart rate and stroke volume[139] (Fig. 10-14). Halothane, enflurane, isoflurane, desflurane, and sevoflurane decrease global left ventricular systolic function at any given left ventricular loading condition or at any given degree of underlying sympathetic tone (Fig. 10-15).

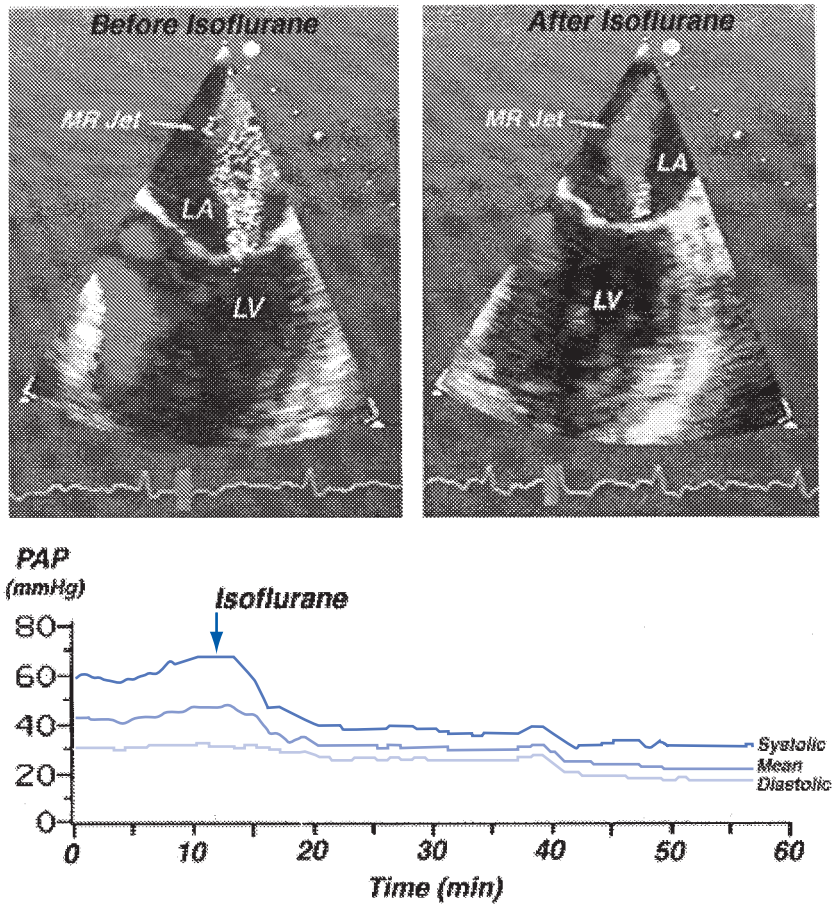


Figure 10-12. The relationship of increasing doses of isoflurane to the magnitude of mitral regurgitation and pulmonary artery pressures. The systemic unloading effects of isoflurane decreased mitral regurgitation from moderate to mild and decreased pulmonary artery pressures almost to normal.

Experimental studies suggest these agents cause minimal changes in left ventricular diastolic compliance but impair left ventricular diastolic relaxation in a dose-dependent manner.[140] These agents have minimal direct effects on left ventricular preload. Left and right ventricular end-diastolic pressures may increase during anesthesia because of impaired diastolic filling and decreased cardiac output. Halothane and enflurane are the most potent direct myocardial depressants, followed by isoflurane, desflurane, and sevoflurane.

Patients in shock or with profound ventricular dysfunction may not tolerate the cardiovascular depressant effects of inhaled anesthetics given in concentrations that are needed to produce anesthesia. Volatile anesthetics have a proportionally greater negative inotropic effect on diseased myocardium than on normal myocardium. In contrast, sympathetic nervous system activation owing to nociception may mask clinical signs of circulatory depression caused by inhaled anesthetics. Cardiodepressants and adrenergic antagonists potentiate the cardiovascular depressant actions of inhaled anesthetics.

The administration of inhaled anesthetics in patients with preexisting cardiovascular diseases has potential advantages. The myocardial depressant and arterial vasodilating actions of anesthetics benefit patients with coronary insufficiency if perfusion pressure is maintained. The negative inotropic properties of inhalation anesthetics decrease myocardial oxygen demand and may create a more favorable myocardial oxygen balance. The vasodilating and antihypertensive actions of anesthetics effectively control an increase in blood pressure in response to surgical pain, but anesthetic-induced hypotension may reduce coronary perfusion pressure and coronary blood flow.

Enflurane is a mild coronary vasodilator, whereas halothane has little effect on coronary vascular tone. Regional wall motion abnormalities and ECG evidence of myocardial ischemia associated with enflurane or halothane are due to decreases in coronary perfusion pressure rather than to a redistribution of myocardial blood flow.[140–142] Isoflurane causes endothelium-dependent inhibition of the contractile response of canine coronary arteries.[143] The direct coronary artery vasodilating action of isoflurane may increase coronary blood flow but also may increase the risk of myocardial ischemia in patients with steal-prone coronary anatomy by attenuating autoregulation of coronary blood flow. Coronary anatomy associated with isoflurane-induced coronary steal is a total occlusion of a major coronary branch and a hemodynamically significant (>50%) stenosis in the artery that supplies the collateral-dependent myocardium. The proposed mechanism is vasodilation and a decrease in coronary perfusion pressure downstream of the stenosis that decreases blood flow through the high-resistance, less-

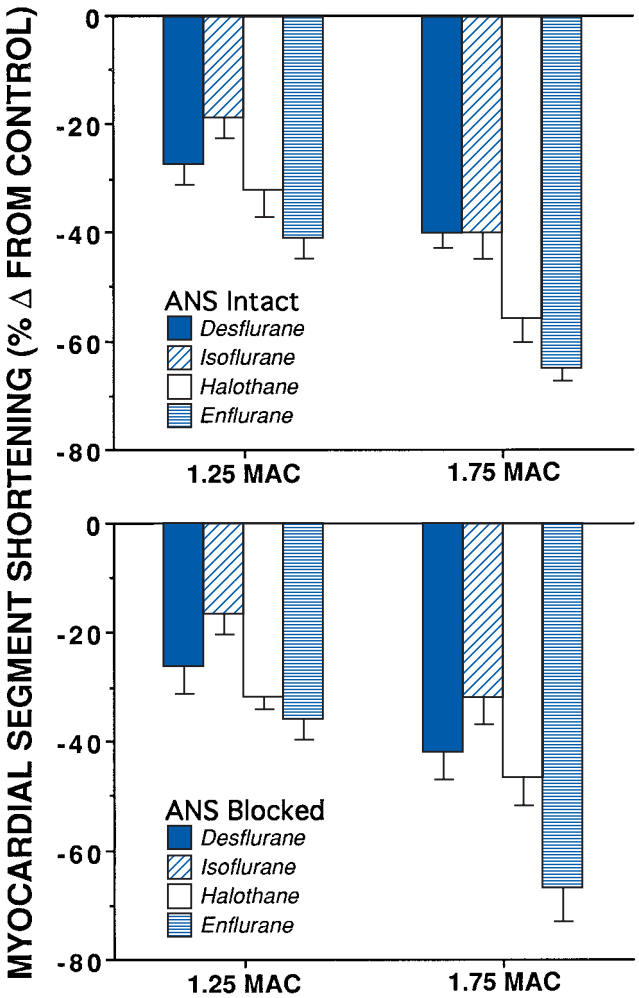


Figure 10-13. The actions of inhaled anesthetics on left ventricular myocardial segment shortening as measured in chronically instrumented dogs with an intact and blocked autonomic nervous system (ANS). All inhaled anesthetics caused a significant decrease in segment shortening at both 1.25 and 1.75 MAC in comparison with awake animals. (*Reproduced with permission from Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, and enflurane in the chronically instrumented dog. Anesthesiology 1991; 74:539.*)

responsive collateral network.[144] However, there is no convincing clinical evidence that isoflurane should be avoided in patients with coronary artery disease any more than other nonselective coronary vasodilators (e.g., nitroprusside).[145] The increase in heart rate and sympathetic tone associated with isoflurane and desflurane increases oxygen demand by producing tachycardia and may cause myocardial ischemia in susceptible patients. This is more important than the theoretical risk of coronary steal.[146–148]

Volatile anesthetics have anti-ischemic preconditioning properties resulting in cardioprotection against myocardial infarction via K_{ATP} channels.[149] Isoflurane, desflurane, and sevoflurane have cardioprotective properties independent of anesthetic improvement of myocardial oxygen supply-demand balance.[150] However, there are no clinical outcome data to suggest that anesthetized patients with coronary artery disease fare better with the use of volatile anesthetics than with intravenous agents.

Halothane sensitizes the myocardium to epinephrine-induced ventricular dysrhythmias and may be problematic in patients at risk for ventricular tachycardia, especially if sympathomimetics are given concurrently. The subcutaneous dose of epinephrine required to cause ventricular premature contractions during anesthesia with isoflurane, enflurane, or desflurane is approximately fourfold greater than the dose required during halothane anesthesia.[151,152] The susceptibility to catecholamine-induced dysrhythmias is exacerbated by hypercarbia.

Junctional rhythms are observed often with all inhaled anesthetics but most commonly with enflurane. The loss of atrial augmentation of ventricular preload with a junctional rhythm contributes to a decrease in blood pressure during inhalation anesthesia. Junctional rhythms are frequently problematic in patients with aortic stenosis and left ventricular hypertrophy who have poor ventricular diastolic compliance. Junctional rhythms can be treated with transesophageal, transvenous, or direct atrial pacing; decreasing the dose of inhalation anesthetic; or administering an anticholinergic drug such as glycopyrrolate or atropine.

Regional blood flow to other vital organs may be modified by inhaled anesthetics because of their effects on metabolic demands and autoregulation. The normal circulatory response to hypotension and low cardiac output is redistribution of blood flow to vital organs (i.e., brain, heart, and kidneys) and a decrease in blood flow to skin, muscle, and the gastrointestinal system. Volatile inhalation anesthetics impair this protective response and compromise vital organ perfusion if administered in high doses during periods of circulatory shock.

Nitrous oxide (N_2O) is also an inhaled anesthetic, but it is not potent enough to be used alone for general anesthesia. It is often used with other anesthetics because it decreases the MAC of halothane and isoflurane. N_2O is used rarely during cardiac operations because it diffuses into and expands the volume of gas-containing cavities and may increase the size of arterial gas emboli.

Rare cases of acute postoperative hepatic necrosis have been attributed to halothane administration.[153] Although the epidemiologic evidence implicating halothane as the cause of this syndrome remains controversial, the incidence of this idiosyncratic reaction is estimated to be in the range of 1 in 10,000 to 1 in 35,000 halothane anesthetics. Repeated exposures to halothane, reduced splanchnic blood flow, obesity, hypoxemia, enhanced reductive metabolism of the drug, and increased levels of hepatic enzymes induced by chronic drug use, malnutrition, and underlying liver disease appear to be risk factors for postoperative hepatitis. The perceived risk of halothane-induced hepatitis has favored increased use of newer anesthetic agents such as enflurane, isoflurane, and desflurane. Sevoflurane, a newer-generation ether volatile agent, offers lack of airway reactivity, nonpungent odor, low

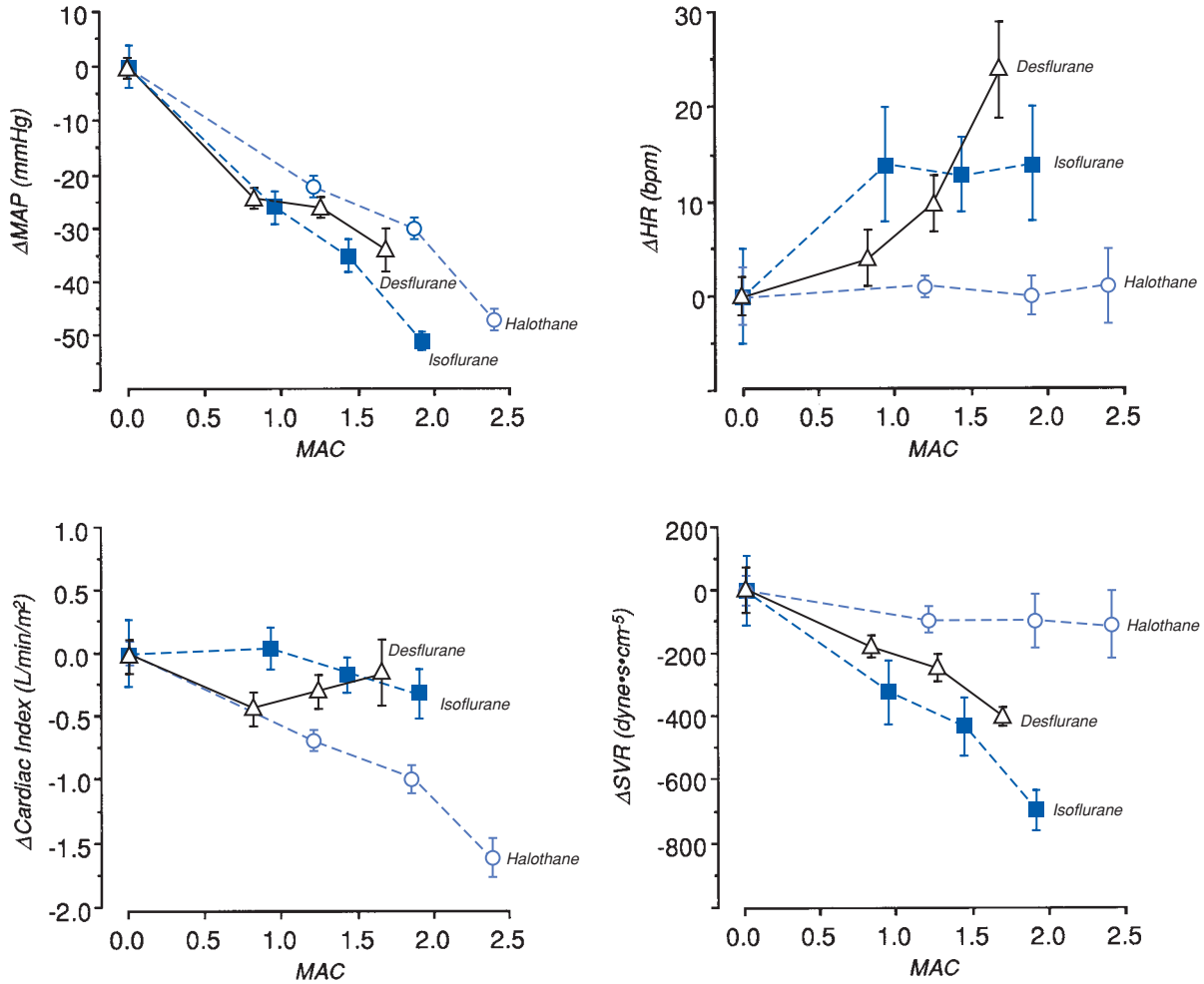


Figure 10-14. Dose-dependent changes in mean arterial pressure, heart rate, cardiac index, and systemic vascular resistance produced by halothane, isoflurane, and desflurane in normocarbic adults. Despite the myocardial depressant effects of isoflurane and desflurane, cardiac output is maintained during anesthesia with these agents in part because of a decrease in left ventricular afterload and increase in heart rate. (*Data from Weiskopf RB, Cahalan MK, Eger EI 2nd, et al: Cardiovascular actions of desflurane in normocarbic volunteers. Anesth Analg 1991; 73:143. Used with permission.*)

flammability, rapid induction and emergence, and minimal cardiovascular and respiratory side effects.[154,155] The accumulation of compound A, a potential renal toxin and by-product of sevoflurane use, has been associated only with low fresh gas flow (<1 L/min). These newer agents undergo minimal hepatic metabolism, do not decrease hepatic blood flow, and have not been implicated in anesthetic-induced liver dysfunction.

In general, carefully conducted clinical trials suggest that almost any inhaled anesthetic can be administered safely to patients with cardiovascular disease if the hemodynamic condition of the patient is controlled closely.[128,152]

Sedative-hypnotics

Sedative-hypnotics are a broad class of anesthetic drugs that includes barbiturates, benzodiazepines, etomidate, propofol, and ketamine. They are used for preoperative sedation, produce immediate loss of consciousness during intravenous induction of general anesthesia, supplement the actions of the inhaled anesthetics, and provide sedation in the immediate postoperative period. The circulatory effects of individual agents are an important consideration for patients with cardiovascular disease. The sedative-hypnotics have direct effects on cardiac contractility and vascular tone, in addition to indirect effects on autonomic tone.

The barbiturates, such as thiopental or methohexital, are negative inotropic agents. They produce dose-dependent decreases in ventricular *dP/dt* and the force-velocity relationship of ventricular muscle.[156] Induction of general anesthesia with a barbiturate is associated with a decrease in blood pressure and cardiac output. In comparison with barbiturates, propofol appears to cause less myocardial depression.[157,158] The decrease in arterial pressure after propofol administration is attributed primarily to arterial and venous dilatation.[159,160] Propofol is well suited for continuous intravenous infusion for sedation because it has a short duration

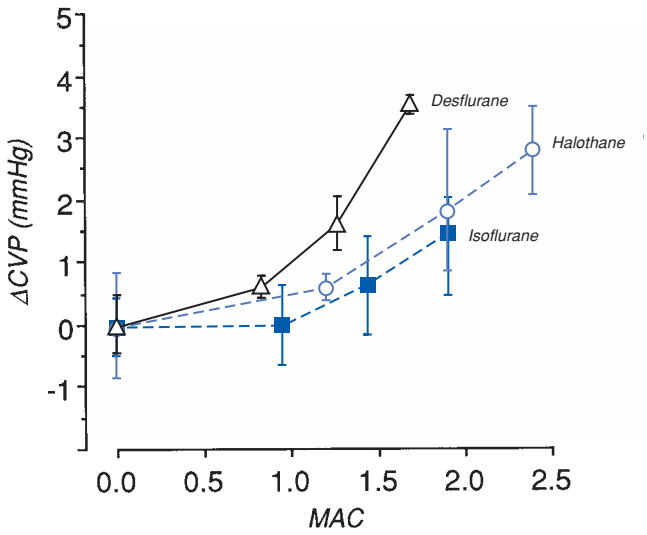


Figure 10-15. Dose-dependent changes in central venous pressure produced by halothane, isoflurane, and desflurane in normocarbic adults. (*Data from Weiskopf RB, Cahalan MK, Eger EI 2nd, et al: Cardiovascular actions of desflurane in normocarbic volunteers. Anesth Analg 1991; 73:143. Used with permission.*)

of action and can be titrated to effect. Propofol given intravenously for sedation in an nonintubated patient requires the presence of an anesthesiologist because respiratory depression is common. Etomidate and ketamine are administrated for rapid induction of general anesthesia in patients with preexisting hemodynamic compromise because they generally cause little or no change in circulatory parameters.[161] These agents are useful for unstable patients undergoing emergency operation, reexploration for bleeding, or cardioversion. Etomidate has virtually no effect on myocardial contractility even in diseased ventricular muscle.[162,163] However, etomidate inhibits adrenal synthesis of cortisol by blocking beta-hydroxylase and therefore is limited to short-term use as an intravenous anesthetic induction agent. Ketamine often increases heart rate and blood pressure after anesthetic induction because it maintains sympathetic tone.[164] The direct negative inotropic and vasodilating effects of ketamine can be unmasked when it is administered to critically ill patients with catecholamine depletion.[165] Ketamine is not used routinely because it may cause postoperative delirium, especially if it is administered in the absence of other sedative-hypnotics.

Centrally acting alpha$_2$-adrenergic agonists such as clonidine possess sedative and analgesic actions but do not produce anesthesia. Preoperative administration of clonidine to cardiac surgical patients decreases narcotic requirements and improves hemodynamic stability during operation.[166] Alpha$_2$ agonists are potent sympatholytic agents and also may be effective at attenuating sympathetically mediated myocardial ischemia.[167] Dexmedetomidine is a highly selective intravenous alpha$_2$-adrenergic agonist with sedative actions.[168] Dexmedetomidine administered at a rate of 0.2 to 0.7 μg/kg per hour intravenously provides effective postoperative sedation for intubated cardiac surgical patients and decreases the need for narcotic analgesics by approximately 50%. Because alpha$_2$-adrenergic agonists have little or no respiratory depressant actions, weaning from mechanical ventilatory support and tracheal extubation can be accomplished without interruption of the dexmedetomidine infusion. The most common adverse effects of dexmedetomidine are hypotension and bradycardia. At dexmedetomidine doses greater than 1.0 μg/kg per hour, arterial pressure may increase owing to direct activation of the alpha$_{2B}$ receptor subtype, which produces peripheral vasoconstriction. Dexmedetomine-induced vasoconstriction causes an increase in systemic vascular resistance, an increase in pulmonary vascular resistance, and a decrease in cardiac output.

Narcotic anesthetics

Narcotics remain an important adjunct for cardiac anesthesia. Analgesic actions are mediated by direct activation of opioid receptors in the central nervous system, spinal cord, and periphery. The three types of opioid receptors most studied are the mu, delta, and kappa receptors. Mu receptors are densely concentrated in the neocortex, brain stem, and regions of the central nervous system associated with nociception and sensorimotor integration.[169] Two different mu receptor subtypes produce analgesia and respiratory depression, leading to the possible development of selective agonist or antagonist compounds.

Narcotic-based anesthetics offer the advantages of profound analgesia, attenuation of sympathetically mediated cardiovascular reflexes in response to pain, and virtually no direct effects on myocardial contractility or vasomotor tone. Narcotics may be administered intravenously, intrathecally, or into the lumbar or thoracic epidural space. Even though narcotics have little direct action on the cardiovascular system, they may cause profound hemodynamic changes indirectly by attenuating sympathetic tone. Narcotics decrease serum catecholamine levels and produce cardiovascular depression indirectly, especially in a patient who is critically ill and dependent on endogenous catecholamines (e.g., those with hypovolemia or cardiac tamponade). Morphine sulfate may decrease blood pressure by provoking the release of histamine.

Problems encountered with narcotic-based anesthetics include difficulty estimating the dose required because of patient variability, predicting the duration of postoperative narcotic-induced respiratory depression, and ensuring hypnosis during operation. Rapid administration of narcotics is associated with muscle rigidity that may impede the ability to ventilate the patient immediately after the induction of general anesthesia.[170] The rigidity usually affects the thoracic and abdominal musculature and is observed commonly with doses of narcotic used in cardiac anesthesia. Myoclonic activity often associated with muscle rigidity easily can be mistaken for grand mal seizures. There is no evidence that opioids induce seizures when there is adequate oxygenation and

ventilation.[171] Opioid-induced muscle rigidity is reversed immediately by the administration of neuromuscular blockers.

The nonselective opioid antagonist naloxone reverses narcotic-induced respiratory depression. Narcotic antagonists must be titrated carefully to effect. Sudden reversal of opioid-mediated analgesia may produce systemic and pulmonary hypertension and tachycardia and is potentially life-threatening for patients with coronary artery disease.[172] The reversing effect of naloxone on narcotic-induced respiratory depression is significantly shorter than the respiratory depressant effects of most opioids, except for ultra-short-acting synthetic narcotics (e.g., alfentanil and remifentanil). A patient who receives a single intravenous dose of naloxone is susceptible to renarcotization after initial reversal of respiratory depression. For this reason, the initial bolus dose of naloxone typically is followed by an intramuscular injection or intravenous infusion, and patients are monitored closely. Longer-acting opioid antagonists include nalmefene, which has an elimination half-life ($t_{1/2B}$) of 8.5 hours, in contrast with the $t_{1/2B}$ of 1.5 hours for naloxone.[173] Mixed opioid agonists-antagonists (e.g., nalbuphine) may decrease the risk of hypertension, tachycardia, and dysrhythmias but do not reverse respiratory depression as reliably as naloxone.[174]

Opioid tolerance is a decrease in response (both analgesia and respiratory depression) to a narcotic owing to prior exposure. Tachyphylaxis is the rapid development of drug tolerance. Drug dependence is a patient condition or disorder that occurs as a consequence of sustained exposure to a drug such that withdrawal or antagonism of the drug prohibits normal function.[175] Perioperative exposure to morphine and synthetic narcotics is unlikely to produce the downregulation and desensitization of opioid receptors believed necessary for narcotic dependence.[176] Acute tolerance to fentanyl in humans is likely to occur only after prolonged infusion and to a lesser extent in the perioperative period. Cardiac surgical patients receiving narcotic infusions in the intensive-care unit develop tolerance and require increasing doses to sustain the desired effect.[177]

The synthetic narcotics such as fentanyl, sufentanil, and alfentanil overcome some of the problems of morphine-based anesthetics because of increased lipid solubility, more rapid onset of action, increased anesthetic potency, absence of histamine release, and independence of renal function for drug clearance. Development of short-acting narcotic anesthetics also may improve the ability to control anesthetic depth without prolonging recovery time. Ultra-short-acting narcotics (e.g., remifentanil) may have a unique niche in cardiac anesthesia because their effect is terminated almost immediately on stopping the drug infusion owing to rapid in vivo ester hydrolysis.[178] Other side effects of narcotics include pruritus, nausea, constipation, and urinary retention.

Neuromuscular blocking drugs

Neuromuscular blocking drugs are administered to facilitate intubation of the trachea, prevent patient movement during operation, improve surgical exposure of the operating field, and attenuate metabolic demands caused by shivering during hypothermia. Except for succinylcholine, the neuromuscular blocking drugs used in clinical practice are typically nondepolarizing competitive antagonists of acetylcholine at the nicotinic acetylcholine receptor at the motor end plate. Succinylcholine is an acetycholine agonist that produces rapid, short-acting muscle paralysis by depolarizing the motor end plate.

Muscle relaxants are chosen based on the desired speed of onset, duration of action, route of elimination, spectrum of cardiovascular side effects, and cost (Table 10-3). The newer neuromuscular blocking drugs such as vecuronium, *cis*-atracurium, doxacurium, and rocuronium have virtually no cardiovascular side effects and do not depend on renal function for elimination. Metocurine and gallamine are completely dependent on renal function for elimination and are used infrequently in clinical practice. Succinylcholine has the most rapid onset of action (90 seconds) but produces unpredictable changes in heart rate; increases serum potassium concentration by approximately 0.5 mEq/L; may cause life-threatening hyperkalemia in patients with denervation, burn, or compression injuries; and can trigger malignant hyperthermia in susceptible individuals. Pancuronium increases blood pressure and heart rate by blocking muscarinic acetylcholine receptors in the sinoatrial node, increases sympathetic activity via antimuscarinic actions, and inhibits reuptake of catecholamines. The neuromuscular blockers D-tubocurarine, metocurine, mivacurium, and atracurium may decrease blood pressure and increase heart rate indirectly by mediating release of histamine. The cardiovascular effects of these neuromuscular blockers may be attenuated by pretreatment with H_1- and H_2-receptor antagonists. Long-term administration of vecuronium is associated with development of myopathy in patients on glucocorticoid therapy.[179]

Discontinuing general anesthesia or sedation before complete recovery from neuromuscular blockade is very distressing for a patient because the awake, alert, and paralyzed patient has no means to communicate discomfort. Discontinuing mechanical ventilatory support in patients with residual neuromuscular blockade may cause acute or delayed respiratory failure. Even mild residual neuromuscular blockade contributes to pulmonary insufficiency by compromising mechanics of breathing and decreasing negative inspiratory force, vital capacity, tidal volume, and the ability to generate an effective cough. Muscle fatigue may produce airway obstruction by decreasing muscle tone in the oropharynx. Recovery from nondepolarizing neuromuscular blockade may be hastened by administering an acetylcholine -esterase inhibitor such as neostigmine or edrophonium that decreases degradation of acetylcholine at the neuromuscular junction and thereby increases the concentration of the neurotransmitter at the motor end plate. The undesirable systemic effects of acetylcholine-esterase inhibitors are bronchospasm, bradycardia, and hypersalivation, which can be minimized by simultaneous administration of anticholinergic

Table 10–3.

Neuromuscular Blocking Drugs

Drug	ED_{95} (mg/kg)	Dose (mg/kg)	Onset (min)	Duration (min)	Effects of drug on: HR	BP	CO	Histamine release	Renal elimination
Succinylcholine	0.25	1.5	1–1.5	12–15	(+)	(+)	(0)	(+)	0%
D-Tubocurarine	0.51	0.6	3–5	180–240	(+)	(−)	(−)	(+++)	60%
Pancuronium	0.07	0.1	3–5	180–240	(++)	(+)	(+)	(0)	70%
Metocurine	0.28	0.4	3–5	240	(+)	(−)	(0)	(++)	90%
Gallamine	3.0	3.5	3–5	180	(+++)	(++)	(++)	(0)	100%
Vecuronium	0.06	0.1	2–3	75–120	(0)	(0)	(0)	(0)	15%
Atracurium	0.25	0.5	2–3	60–90	(0)	(−)	(0)	(+)	<5%
Doxicurium	0.04	0.06	3–5	180–240	(0)	(0)	(0)	(0)	75%
Rocuronium	0.3	0.6	1–2	45–90	(0)	(0)	(0)	(0)	0%
Mivacurium	0.1	0.2	2–3	40–60	(0)	(0)	(0)	(+)	<5%

ED_{95} = dose required to produce 95% suppression of muscle twitch in response to nerve stimulation; dose = initial dose required for intubation of the trachea; onset = time required to achieve conditions required for tracheal intubation; duration = time after injection required for recovery to 95% of baseline function; (+) = increase; (−) = decrease; (0) = no effect; HR = heart rate; BP = arterial pressure; CO = cardiac output; histamine release = drug-induced histamine release; renal elimination = percentage of injected dose that is dependent on renal function for excretion

agents such as atropine or glycopyrrolate. Severe bradycardia has been described in heart transplant patients after reversal of neuromuscular blockade, possibly owing to the nonantagonized parasympathetic activity associated with acetylcholinesterase inhibitors in the denervated heart.[180] Reliable reversal of neuromuscular blockade with cholinesterase inhibitors usually is achieved only after muscle strength has recovered spontaneously to approximately 25% of baseline levels. Recovery of neuromuscular function is measured by a train-of-four twitch monitor applied to the ulnar nerve.

Local anesthetics

Local anesthetic drugs block the propagation of action potentials in electrically excitable tissue. Local anesthetics can be delivered by topical application to mucosa, infiltration into tissues, injection into the region of a peripheral nerve, infusion into the epidural space, or injection intrathecally into cerebrospinal fluid. Regional nerve blocks can be used to supplement a general anesthetic or to provide postoperative analgesia. Epinephrine often is added to local anesthetic solutions to prolong the anesthetic duration but may cause tachycardia or cardiac arrhythmias when absorbed into the systemic circulation. Inadvertent intravascular injection of a local anesthetic may cause seizures, myocardial depression, hypotension, bradycardia, ventricular arrhythmias, or even cardiac arrest. Among the local anesthetics, bupivacaine has the greatest potential for cardiac toxicity. Ropivacaine is less cardiotoxic than bupivacaine.[181,182]

Special Anesthetic Techniques

Emergency airway management

Establishing a patent and secure airway is essential for the conduct of general anesthesia and is the first step in emergency life support for cardiovascular resuscitation. Tracheal intubation for airway protection and mechanical ventilation can be challenging in a patient with cardiovascular disease. Anesthesia is often necessary to facilitate tracheal intubation; however, the effects of general anesthetics on respiratory and circulatory function typically produce respiratory depression and may cause apnea, instability of the patient's airway, aspiration pneumonitis, hypoxia, hypercarbia, and cardiovascular collapse. Inadequate anesthesia during tracheal intubation may provoke myocardial ischemia or tachyarrhythmias in susceptible patients. The American Society of Anesthesiologists has established practice guidelines for the emergency management of the difficult airway.[183] The difficult airway (e.g., Mallampati class 4) often can be

intubated with the patient in a sedated state using fiberoptic bronchoscopy. This technique requires time and special equipment. The risk of hypertension, tachycardia, and discomfort during tracheal intubation in an awake patient can be offset partially by topical anesthesia. Other techniques include mask ventilation, laryngeal mask ventilation, esophageal-tracheal combitube ventilation, blind oral or nasal intubation, direct laryngoscopy, rigid ventilating bronchoscopy, light wand intubation, retrograde intubation, transtracheal jet ventilation, cricothyroidotomy, and tracheostomy.

Single-lung ventilation

Single-lung ventilation, or the ability to collapse one lung and selectively ventilate the contralateral lung, is necessary for operative exposure when the heart or great vessels are approached through a lateral thoracotomy incision. Selective lung ventilation is integral in the intraoperative management of patients undergoing minimally invasive direct coronary artery bypass (MIDCAB) procedures. Adequate surgical exposure with minithoracotomy for coronary revascularization without cardiopulmonary bypass requires deflation of the left lung. Single-lung ventilation is also used in patients undergoing thoracoscopic procedures, lung transplantation, thoracic aortic operations, mitral valve surgery through a right thoracotomy, closure of large bronchopleural fistulas, intrathoracic robotic surgery, or life-threatening hemoptysis. Single-lung ventilation may be achieved using double-lumen endobronchial tubes (Fig. 10-16) or bronchial blockers (Fig. 10-17).

Wire-guided bronchial blocker kits often contain an adapter for a standard endotracheal tube with ports for the bronchial blocker and fiberoptic bronchoscope. A central lumen for the blocker contains a monofilament loop that passes out the end of the catheter. Placement of the loop over a fiberoptic bronchoscope permits the bronchial blocker to be guided directly into position using the bronchoscope. Removal of the monofilament loop from the central lumen

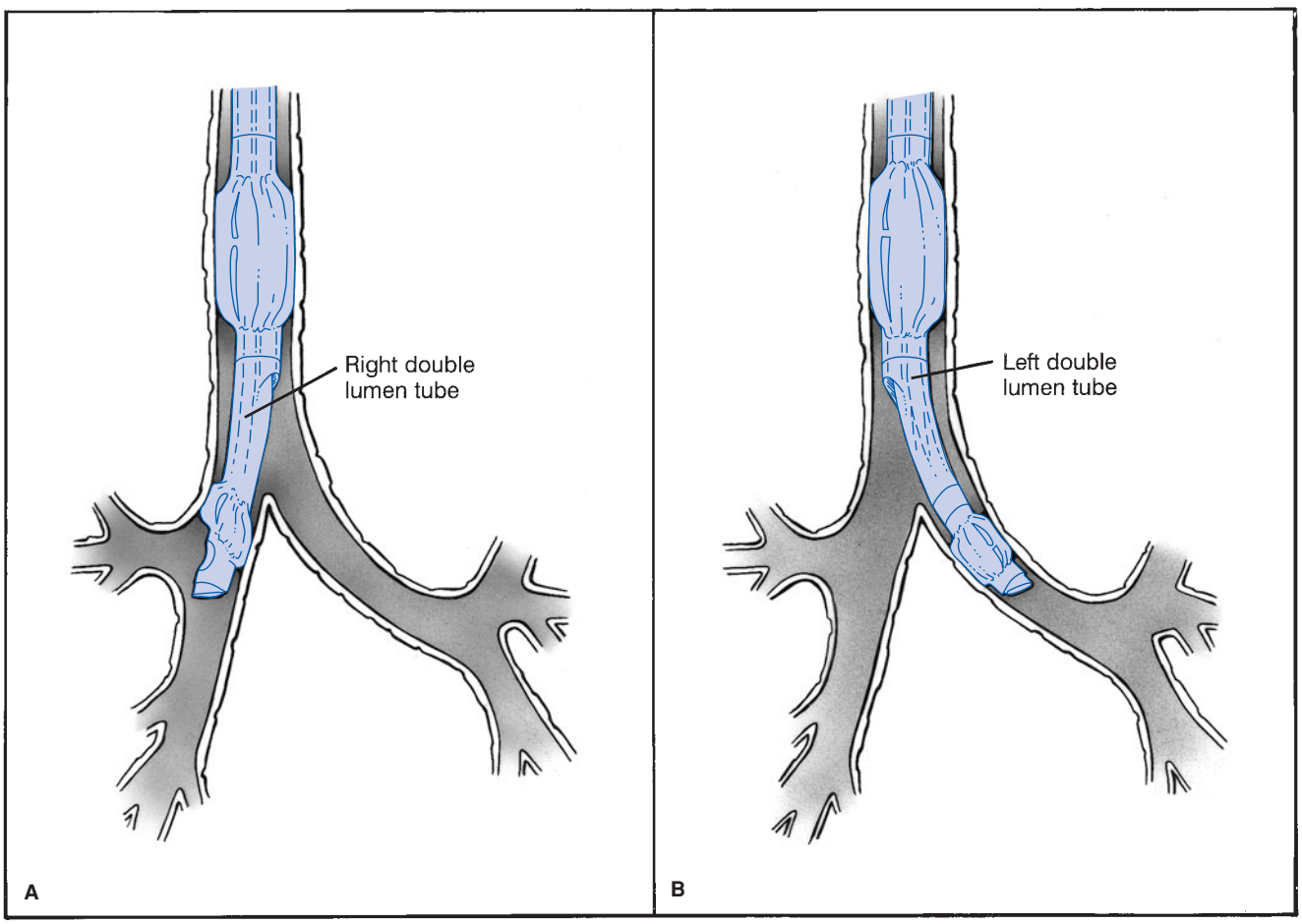


Figure 10-16. (*A*) Right-sided double-lumen endobronchial tube positioned such that Murphy's eye is aligned with the orifice of the right upper lobe bronchus. Indications for a right-sided tube are surgery involving the left main stem bronchus; patients with a prior left pneumonectomy, stenosis, compression, or mass in the left main stem bronchus; and circumstances in which the trachea needs to be protected from soilage from contents in the right lung (e.g., abscess). (*B*) Left-sided double-lumen endobronchial tube.

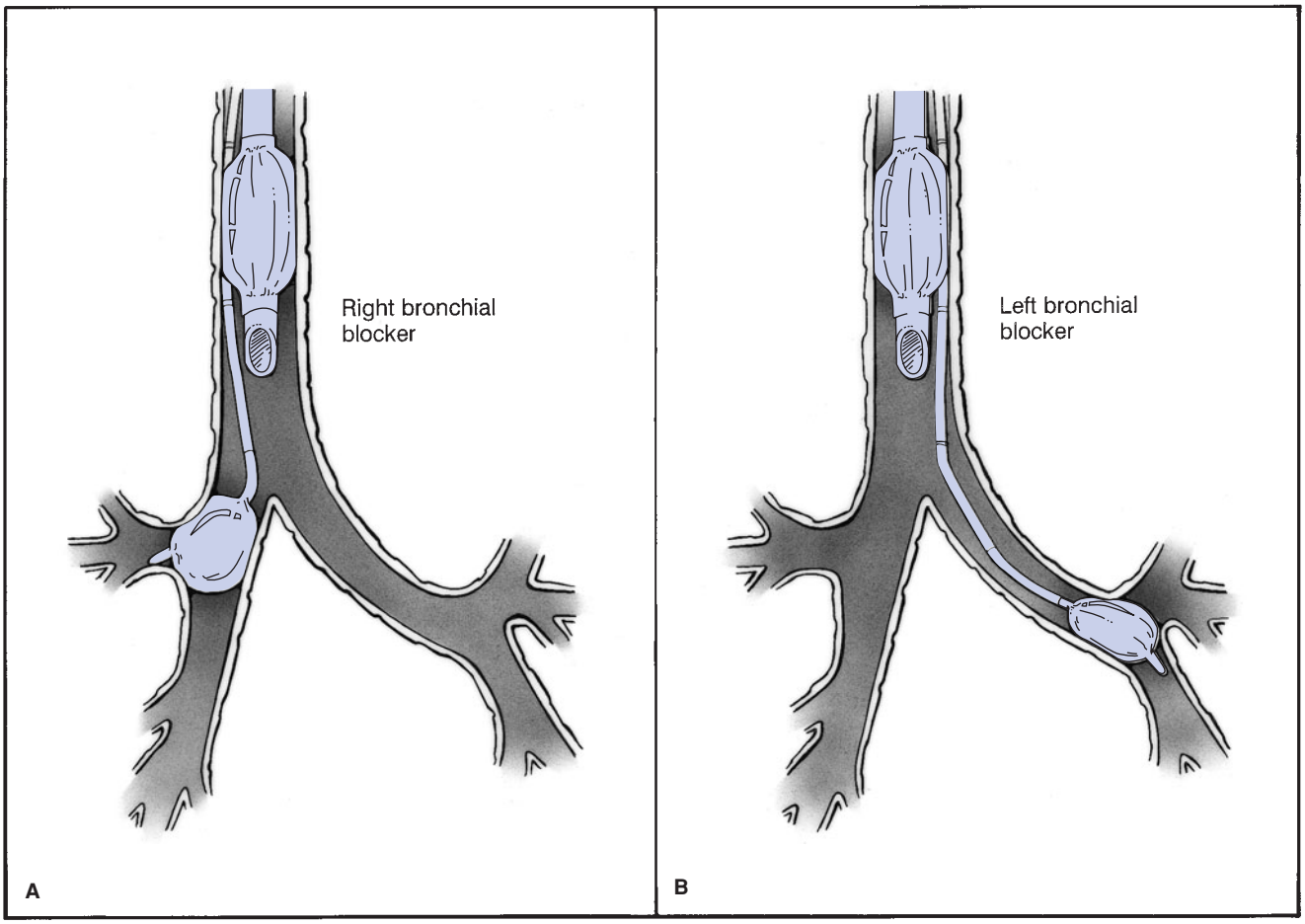


Figure 10-17. Bronchial blockers permit single-lung ventilation but do not permit suctioning or rapid deflation of the nonventilated lung. Position of the bronchial blocker is less stable compared with a double-lumen endobronchial tube.

provides a port for venting the nonventilated lung. Bronchial blockers for lung isolation are preferred when the larynx is too small to accommodate a double-lumen endobronchial tube (rare in the adult patient), when it is difficult or dangerous to change an existing endotracheal tube, or when the tracheal or main stem bronchus is distorted by a mediastinal mass or aortic aneurysm.

The routine use of fiberoptic bronchoscopy has decreased the complication rates and eliminated uncertainty regarding positioning of these devices in the airway. Hypoxemia caused by transpulmonary shunt through the nonventilated lung during single-lung ventilation often requires modification of the anesthetic technique to preserve hypoxic pulmonary vasoconstriction.

Regional anesthesia and analgesia

Epidural or intrathecal administration of local anesthetics and narcotics can provide profound postoperative analgesia after thoracic and major abdominal operations with less sedation or respiratory depression than parenteral narcotic analgesia.[184–186] However, the risk of hematoma in the spinal canal during or after cardiopulmonary bypass and heparinization has limited the use of epidurals for cardiac surgery. Patient-controlled epidural analgesia using infusion pumps can be triggered by patient demand with a predetermined maximum lockout dose to prevent overdose. Patient-controlled epidural analgesia is an effective method to titrate the dose of epidural local anesthetic and narcotic based on clinical need. The potential clinical advantages of epidural or intrathecal analgesia are less postoperative pain, decreased duration of postoperative ventilatory support, attenuation of the surgical stress responses, and improved pulmonary function.[187]

The epidural catheter most often is inserted prior to operation before systemic anticoagulation. Instrumentation of the epidural space for insertion of the catheter or removal of the epidural catheter is contraindicated in anticoagulated patients and in patients with coagulopathy because of the risk of epidural hematoma formation.[188,189] Epidural analgesia is provided by administering a continuous infusion of dilute solution of local anesthetic or narcotic, or a combination of the two, into the epidural catheter (e.g., bupivacaine 0.05% and fentanyl 2μg/mL at a rate of 4 to 8 mL/h).

The most common side effect of epidural analgesia is hypotension caused by local anesthetic blockade of the pre-

ganglionic vasomotor efferents of the sympathetic nervous system and loss of compensatory vasoconstriction. This side effect can be decreased by decreasing the concentration of the local anesthetic relative to the narcotic analgesic used in the epidural infusion. Respiratory depression also can occur with systemic absorption of the narcotic. The onset of respiratory depression sometimes is delayed or unpredictable. Nausea and pruritus are also common side effects of epidural or intrathecal narcotics. Epidural hematoma formation causing spinal cord compression is a rare but potentially catastrophic complication of epidural and intrathecal analgesia, with an estimated frequency of 1 in 150,000 patients.[190] Insufficient evidence to characterize the risks and benefits of epidural anesthesia compared with more conventional analgesic techniques has precluded the widespread acceptance of epidurals in cardiac surgery.[191]

Thoracic epidural anesthesia has been employed successfully for treatment of refractory angina.[192,193] Selective anesthesia of T_1 to T_5 thoracic dermatomes with epidural local anesthetic inhibits sympathetic innervation of the heart and regional vasculature. Thoracic epidural anesthesia decreases left ventricular contractility and heart rate while prolonging phase IV of the cardiac action potential.[194] The decrease in myocardial oxygen consumption, reduced arrhythmogenicity, and increase in diameter of the stenotic coronary arteries are the proposed mechanisms for the abolition of chest pain in unstable angina patients who receive thoracic epidural local anesthetic.[195–199] With exercise testing, these patients have a smaller ischemic burden (less ST-segment depression) for a given workload with epidural anesthesia compared with control exercise without epidural anesthesia. Treatment of myocardial ischemia with an infusion of local anesthetics or opioids into the epidural space is not without risk in patients who are likely to receive anticoagulants and/or thrombolytics and who may have significant preexisting left ventricular dysfunction.

Controlling lumbar cerebrospinal fluid pressure

Spinal fluid drainage may improve neurologic outcome from spinal cord ischemia during thoracoabdominal aortic (TAA) operations.[200–202] Lumbar CSF drainage is part of a multimodal approach to prevent paraplegia after thoracoabdominal aortic surgery.[203,204] Although the clinical efficacy of lumbar CSF drainage remains controversial, the technique is routine at some institutions.[205,206] CSF drainage and a decrease in the lumbar CSF pressure can be achieved by aseptically inserting a subarachnoid catheter through a Tuohy needle positioned in a lower lumbar vertebral interspace. The insertion of a CSF drain prior to a patient undergoing extracorporeal circulation with anticoagulation appears safe.[207,208] The catheter typically is inserted 1 to 2 hours before systemic anticoagulation with the patient in a lateral decubitus position. CSF is drained passively to reduce lumbar CSF pressure to approximately 10 to 12 mm Hg during operation. Reducing CSF pressure further may cause an abducens nerve palsy and postoperative diplopia. The catheter is secured, and CSF drainage is continued typically for 24 hours after operation. In the absence of spinal cord ischemia, the catheter is capped at 24 hours after operation and removed at 48 hours after operation. Arterial blood pressure augmentation is an important adjunct to treatment of spinal cord ischemia after TAA surgery or stent placement.[209] Emergent implementation of lumbar CSF drainage to a target lumbar CSF pressure of 10 mm Hg, combined with augmentation of the mean arterial pressure to 100 mm Hg, has been reported to successfully reverse delayed-onset paraplegia or paraparesis in some patients after thoracic aortic reconstruction.[210,208] Complications associated with lumbar CSF catheters include meningitis, persistent CSF leak, breakage and retention of catheter fragments, and epidural hematoma. The risk of epidural hematoma is increased when the CSF catheter is inserted or removed in anticoagulated patients.

THE CONDUCT OF ANESTHESIA, SURGERY, NURSING, AND PERFUSION

Cardiac surgery is conducted in an interdisciplinary environment among surgeon, anesthesiologist, perfusionist, and nursing staff. The operating room requires a minimum of 800 ft^2 to comfortably accommodate the patient, health care providers, standard operating room equipment, intraoperative cell salvage machine, heart-lung machine, and assist devices, if needed.[211] The required square footage may be greater for the higher-technology procedures such as robotic surgery.

The anesthetic begins before the patient arrives in the operating room. Patients are premedicated with a sedative-hypnotic (e.g., scopolamine or benzodiazepine) and an analgesic (e.g., morphine) unless the associated mild degree of respiratory depression is unwarranted. The patient's identification and scheduled procedure are verified immediately on arrival in the operating room. The patient is escorted into the operating room and placed onto the operating table, and routine noninvasive monitors are applied. The physical condition of the patient is assessed clinically, and medical events that occurred over the previous 12 to 24 hours are reviewed. For elective surgery, the patient should have fasted for a minimum of 6 hours prior to induction of general anesthesia. Prophylactic antibiotics are administered after insertion of an intravenous catheter. A catheter is inserted in the radial artery. A blood sample is acquired for laboratory analysis, and a blood type and crossmatch are requested, if not done already. A central venous catheter is always indicated, although in many patients it can be inserted after the induction of general anesthesia. A pulmonary artery catheter is used commonly to provide measures of cardiac output and estimates of ventricular filling pressures.[212] Large-bore intravenous catheters are inserted for patients who are undergoing reoperation because of the possibility of rapid blood loss during sternotomy. The immediate availability of typed and crossmatched blood is verified before skin incision. Patients undergoing reoperation

are more likely to have a positive antibody screen that delays the availability of blood products. External defibrillation pads are always applied to patients undergoing reoperation or in procedures in which access to the heart with internal paddles is not readily available.

Anesthesia care begins in the preinduction period, documents significant events of surgery, and becomes part of the patient's medical record. Prior to induction of general anesthesia, a baseline set of hemodynamic measurements is obtained and recorded. These measures often guide the choice of anesthetic drugs and technique, provide a baseline for comparison later, and confirm hemodynamic data acquired during cardiac catheterization. Automated record keepers eventually may relieve the anesthetist of recording these data.

Induction of general anesthesia is achieved by inhalation of volatile potent anesthetics, intravenous administration of sedative-hypnotics, or both. Inhalation inductions permit maintenance of spontaneous ventilation and a controlled titration of anesthetic dose but prolong the excitatory phase of anesthesia when the patient is prone to cough, move, develop laryngospasm, or vomit and aspirate. Inhalation inductions are not used commonly in adults. Intravenous induction produces rapid apnea that requires immediate ventilatory support. Administration of neuromuscular blocking drugs produces profound muscle paralysis and facilitates laryngoscopy and tracheal intubation. Vasoactive drugs are titrated, if necessary, to counteract the cardiovascular effects of anesthetics. Laryngoscopy is extremely stimulating (painful) and, if the patient is inadequately anesthetized, causes severe hypertension and tachycardia and stimulates vasovagal reflexes. The inability to ventilate or intubate the trachea in a patient after the induction of general anesthesia is a medical crisis and may require transtracheal jet ventilation, cricothyroidotomy, or tracheostomy. Patients with a history of a technically difficult tracheal intubation, poor dentition, large tongue, limited mouth opening, inability to sublux the mandible, or a recessed chin are at increased risk of airway complications, and it may be prudent to secure the airway while they are still awake. Successful intubation of the trachea is verified by the appearance of a carbon dioxide expirogram. Most adult patients can be intubated with an 8.0-mm internal-diameter polyvinyl chloride endotracheal tube that accommodates an adult flexible bronchoscope. The tip of the tracheal tube is secured above the carina by documenting breath sounds bilaterally. The patient is positioned prior to surgical preparation and draping. Regions susceptible to pressure injuries are protected and padded. Arm abduction is limited to less than 90 degrees. The patient is positioned to decrease pressure on the postcondylar groove of the humerus.[213] ECG wires, tubes, and lines are not run under the arm. The incorporation of a simple examination of extremity nerve function during the postoperative visit provides a means to detect peripheral nerve injury.

Maintenance of general anesthesia is achieved by continuous or intermittent administration of anesthetic drugs titrated to effect while monitoring the conduct of the operation and vital physiologic functions. Short-acting vasoactive agents with rapid onset of action usually are preferred for controlling the circulation because conditions change constantly. The cardiovascular actions of inhaled anesthetics are used often for short-term blood pressure control because effective concentrations can be reached quickly and monitored in real time by expired gases. Direct-acting vasodilators may be required for blood pressure control if the patient cannot tolerate the myocardial depressant effects of an inhaled anesthetic. Vasopressors and inotropic agents sometimes are required to support the circulation in response to anesthetic-induced vasodilation and cardiac depression. Using nitroglycerin to modify venous capacitance permits buffering acute changes in intravascular volume. Heart rate can be controlled by short-acting cardioselective beta-adrenergic agonists and antagonists, vagolytic agents, or chronotropic drugs or, alternatively, by direct cardiac pacing. The urgency to control hemodynamic parameters with pharmacologic therapy must be tempered by recognizing the risk of drug overdose from overzealous treatment. Intraoperative events associated with acute increases in anesthetic requirements are sternotomy, chest wall retraction, manipulations and cannulation of the aorta, rewarming during cardiopulmonary bypass, and sternal wiring. Intraoperative awareness from insufficient anesthesia may occur during cardiac surgery, especially if the anesthetist places a greater emphasis on avoiding cardiovascular actions of anesthetic agents than on providing sufficient anesthesia.

Initiation of cardiopulmonary bypass acutely changes circulating drug concentrations. The addition of 2 L of pump prime has a negligible effect on plasma concentrations of lipophilic drugs with a large volume of distribution but significantly decreases the concentration of drugs distributed primarily in the intravascular space. Despite measurable decreases in blood anesthetic concentrations during cardiopulmonary bypass, the anesthetic level may not change because systemic hypothermia decreases anesthetic requirements, potentiates the effects of neuromuscular blocking drugs, and increases the solubility of volatile anesthetics in blood. Rewarming returns anesthetic requirements to baseline levels and predisposes to inadequate anesthesia if therapeutic drug concentrations are not maintained. The judicious use of sedative-hypnotics, analgesics, and amnestic agents during rewarming decreases the incidence of recall but does not guarantee unconsciousness. Volatile inhalation anesthetics can be given during cardiopulmonary bypass by adding them to the oxygen-rich gas mixture ventilating the pump oxygenator. This use of volatile anesthetics requires an effective scavenging system to prevent accumulation of anesthetic gases in ambient air.

Separation from cardiopulmonary bypass requires effective communication among members of the intraoperative team. Similar to an airline pilot preparing to land, the cardiac anesthesiologist has a checklist that ensures that all systems are in working order (Table 10-4).

Table 10–4.

Checklist for Preparation to Separate from Cardiopulmonary bypass

1. Stable rhythm preferably with a synchronized atrial contraction
2. Pacemaker and cables available
3. Positive inotropes available (e.g., epinephrine, dopamine)
4. Vasodilators available (e.g., nitroglycerine, nitroprusside)
5. Vasopressors available (e.g., phenylephrine, norepinephrine)
6. Adequate levels of anesthesia and paralysis
7. Normothermia: nasopharyngeal temperature = 37°C, rectal or bladder temperature = 35°C
8. Normal serum electrolyte concentrations: K^+, Ca^{+2}
9. Normal serum glucose
10. Normal blood acid-base status
11. No systemic oxygen debt: oxygen saturation in cardiopulmonary bypass venous inflow >70%
12. Acceptable O_2-carrying capacity: hemoglobin concentration
13. Normal systemic vascular resistance
14. Recalibration of pressure transducers
15. ECG in diagnostic mode
16. Clearance of air by TEE
17. Hemothorax evacuated
18. Ventilation with 100% oxygen and atelectatic lungs reexpanded

ANESTHESIA IN THE IMMEDIATE POSTOPERATIVE PERIOD

Continuous monitoring of physiologic functions during transport to the postoperative intensive-care unit is paramount because of the possibility of hemodynamic instability. Cardiac output, blood pressure, and vascular tone decrease acutely in the immediate postoperative period because surgical stimulation no longer increases sympathetic tone. Vasodilation also occurs from increases in cutaneous blood flow during active rewarming. Reducing positive-pressure ventilatory support during weaning from mechanical ventilation may alter hemodynamic function by increasing venous return and decreasing pulmonary vascular resistance. Sedative-hypnotic or analgesic drugs administered in the immediate postoperative period contribute to changes in the circulatory state.

Anesthesia is required in the early postoperative period because of mechanical ventilatory support, hypothermia, and the possibility of hypertension and tachycardia from pain and tracheal intubation if abrupt emergence occurs. Several hours may be needed to achieve criteria for tracheal extubation (e.g., minimal bleeding, cardiovascular stability, and systemic rewarming). Arrival in the intensive-care unit triggers a battery of laboratory tests designed to assess rapid changes in vital organ function and prompt corrective therapy. These tests include a chest radiograph, complete blood and platelet count, chemistry battery with blood urea nitrogen and serum creatinine determinations, a serum glucose determination, ECG, prothrombin time and partial thromboplastin time, and arterial blood gas determination.

Preemptive patient management during operation and in the early postoperative period can decrease intensive-care-unit and hospital length of stay after cardiac surgery.[214] Traditionally, high-dose narcotic anesthesia provided profound analgesia, sympathetic blockade, and a gradual emergence that was managed over a time course of 8 to 12 hours. With high-dose narcotic anesthesia, patient recovery often was determined by the duration of action of the anesthetic given in the operating room. The time required for recovery from general anesthesia may be decreased by short-acting sedative-hypnotics (e.g., propofol) or analgesics administered by infusion that continues into the postoperative period and permits recovery according to the patient's condition rather than the anesthetic. Implementation of protocol-based care plans designed to expedite patient recovery after cardiac operations requires a coordinated effort and mutual understanding between the anesthesiologist, surgeon, and critical care team.

Hemodynamic management of cardiac surgical patients is integrated with anesthetic management. The ability to establish a diagnosis and circulation rapidly during anesthesia is essential for safe conduct of cardiac operations. The challenge to maintain control of the cardiovascular system during the course of a typical operation is complicated by actions of the anesthetic drugs on the circulation, autonomic nervous system reflexes, variability in individual responses to vasoactive drug therapy, continuous fluctuations in the intensity of painful stimuli, rapid intravascular volume shifts, the patient's underlying medical condition, and the urgency of operation.

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CHAPTER 11

Principles and Practice of Echocardiography in Cardiac Surgery

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Echocardiography is an imaging modality that, in the past 25 years, has developed to be the major imaging and diagnostic modality of cardiac disease, so all cardiac specialists, clinicians, invasive cardiologists, and surgeons need to understand the basic principles, approaches, indications, physiologic determinants, pitfalls, and expected results of echocardiography to make an appropriate interpretation. Beyond physical principles affecting the imaging results, Doppler echocardiography is, like all complex testing modalities, subject to operator-dependent factors and Bayesian interpretation of results. Hence it is essential that quality of imaging and integration of reported results be challenged critically by the clinician "consumers." The goal of this chapter is to provide basic to advanced knowledge of the echocardiographic aspects of major cardiac conditions (mostly acquired) to ensure proper functioning of the team echocardiographer/cardiac surgeon.

PRINCIPLES OF ECHOCARDIOGRAPHY FOR THE CARDIAC SURGEON: A PRIMER

Echocardiography uses high-frequency ultrasound (2.0 to 7.5 MHz) to generate images of the heart and measure blood flow velocity. It is important to understand some principles of ultrasound for proper interpretation. Images are produced by reflection of ultrasound (produced by crystals contained in the transducer) off cardiac walls. To achieve reflection, ultrasound first must penetrate body tissues. Water (blood) allows excellent penetration of ultrasonic energy, and penetration is less through fat and is minimal through air; bones are such strong reflectors that no energy is left to progress into the cardiac tissue. Therefore, echocardiographers use "windows" (between the ribs, sternum, and lungs) such as the parasternal, apical, subcostal, suprasternal, transesophageal, and intracardiac windows to ensure good penetration of ultrasound into the heart and thus good images. Ultrasonic imaging is not photography, and images of the cardiac structures (e.g., aortic walls) are generated by a scan converter that counts the time between emission of ultrasound and the return of the reflected wave to the same crystal and calculates the distance from transducer to reflective structure, assuming a constant speed of progression of ultrasound energy in blood. This mostly true assumption ensures excellent measurement of depth, but lateral resolution is less precise because strong reflectors tend to diffract the ultrasound energy, which rebounds not only toward the original crystal but also toward adjoining crystals. Thus a point is well defined in depth but appears fattened laterally (lateral lobes). Clinically, this lateral "thickening" of echoes tends to minimize the apparent size of cavities. Strong reflectors (e.g., calcified walls) also reflect so much ultrasound energy back to the transducer, the wall again, and the transducer again that artifact at double depth may be generated. Single-crystal imaging is time-motion echocardiography, whereas most usually two-dimensional (2-D) echocardiograms are produced by a series of crystals. 2-D echocardiography is a tomograph slicing the heart and requires comprehensive imaging to reconstruct the heart. Newly developed three-dimensional (3-D) imaging produces an ultrasonic cone that reflects the true 3-D structure of the heart, but diffraction of ultrasound waves and computational issues degrade image definition. Hopefully, future development will provide high-resolution and 3-D imaging.

Intracardiac velocity is measured based on the Doppler effect; i.e., a moving target changes the wavelength of the reflected sound. The magnitude of frequency change (the Doppler shift) is proportional to the velocity of the moving target and the direction of the frequency change, indicating the direction of the moving target (toward or away from the transducer). Velocity measurement is very precise if the ultrasound beam and moving target directions are identical (Fig. 11-1). With angulation of these directions, measured velocity decreases with the cosine of the angle (cosine 90° = 0,

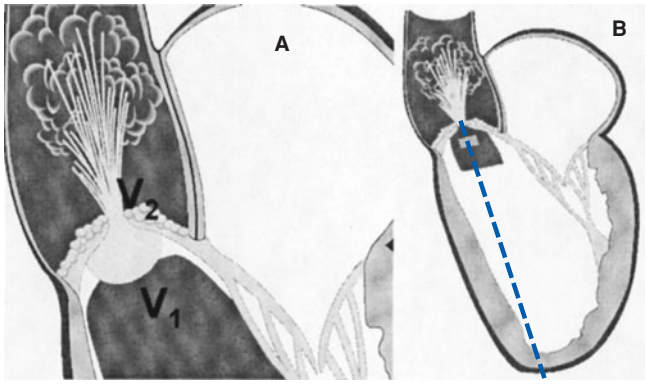

Figure 11-1. Flow through a restrictive orifice and Doppler measures. *A.* A restrictive orifice creates a pattern of flow convergence proximal to the orifice with acceleration of flow through the narrowest portion of the orifice (vena contracta) and expansion with deceleration beyond the orifice. *B.* The necessary alignment of the ultrasound beam and flow is shown to measure velocity accurately. The small box proximal to the jet represents a sample volume of pulsed-wave Doppler. (*Cortesy of Dr. F. A. Miller.*)

no signal). Thus, to measure blood velocity, appropriate alignment is required. Since alignment is uncertain, a multiwindow search of the peak measured velocity (indicating alignment) is indispensable. Blood and tissue velocities can be measured with the use of filters. Two types of Doppler ultrasound can be used: pulsed Doppler (velocity is measured through a small gate), precisely locating the measure but limited in peak velocity measurement, and continuous-wave Doppler, which does not discriminate location of the ultrasonic beam but allows measurement of high velocity, i.e., of gradients. Indeed, a small orifice (stenosis) forces blood (incompressible fluid) to accelerate (constant flow through a smaller orifice means higher velocity). Velocity (V) allows calculation of gradients usually with the simplified Bernoulli equation (gradient $= 4V^2$), which ignores some components (e.g., viscosity and inertia) but generally is accurate for clinical purposes. It should be noted that compared with catheterization, a gradient may be underestimated owing to angulation but also can be slightly overestimated owing to pressure recovery.[1] This phenomenon is due to energy conservation (constant through a stenotic orifice) such that when kinetic energy (velocity) is maximum at the stenotic orifice, potential energy (pressure) is lowest. However, after the orifice, when blood decelerates, potential energy (pressure) increases. Thus, slightly downstream from the orifice, where catheters usually are placed, pressure is higher and the gradient is lower than at the valve orifice itself. This phenomenon is usually minimal but can be clinically significant with some prostheses and with small aortas. Color-flow imaging is based on velocity measurement by Doppler and is coded yellow for flows toward the transducer and blue for flows away. It is important to remember that color-flow imaging does not measure volumetric flow but indicates displacement of red blood cells and that it is Doppler, so flows at a 90-degree angle are not seen and appear black, and high velocities are shown as "aliasing," whereby when the maximum blue color is reached, the color switches to yellow for higher velocity (and so on), giving high-velocity jets their mosaic appearance.

Jet imaging is a major application of color-flow Doppler. Jet extent is influenced by technical, physiologic, and physical factors. For example, a lower scale of color will allow detection of lower velocities and increase the jet area artificially. Physiologically, jet extent is determined by jet momentum, i.e., the product of flow and velocity. This means that very small jets have very low flow, but larger jets can be due to higher jet velocity (e.g., development of hypertension enlarges the jet of mitral regurgitation with unchanged flow). Physically, jets are constrained by cavity size, so larger cavities contain larger jets. In addition, jets directed on a wall are constrained irrespective of their flow. Thus interpretation of jet extent should be made with an awareness of these pitfalls.

MODALITIES OF DOPPLER ECHOCARDIOGRAPHY

Echocardiography provides essential information about most adult cardiovascular diseases requiring cardiac surgery, including detailed information on cardiac structure, function, and hemodynamics. Thus it is essential in indicating and planning surgery and anesthesia, in managing patients intraoperatively, and in monitoring patients postoperatively to ensure the best possible clinical outcome. However, there are multiple echocardiographic modalities that respond to different clinical questions, and it is important that these modalities and their indications be clearly understood by the managing team for optimal use.

Transthoracic Echocardiography

Transthoracic echocardiography (TTE) is completely noninvasive and safe. It is crucial that all windows and views be used with multiple tomographic slices to obtain high-resolution assessment of anatomy and function of the heart and great vessels.[2] There are several submodalities that should be selected carefully:

Standard TTE. This includes 2-D morphologic assessment and 2-D derived M-mode imaging measurement of cardiac dimensions with pulsed and continuous-wave Doppler.[3] Color-flow imaging verifies normalcy of valve function and intracardiac flows. Visual assessment of ejection fraction is often appropriate and can be combined with M-mode measurements.[4,5] Using continuous-wave Doppler (CWD), tricuspid regurgitation allows estimation of right ventricular systolic pressure.[6]

TTE with advanced hemodynamics. This is indicated for most patients with valve disease or poor hemodynamics. Doppler echocardiography calculates stroke volume, cardiac output, and cardiac index. Flow across an orifice is the product of cross-sectional area (CSA, often

assumed circular, where area = πr^2) and flow velocity, and stroke volume (SV) sums flow over the cardiac cycle [product of CSA and summed velocities, called the *time-velocity integral* (SV = CSA × TVI)]. Cardiac output is SV multiplied by hear rate and cardiac index, the ratio of output to body surface area.[7] These principles are simple, but pitfalls have to be recognized: The only valve orifice where SV is consistently measurable is the aortic valve because it is circular, and the flow profile is usually flat (meaning that velocities are identical throughout the orifice). SV measurement is more difficult on the mitral valve and virtually impossible on the tricuspid valve. Even aortic SV can be underestimated if the diameter (squared in calculation of CSA) is underestimated. CVD measures velocity and pressure gradients for stenotic valves with the simplified but accurate Bernoulli equation (gradient = $4V^2$).[8–10] Note that catheterization peak-to-peak gradient (not recommended as an adequate measure) is not the peak gradient but is closer to the mean gradient. Mean gradient obtained by Doppler correlates extremely well with that obtained by catheterization. Velocity decay through a diastolic orifice (mitral stenosis or aortic regurgitation) is faster through a larger orifice and allows assessment of the severity of disease.[11]

Another important principle in advanced Doppler hemodynamics is the conservation of mass.[12] Blood is incompressible, and when it passes through a stenotic orifice, flow remains constant through an increase in velocity (smaller area means higher velocity). This principle, also the basis of Gorlin's formulas, is the basis of stenotic[13] and regurgitant[14] effective area measurement by Doppler, whereby orifice area equals flow/velocity. The flow measurement can be deduced from stroke volumes or, for regurgitant valves, can be measured by the proximal isovelocity surface area (PISA) method.[15] In this method, the flow convergence proximal to a regurgitant orifice (i.e., blood converging toward the orifice) is analyzed by color-flow imaging, which provides the speed of blood and the size of the flow convergence, allowing calculation of flow (flow = $2\pi r^2\ V_r$, where r is the radius of the flow convergence, and V_r is the blood velocity indicated by the machine as aliasing velocity) and regurgitant volume. Thus comprehensive hemodynamic assessment should provide cardiac index, pulmonary pressures, valve lesion severity (orifice area regurgitant or stenotic), and overload severity (gradient or regurgitant volume).[16]

TTE with advanced cardiac size and function assessment. This involves ventricular and atrial characterization. Left ventricular (LV) size usually is characterized as end-diastolic and end-systolic diameters. These dimensions are useful but have important limitations in that they poorly estimate LV dilatation and are biased in terms of women, who, with smaller body size, have smaller LV dimensions. Measurement of LV volumes has been codified by the American Society of Echocardiography.[17,18] One limitation of LV volume measurement is underestimation of true volumes owing to LV trabeculations and echolateral lobes, which can be addressed by using contrast agents that pass into the left side of the heart. These agents allow visualization of the entire left ventricle and accurate measurement of LV volume and stroke volume with minimal inter- and intraobserver variability, and their use should be generalized for patients with LV overload or enlargement.[19] LV diastolic function is critical information to obtain in many diseases. While the reference standard is LV filling pressure obtained by high-fidelity catheters, routine LV diastolic function can be obtained by Doppler echocardiography by compounding Doppler signals of mitral inflow, LV myocardial velocity, and pulmonary venous inflow.[20] Assessment of right ventricular size and function is mostly qualitative, and much progress remains to be made.

Left atrial (LA) dimension from parasternal views is a useful measure of LA enlargement but usually underestimates LA posterior development. The American Society of Echocardiography preferred measure of LA size is the LA volume by the area-length method from two orthogonal views. This measure is simple and reproducible, and LA volume indexed to body surface area of 40 cm/m^2 or greater is considered marked LA enlargement. Information on right atrial size is limited, and volume measurements are possible.[18]

TTE with respirometer study. This is used when pericardial versus restrictive myocardial disease is suspected.[21] It allows characterization of the excessive flow changes with respiration observed in pericardial diseases with cardiac compression (e.g., tamponade or constriction). Pericardial effusion is readily visible by echocardiography, but 2-D signs of tamponade are insensitive. Pericardial thickening is difficult to measure by echocardiography. Observation of excess LV septal displacement with respiration, mitral inflow increase with expiration and reduction with inspiration, and the opposite changes of tricuspid inflow is helpful in diagnosing pericardial compression.

Stress with TTE. This is used much more than with transesophageal echocardiography and mostly in myocardial diseases.[22–24] Several goals can be achieved. First, diagnosis of ischemia is based on maximum stress with either exercise (preferred) or dobutamine administration in patients who have a noncardiac impairment to exercise.[25] Rarely, other stressors have been used. Second, myocardial viability can be assessed in patients with reduced LV function by low-dose dobutamine administration, which stimulates function of viable myocardium, and a biphasic response (improved contraction at low doses and then ischemia with reduced contraction at high doses) is suggestive of viability. Third, hemodynamic stress usually is performed on a recumbent bike with continuous imaging.[26] It is particularly useful in mitral stenosis to characterize the exertional increase in gradient and pulmonary pressure. It also has been used in patients with mitral regurgitation to measure a dynamic increase in regurgitation with stress.[26]

TTE with three-dimensional (3-D) imaging. This was added to our armamentarium recently. While the ability to display the 3-D structure is certainly interesting, the current tradeoff is a loss of resolution that results in increased apparent thickness of tissue and increased complexity of lesion definition.[27]

Interventional echocardiography: Echo-guided interventions. Echocardiography plays an essential role in guiding interventions. The most direct is guidance of pericardiocentesis by TTE, which ensures safe access to the pericardium for drainage of compressive (including postoperative) effusions.[28] Echocardiographic guidance by TTE is also essential in mitral balloon valvuloplasty success[29] and is likely to have a growing role in the promises of percutaneous and perapical insertion of sutureless prostheses or percutaneous mitral repair procedures.[30] The role of transesophageal echocardiography versus TTE remains uncertain.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) provides superior quality in imaging the heart and great vessels owing to excellent ultrasound penetration from the esophagus, which allows use of higher ultrasonic frequencies and provides higher resolution.[31] TEE allows multiplane 2-D imaging (Fig. 11-2) with color, pulsed, and continuous-wave Doppler

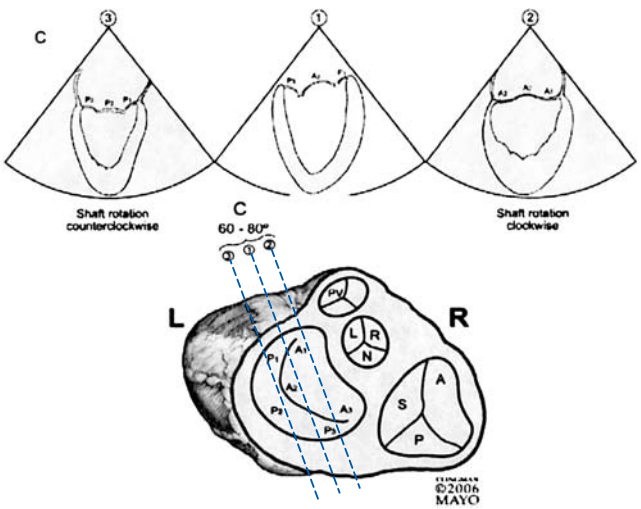

Figure 11-2. Imaging of the mitral valve by transesophageal echocardiography. This schematic description shows the four-chamber cut (*C*) and the segment of the mitral valve observed by clockwise and counterclockwise rotation of the probe (shaft). The heart is see from a posterior view, with the planes of imaging in the lower part (numbered 1, 2, and 3), represented as two-dimensional views above. L = left; R = right; A, S, P = anterior, septal, and posterior leaflets of the tricuspid valve; L, R, N = left, right, and noncoronary cusps of the aortic valve; PV = pulmonary valve; A_1, A_2, A_3 = segments of anterior mitral leaflet; P_1, P_2, P_3 = scallops of the posterior leaflet.

and is the test of choice with difficult or nonfeasible (such as during surgery) TTE images or for detection with superior sensitivity of vegetations, abscesses, mitral ruptured chords, intra-atrial (particularly appendage) thrombi, pulmonary venous abnormalities, interatrial shunt, aortic dissection, and severe atherosclerosis.[32]

The risks attached to TEE are extremely low but not absent. In a multicenter survey of 15 European institutions, among 10,218 successful TEEs, 1 patient with previous esophageal pathology died (mortality = 0.01%).[33] Overall complications are approximately 0.2%,[33,34] and odynophagia occurs in 0.1%.[35,36] There is no known esophageal damage owing to thermal or barometric injury with TEE,[37,38] but poor perfusion, descending thoracic aortic aneurysms, previous prolonged use of steroids, previous thoracic irradiation, large left atria, and advanced age[39,40] predispose to esophageal injury. Carefully ruling out esophageal disease is essential prior to TEE, and continuous cardiopulmonary monitoring of blood pressure, heart rate, respiration, and oxygen saturation is necessary. Esophageal perforation should be suspected in the presence of pneumothorax, pleural effusion, sepsis, and/or respiratory distress in the early postoperative period[39] and should lead to a prompt contrast swallow study with Gastrografin.

Drawbacks and limitations of TEE are related to (1) the hemodynamic effect of conscious sedation or anesthesia on the evaluation of cardiac diseases, particularly valve regurgitations, (2) the limited ability to modify the position of the transducer (thus hemodynamic assessment by TEE usually is limited), and (3) the loss of image quality in the distant field so that LV apical abnormalities most often are better defined by TTE. Multiplane TEE transducers are now the rule, and rotation of 180 degrees allows recording of most imaging planes.[32] Standard views place the transducer in the midesophagus (about 25 to 30 cm from incisors), distal esophagus (about 30 to 35 cm from incisors), and stomach fundus (about 35 to 40 cm from incisors) and allow for complete cardiac morphologic and functional assessment.

Intraoperative (IO) echocardiography detects unexpected findings, confirms morphologic findings, and monitors LV performance[41,42] and surgical results.[43,44] Unsuspected findings were reported in 12 to 15% of patients.[45–47] These unexpected findings lead to alteration of the surgical plan in 8 to 14% of patients. Post–cardiopulmonary bypass findings of significance are noted in 5 to 6% of patients and may lead to second pump runs,[47,48] the indications for which are closely related to the original surgical indication and hemodynamic instability.[46,49,50] Thus IO TEE is a cost-effective procedure that avoids later reoperations.[51–53] IO TEE also allows detection of residual air in cardiac cavities after cardiopulmonary bypass, which suggests the need for more thorough deairing maneuvers.[54] Aortic atheroma can be detected by TEE and may contribute to postoperative embolisms and strokes.[55,56] The suggestion that altered handling of the aorta may reduce strokes[57] should be further evaluated. Postoperatively, IO TEE may be helpful in the assessment of patients with poor hemodynamics. Observation

of markedly reduced LV function or of regional wall motion abnormalities may reveal ischemia, particularly owing to bypass graft dysfunction or air embolism. Signs of dysfunction of the implanted device or repaired valve or vessel also should be sought carefully to support a revision. Unexpected complications such as aortic dissection or hematoma may require urgent correction. Finally, in patients in whom an intra-aortic balloon pump is required, examination of the aorta may reveal atheroma with floating debris that may lead to thromboembolic complications. Overall, IO TEE has been shown to be an essential addition to intraoperative monitoring.[46,47,58–60]

Use of Echocardiography in Cardiac Surgery

Echocardiography is used before, during, and after cardiac surgery to ensure appropriate indications for surgery, to verify the progress of the intervention, to diagnose complications, and to assess the long-term results of surgery. Preoperatively, echocardiography defines the morphology of cardiac lesions and thus often defines the etiology and mechanism of disease but also provides hemodynamic information, characterizes disease severity, and often defines markers of poor outcome. This role usually is the province of TTE, which records patient status under routine hemodynamic conditions reflective of daily-living circumstances. Intraoperative assessment is performed mostly by TEE to detect unexpected findings, verify preoperative assessment, and assess the postoperative result when hemodynamic conditions are restored (and the possible use of second bypass runs). Postoperatively, echocardiography, usually TTE, detects early complications and defines the early and long-term quality of operative result and LV function.

ECHOCARDIOGRAPHY IN SPECIFIC CARDIAC DISEASES TREATED BY CARDIAC SURGERY

The diagnostic value of echocardiography pre-, intra-, and postoperatively depends on the type of cardiac disease.

Valve Diseases

Native valve disease

Preoperatively, it is essential that echocardiography sequentially reports valvular disease etiology, specific mechanism, and valve dysfunction type and severity (e.g., rheumatic disease with valvular retraction, mixed mitral valve disease with severe mitral regurgitation and mild mitral stenosis), as well as the associated ventricular and atrial alterations that may affect treatment.

MITRAL VALVE DISEASES: Mitral valve diseases are now dominated by mitral regurgitation owing to degenerative diseases and by functional regurgitation owing to primary LV disease, which are approached quite differently clinically.

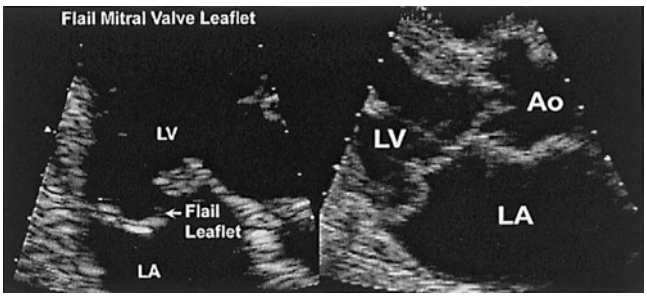

Figure 11-3. Examples of morphologic examination of organic mitral regurgitation in transthoracic echocardiography. (*Left*) The patient has a flail segment of the posterior leaflet with marked gap between the anterior and posterior leaflets during systole and the tip of the posterior leaflet in the left atrium. (*Right*) Simple mitral valve prolapse (or billowing mitral valve) shows posterior movement of the leaflet in the left atrium but no gap between the leaflets, and the tip of the posterior leaflet remains in the left ventricle in systole. Ao = aorta; LV = left ventricle; LA = left atrium; MVP = mitral valve prolapse.

ORGANIC MITRAL REGURGITATION

PREOPERATIVE ASSESSMENT: ETIOLOGY AND MECHANISM: Organic mitral regurgitation results from diseases affecting the valve leaflets or supporting structures resulting in improper coaptation of the valve. Etiology and mechanism are important to define because these determine reparability, which is an essential determinant of improved outcome.[61] TTE usually can determine organic mitral regurgitation etiology (Fig. 11-3), the most frequent of which is degenerative myxomatous mitral valve disease with prolapse (with oe without flail segment) or fibroelastic degeneration of the mitral leaflets generally associated with primary flail leaflet or annular (with or without valvular) calcification.[62,63] The distinction between the diffusely myxomatous valve and fibroelastic degeneration is not accepted by all investigators, but the echocardiographic presentation usually is strikingly different with diffuse valve thickening and excess tissue (hooding) in the former, whereas the latter is characterized by a normal-appearing leaflet apart from in the flail segment. Rheumatic valves are characterized echocardiographically by thickening (with distal predominance) and valve retraction leading to shortened (sometimes absent) coaptation and limited mobility of leaflets (particularly the posterior leaflet). These rheumatic lesions are difficult to distinguish from those due to lupus, anticardiolipin syndrome, radiation, or drugs (diet pills or ergot).[64] Endocarditis creates destructive lesions with, in addition to vegetations, ruptured chordae or perforations. Cleft anterior leaflets are rare and easily recognized in short-axis views, but smaller posterior leaflet clefts may be missed. In analyzing mitral regurgitation mechanisms, Carpentier's classification[65] simplified description into three basic types based on leaflet motion—type 1: normal; type 2: excessive; and type 3: restricted motion—and on anatomic localization (two commissures and three segments by leaflet starting with A1 and P1 for the anterior and posterior leaflets close to the external commissure). Beyond these important and useful

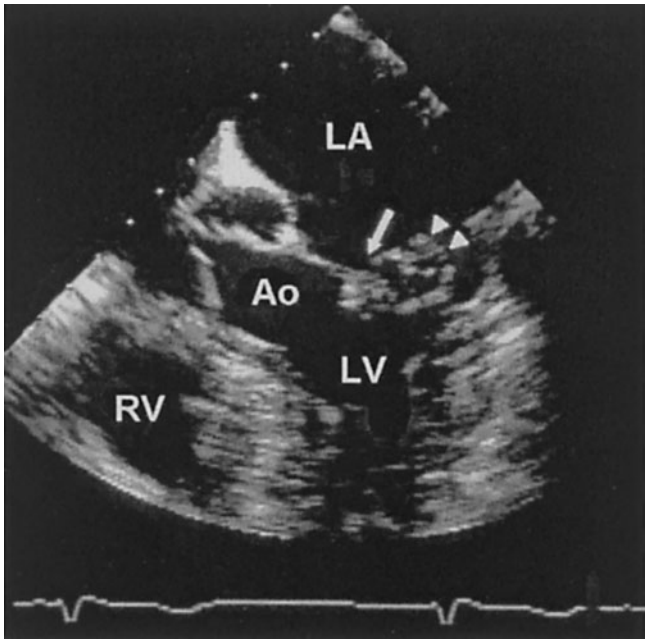

Figure 11-4. Morphologic examination of organic mitral regurgitation in transesophageal echocardiography. The patients presents with a flail posterior leaflet imaged in a long-axis view. The long arrow shows the ruptured chorda of the posterior leaflet. The arrowheads show the flail segment of P_2. Ao = aorta; LV = left ventricle; LA = left atrium; RV = right ventricle.

classifications, a detailed description should be provided by echocardiography (e.g., for an endocarditic etiology, mechanisms can be type 1, perforation, located on A2, for example, versus type 2, ruptured chordae, located on P3). Complete etiology and mechanism description usually is obtained by TTE (85 to 90% in our institution) and is supported by the direction of jets,[66] but it may require TEE (Fig. 11-4). In operated patients, TEE currently is used widely (pre- or intraoperatively) so that the correspondence of echocardiographic view with anatomic presentation is important to memorize. In the midesophageal position, the electronic dial can draw a 180-degree inspection arc and can render a complete anatomic mitral valve examination.[67–69] Evaluation of the mitral valve with the transgastric short-axis approach is difficult but may confirm the location of defects.[70] Color-flow imaging, by showing where the flow convergence is located and by showing the initial direction of the jet, is useful to confirm mitral regurgitation mechanism.[66] This complete etiologic and mechanistic analysis is particularly important for each surgeon to define the probability of valve repair in view of the lesions. Degenerative lesions, unless extensive annular calcification is present, are particularly susceptible to repair, which provides the best postoperative outcome.[62,63]

PREOPERATIVE ASSESSMENT: VALVE DYSFUNCTION SEVERITY: Color-flow Doppler alerts to the presence of mitral regurgitation[71] (Figs. 11-5 and 11-6), but estimation of the severity of mitral regurgitation should rely on comprehensive assessment (Fig. 11-7) based on American Society of Echocardiography criteria[16] and not just on jet extent in the left atrium because jet constraints by the LA wall make this measurement unreliable.[72,73] The signs of severe mitral regurgitation are classified as specific (e.g, flail, large flow convergence, large vena contracta, and pulmonary flow reversal), supportive (e.g., dense jet, high E velocity, and enlarged left ventricle and left atrium), and quantitative (e.g., regurgitant volume ≥ 60 mL and effective regurgitant orifice ≥ 40 mm^2). It is important to note that pulmonary venous

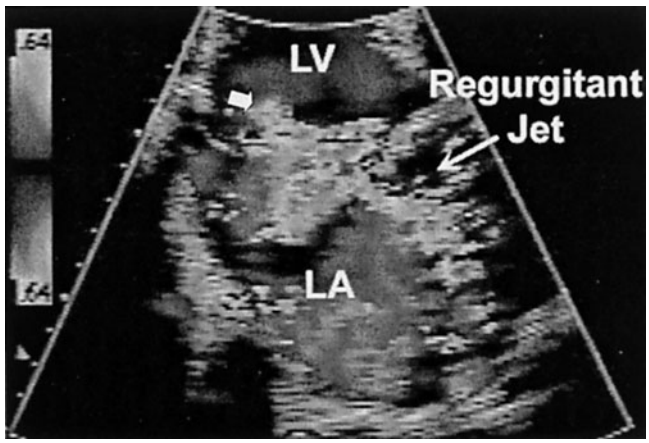

Figure 11-5. Eccentric jet of mitral regurgitation (MR) seen as a thin layer of color, with aliasing appearing as a mosaic color in the left atrium (LA). MR severity is often underestimated with this type of jet, but visualization of a large flow convergence (*large arrow*) in the left ventricle (LV) suggests severe MR.

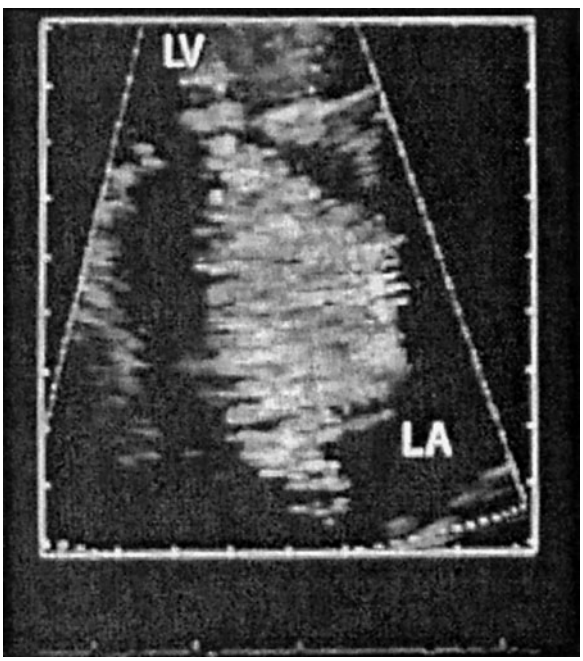

Figure 11-6. Central jet of mitral regurgitation (MR) seen as a large area of mosaic flow in the left atrium (LA). MR severity often is overestimated with this type of jet. LV = left ventricle.

Table 11–1.

Qualitative Signs of Severe Valve Regurgitation

	AR	MR	TR
Specific signs	• Central jets of width ≥65% of LVOT • Vena contracta >0.6 cm	• Vena contracta ≥0.7 cm with large central jet or swirling eccentric jet • Large flow convergence • Systolic reversal in pulmonary veins • Flail leaflet or ruptured papillary muscle	• Flail, incomplete coaptation • Central jet with area ≥10 cm^2 • Vena contracta >0.7 cm • Systolic reversal in hepatic veins
Supportive signs	• PHT <200 msec • Holodiastolic aortic reversal • ≥moderate LV enlargement	• Dense triangular jet by CWD • E-wave dominant • Enlarged LV and LA	• Dense triangular jet by CWD • Large flow convergence • EnlargedRV

CWD, continuous wave Doppler; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; PHT, pressure half time; RV, Right ventricle

flow systolic blunting is not interchangeable with reversal; blunting can be seen in all grades of mitral regurgitation and has a very low predictive value for the severity of mitral regurgitation.[74,75] The suboptimal sensitivity of pulmonary vein flow reversal is another reason that highlights the importance of quantifying mitral regurgitation[75] (Fig. 11-8).

Quantitative methods derived from PISA, quantitative Doppler (Fig. 11-9), and quantitative 2-D echocardiography (LV volumes) have been validated extensively in mitral regurgitation.[14,15,76–79] Although surgery is mostly reserved for patients with severe mitral regurgitation, the severity of the regurgitation is a continuum better quantified than categorized.[80] Mitral regurgitation severity tends to progress by 5 to 7 mL per beat of regurgitant volume per year,[81] so patients who are not operated on immediately should be monitored regularly. As indicated in the guidelines, acquiring proficiency in quantification of the degree of mitral regurgitation in an important step in developing advanced valve centers.

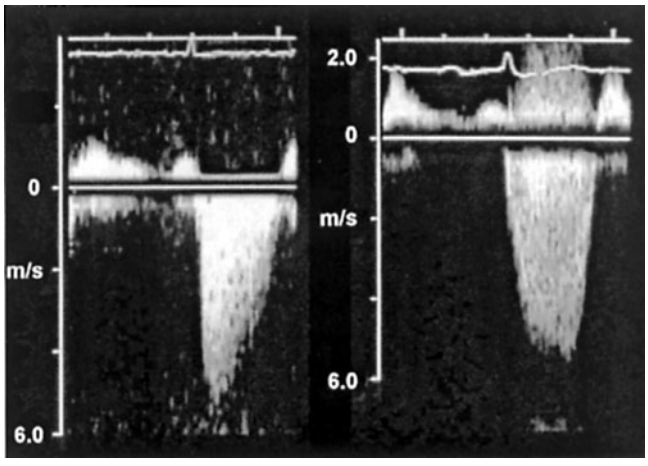

Figure 11-7. Continuous-wave Doppler of mitral regurgitant (MR) jets. (*Left*) The jet is holosystolic, but the peak velocity is reached during the first half of systole, suggesting the existence of a large *v* wave on the left atrial pressure, which leads to rapid equalization of pressure between ventricle and atrium. This type of jet is seen often in acute MR. (*Right*) The jet is also holosystolic, but the peak velocity is reached in middle to late systole without late effacement of velocity. This type of jet is seen often in patients with chronic MR without a large *v* wave.

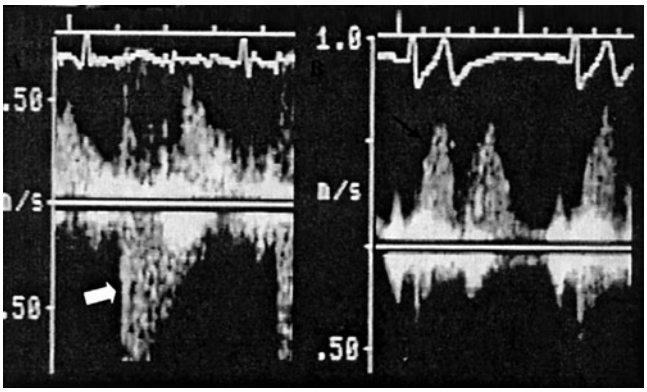

Figure 11-8. Pulsed-wave Doppler of pulmonary venous flow in two cases of mitral regurgitation. (*Left*) There a systolic flow reversal (negative flow in systole, *large arrow*) consistent with severe mitral regurgitation (MR) and a large *v* wave on the left atrial pressure. (*Right*) There is a normal forward flow (positive flow in systole, *thin arrow*) suggestive of the absence of a *v* wave. The systolic pulmonary venous flow reversal is a specific sign with high positive predictive value but of low sensitivity for severe MR.

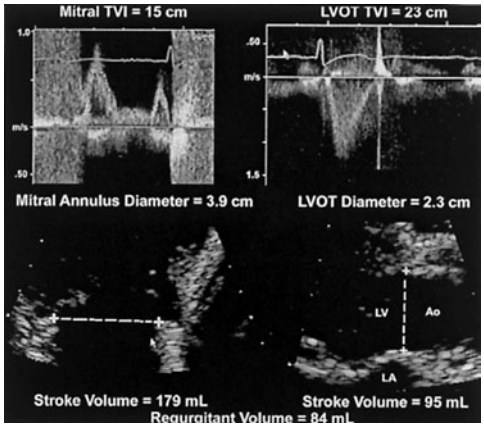

Figure 11-9. Quantitative Doppler assessment of mitral regurgitation (MR) based on stroke volume measurement using the annular diameter to calculate the annular area and its product with the pulsed-wave Doppler as the stroke volume traversing the specific annular area. The left part of the figure measures the mitral stroke volume (179 mL/beat), whereas the right side measures the aortic stroke volume (95 mL/beat). Thus the regurgitant volume is calculated as the difference between mitral and aortic stroke volumes, or 84 mL/beat.

PREOPERATIVE ASSESSMENT: PROGNOSTIC INDICATORS: Assessment of the left ventricule usually is performed by measuring LV diameters and ejection fraction.[82] End-systolic diameter of 40 to 45 mm or more[83–85] and ejection fraction of less than 60%[86,87] are markers of poor outcome. These characteristics are considered class I indications for surgery, but the postoperative outcome when these characteristics are observed[86] is not optimal, so these markers should be considered as advanced signs indicating rescue surgery. LA diameter of 50 mm or more is associated with high risk of subsequent atrial fibrillation under medical management[88] but also after successful surgery.[89] Therefore, LA dilatation should alert the clinician early for the need for surgery. Pulmonary hypertension is considered a marker of poorly tolerated mitral regurgitation, although its association with subsequent prognosis is uncertain.[82] Mitral regurgitation severity assessment is essential for prognosis.[90] Although assessment of mitral regurgitation may be qualitative, quantitation provides stronger prognostic information.[91] In asymptomatic patients with organic, holosystolic mitral regurgitation,[91] the risk of death under medical management increased by 18% for each 10 mm^2 of effective regurgitant orifice (ERO). ERO was the strongest echocardiographic predictor of outcome. With an ERO of 40 mm^2 or more, the risk of death is multiplied by 5 and that of cardiac events by 8 compared with mild mitral regurgitation, and excess mortality is observed as compared with the general population. Importantly, surgery restores life expectancy in these asymptomatic patients. Therefore, echocardiographic data participate importantly to the indication for surgery.

INTRA-OPERATIVE ASSESSMENT: Before cardiopulmonary bypass, TEE confirms the mitral lesions[62,66,92,93] but also identifies associated conditions that may benefit from surgical therapy (e.g., patent foramen ovale and appendage or LA thrombus). Whether the valve is amenable to repair should be resolved preoperatively,[62,63] but rarely, there are surprises regarding the extent or type of lesion that may lead to a change in strategy.[94,95] After cardiopulmonary bypass, intraoperative TEE assesses the result of mitral valve repair[96] and the need for a second pump run based on the presence of residual mitral regurgitation. The timing of evaluation is essential. Postbypass TEE performed too early with inappropriate loading conditions will result in faulty assessment of residual mitral regurgitation. Insufficient preload and low ventricular pressure result in a decline of regurgitant orifices and underestimation of residual mitral regurgitation. When performed adequately, excellent correlation between post-bypass TEE and pre-discharge assessment of residual mitral regurgitation is observed.[97] It is essential not to tolerate mitral regurgitation after bypass, unless very trivial, because more patients with or without residual mitral regurgitation require reoperation during follow-up.[98] Thus post–cardiopulmonary bypass IO TEE serves as a tool in deciding which patient should return to cardiopulmonary bypass for a second repair or replacement. Over time, surgical management of anterior leaflet pathology and bileaflet prolapse has evolved,[99–102] and new techniques have emerged that provide better results. IO TEE still plays a pivotal role in adequate identification of mechanisms and anatomic location of disease as well as post–cardiopulmonary bypass evaluation of results.

After mitral valve repair, major repair failures are threefold: insufficient correction of the mitral lesion with residual mitral regurgitation (e.g., residual prolapse) and LV outflow tract obstruction by systolic anterior motion of the mitral apparatus owing to inadequate repair or stenotic repair. Severe residual mitral regurgitation obviously is rare but requires immediate correction. Observation of milder residual mitral regurgitation by IO TEE immediately after repair[103] with "less than echo-perfect"[104] result leads to higher long-term reoperation risk for mitral regurgitation.[98] It is essential to define by IO TEE the mechanisms and anatomic location of the defect causing residual mitral regurgitation to establish the best correction strategy and the possibility of re-repair. LV outflow tract obstruction is due to systolic anterior motion of the mitral valve with contact with the LV septum, to which contribute excess or deformed mitral tissue, small LV size, and hyperdynamic LV function.[105] LV outflow tract obstruction occurs in 1 to 4% of mitral valve repairs[106–108] and is diagnosed by visualization of the systolic motion combined with increased velocity through the LV outflow tract. LV outflow tract obstruction results generally in notable residual mitral regurgitation owing to the deformation of the mitral valve in systole, and it is essential in patients with residual mitral regurgitation to rule out LV outflow tract obstruction before recommending a second pump run.[96] Usually, increasing LV filling, reducing or discontinuing inotropic drug administration, and in some cases adding beta blockers result in elimination of LV

obstruction.[96] If the obstruction persists, consideration should be given to a second cardiopulmonary bypass run for sliding valvuloplasty, although the systolic anterior motion tends to improve over time,[106] and most patients can be managed medically. Prevention of LV outflow tract obstruction is based on careful examination of excess tissue on prebypass IO TEE[109,110] to select the patients who may benefit from specific repair techniques such as sliding annuloplasty.[108,111,112] Markedly restrictive repairs with stenosis result from the combination of anatomic alterations such as diseased, rigid leaflets (e.g., rheumatic), commissural fusion, or markedly protruding calcification of the mitral annulus, with excessive repairs involving rings too small and/or large edge-to-edge sutures. Diagnosis is based on high transvalvular gradients of 8 to 10 mm Hg or more by Doppler. Normal postrepair gradients (3 to 6 mm Hg) may be exacerbated by high output and tachycardia reducing the diastolic filling period. It is thus prudent before a second pump run to reassess the mitral gradient after cardiac output has stabilized and administration of beta blockers to control tachycardia.

The most common immediate complications after mitral valve replacement are periprosthetic leaks and mechanical dysfunction of the prosthesis owing to interaction of tissue remnants with the mobile elements of the prosthesis.[113,114] In contrast to TTE, TEE has no shadowing from the mitral prosthesis,[115] so periprosthetic mitral regurgitation should be sought carefully after bypass, and that which is clinically relevant should be distinguished from the minor paravalvular[116] or intravalvular[117,118] leaks often noted. Diagnosis is quite accurate and should lead to prompt consideration of a second pump run,[115,119] particularly if the paravalvular leak persists after protamine administration.[120] The location and severity assessment of the leak are critical information to evaluate in multiple planes to enhance the probability of a simple repair of the leak avoiding dismounting the prosthesis. The mobile prosthetic element or leaflet can be impinged on by suture or valve material, leading to obstruction or most often regurgitation, which sometimes can vary from beat to beat owing to a variable interaction. Thus it is important to examine the mobile element in 2-D and color-flow images for a sufficient time to ensure consistent and appropriate function.

POSTOPERATIVE ASSESSMENT: VALVULAR RESULT: Postoperative assessment is performed consistently at predischarge and yearly and often in our practice 3 to 6 months postoperatively. While the IO TEE is quite accurate in the assessment of residual valve dysfunction, changes in loading conditions and remodeling may reveal changes in valvular function. The rate of recurrence of mitral regurgitation after valve repair is 5 to 10% at 10 years[98,99] and is due in two-thirds of patients to new valve lesions (e.g., new ruptured chordae), whereas in one-third it is due to defective repair (e.g., insufficiently corrected prolapse of the anterior leaflet in bileaflet prolapse).[121] TTE provides the mechanism and location of the mitral regurgitation and allows discussion of the possibility of re-repair. It also allows assessment of mitral regurgitation severity. Qualitative assessment of mitral regurgitation is even more difficult after than before repair, and quantitative techniques (particularly the PISA method) are of particular importance. We rarely refer patients with moderate regurgitant volumes (30 to 60 mL/beat) for reoperation. Development of stenotic repair is rare and is observed mostly with rheumatic or rigid leaflets, sometimes after edge-to-edge repair. Standard repair represents a mild stenosis but, in combination with an enlarged left atrium, may lead to new atrial fibrillation[89] and thrombus formation with possible stroke, for which TEE allows thorough examination of the LA appendage. New dysfunction of a mitral prosthesis often requires TEE examination, particularly for detection of prosthetic thrombosis or tissue degeneration.

LEFT VENTRICULAR ASSESSMENT: After surgical correction of mitral regurgitation, preload is decreased with decline of end-diastolic volume, but end-systolic indices are little changed, so ejection fraction falls by an average of 10%.[85,122] However, there is a large individual variation, and changes in LV function with changes in LV reverse remodeling may be quite different between patients. There are no definite predictors of the changes in LV end-systolic indices, which need to be monitored closely during the first postoperative year.[84] The value of medical therapies shown to result in reverse remodeling in patients with primary LV dysfunction (e.g., beta blockers and angiotensin-converting enzyme inhibitors) is not established, but early diagnosis may lead to early intervention. Irrespective, residual postoperative LV ejection fraction is an important predictor of postoperative survival and should be monitored. The result seen early after surgery usually is stable unless marked LV dilatation results in further dysfunction or coronary artery disease leads to intrinsic myocardial deterioration.[123]

FUNCTIONAL MITRAL VALVE REGURGITATION: Functional mitral regurgitation is the regurgitation occurring on structurally normal valves owing to primary LV alteration, such as those due to coronary artery disease, cardiomyopathy, myocarditis, or transient LV dysfunction.[124] Although the disease is primarily myocardial, functional mitral regurgitation diagnosed by angiography[125] or echocardiography[126–129] exerts an important influence on outcome, but major controversy persists regarding the role of mitral surgery in these patients.[130,131]

PREOPERATIVE ASSESSMENT: The diagnosis of functional mitral regurgitation is based on the presence of LV dysfunction (generalized most often but sometimes localized, requiring a thorough regional assessment) and on a structurally "normal" mitral valve with normal tissue or at most minor degenerative calcifications (Fig. 11-10). It is also important to demonstrate the deformation of the mitral valve leading to functional mitral regurgitation. There is apical and posterior displacement of the papillary muscles with traction through the inextensible chordae on both leaflets, which

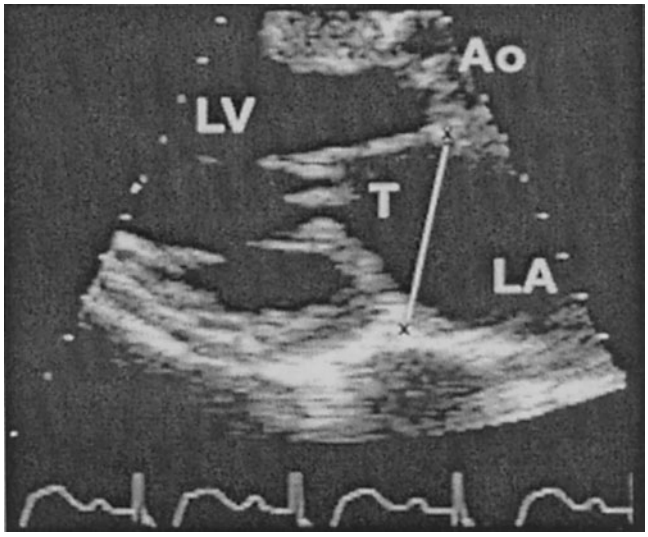

Figure 11-10. Two-dimensional echocardiography showing the parasternal long-axis view of a patient with functional mitral regurgitation (MR). Note the protrusion of the mitral leaflets toward the left ventricle (LV), resulting in a large tenting area (T) between the leaflets and the annulus (white line with x marking the mitral annulus) and an insufficient coaptation surface available on each leaflet to prevent MR. LA = left atrium; Ao = aorta. (*Reproduced with permission of the American Heart Association.*)

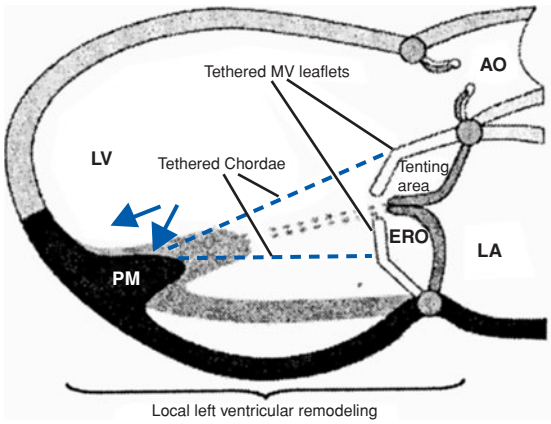

Figure 11-11. Schematic representation of the mechanism of functional mitral regurgitation (MR). In light gray is represented the normal position of the papillary muscle (PM) chordae (*dashed lines*) and mitral leaflets shown with adequate coaptation surface. With local left ventricular (LV) remodeling, the papillary muscle is repositioned apically and posteriorly (*dark gray*) and exerts traction through the nondistensible chordae on the leaflets. Traction on the strut chords (inserted on the midportion of each leaflet) is most manifest, leading to deformation of the mitral leaflet, tenting, reduced coaptation, and creation of an effective regurgitant orifice (ERO). LA = left atrium; Ao = aorta.

results in apical displacement of the leaflet body leading to absent or reduced coaptation to the leaflet tipS.[132,133] This deformation of normal leaflets, called *tenting,* is the direct determinant of the functional severity of the mitral regurgitation. The mechanism of mitral regurgitation usually is a central gap in coaptation, usually worse during isovolumic contraction and relaxation, when the left ventricle exerts a low pressure on the leaflets.[134] With ischemic LV dysfunction, the mitral regurgitation may originate from the medial commissure, where the traction may be predominant,[135] but apart from scars from myocardial infarction, there are no specific sign of ischemic versus myopathic mitral regurgitation. The traction of the chords on the leaflets may be inhomogeneous and predominate on one leaflet.[136] In such cases, an "overshoot" of the other, less tethered leaflet behind the tethered leaflet is observed, should not be mistaken for a prolapse, and may lead to unusual eccentric jets.[137] Therefore, the mechanism of functional mitral regurgitation is not just the frequent annular dilatation but is more complex, involving a combination of annular and leaflet tethering alterations (Fig. 11-11). Mitral regurgitation severity assessment is particularly crucial in view of the notable surgical risk (Table 11-2). Mitral regurgitation jets that are central tend to be overestimated, and diastolic function alterations may mimic the tall E wave, low systolic venous flow, usually suggestive of severe mitral regurgitation. Thus it is essential to quantify the mitral regurgitation, but two essential issues need to be examined. First, functional mitral regurgitation is prominent during isovolumic contraction and relaxation,[134] but since these phases involve little regurgitant driving force, their contribution to the regurgitant volume is small, and it is essential with the PISA method to quantify mitral regurgitation in midsystole. Second, the grading of mitral regurgitation has been established in organic mitral regurgitation, but recent data[26,127,138] suggest that thresholds of effective regurgitant orifice (ERO) associated with poor outcome are lower in functional than in organic mitral regurgitation. Thus, pending further

Table 11–2.

Quantitative Thresholds for Severe Regurgitation

	AR	Organic MR	Functional MR	TR
ERO	≥0.30 cm^2	≥0.40 cm^2	≥0.20 cm^2	≥0.40 cm^2
RVol	≥60 mL	≥60 mL	≥30 mL	≥45 mL

confirmation, patients with functional mitral regurgitation and an ERO of 20 mm^2 or greater should be considered as having severe mitral regurgitation, and this prognostic effect comes in addition to ejection fraction and left atrial volume.[139] Also, functional mitral regurgitation is dynamic, and ERO often increases during exercise, which may have important functional[140] and outcome[26] implications, but decreases during dobutamine echocardiography,[141] making this test useless for the assessment of functional mitral regurgitation. While the role of imaging during exercise in defining the surgical indications needs further evaluation, a dynamic ERO also may decrease with interventions such as vasodilatation[142] or beta blockade.[143,144] Not surprisingly, sedation or anesthesia necessary for TEE may result in regression of mitral regurgitation and underestimation of the degree of mitral regurgitation[145] compared with habitual life conditions. Preoperative assessment of functional mitral regurgitation should assess not only the mitral regurgitation but also other components of the disease, namely, LV remodeling, systolic dysfunction, and diastolic dysfunction, because severe LV remodeling may be a marker for poor response to valve repair.[146]

INTRAOPERATIVE ASSESSMENT: Before bypass, it is essential to confirm the structural normality of the mitral leaflet and to avoid the pitfall in the assessment of mitral regurgitation of reduced loading owing to anesthesia. Thus, if the degree of mitral regurgitation is in doubt, assessment with increasing loading conditions similar to those of outpatient evaluation should be performed by a loading challenge,[147] but this does not replace an appropriate outpatient evaluation. Postbypass IO TEE evaluates residual mitral regurgitation. After repair, reduced loading conditions may lead to major underestimation of residual functional mitral regurgitation, emphasizing the importance of adjusting pre- and afterload. Functional mitral regurgitation is particularly prone to recurring after surgical correction owing to continued LV remodeling, continued displacement of papillary muscles, and mitral valve tenting[148,149] despite a repair judged as adequate intraoperatively. Thus postbypass assessment is difficult and may be overly optimistic, and a careful judgment of residual tenting and valve deformation is essential. Contrary to organic mitral regurgitation, the most advanced subsets of patients benefit as much from bioprosthetic replacement as they do from repair.[150] Thus doubts on repair quality should be pursued aggressively to decide if a new pump run and valve replacement should be recommended.

POST-OPERATIVE ASSESSMENT: Postoperative assessment focuses on potential recurrence of mitral regurgitation, which has been reported as rare[151] or frequent in various clinical series, and on its mechanism, if present (increased tenting versus insufficient annular restriction).[130,148] Postoperative mitral regurgitation also should be quantified if more than mild. Beyond mitral regurgitation, echocardiography focuses on the assessment of LV dysfunction, its systolic and diastolic components, and its consequences on LA and pulmonary pressures. Active prevention of further LV remodeling is recommended and should be monitored by echocardiography.[143,144]

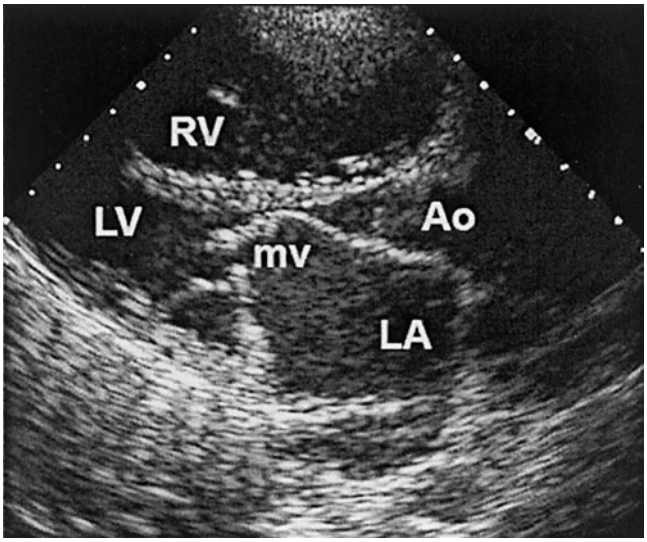

Figure 11-12. Parasternal long-axis view of a patient with mitral stenosis. Note the thickening and hockey-stick deformation of the anterior leaflet of the mitral valve (mv) and the protrusion of the posterior leaflet. Note also the normal left ventricle (LV) contrasting with the enlarged left atrium (LA) and right ventricle (RV). Ao = aorta.

MITRAL VALVE STENOSIS: Mitral stenosis is currently treated preferentially by balloon valvuloplasty,[152] so the role of surgery is relatively limited at present. However, there are patients who benefit from surgery rather than balloon valvuloplasty, so the role of echocardiography in defining these subsets should be examined carefully.

PREOPERATIVE EVALUATION: Classic mitral stenosis (MS) is invariably due to rheumatic valve disease, and its features are characteristic (e.g., immobile posterior leaflet, fused commissures with reduced orifice area, and hockey-stick deformation of the anterior leaflet in diastole)(Fig. 11-12). Other causes of stenosis are lupus and anticardiolipin heart diseases (producing very similar lesions), ergot heart disease,[153] and other iatrogenic valve diseases that thicken leaflets without fusing commissures and produce protruding annular calcifications that restrict the orifice without commissural fusion.[154] Anatomic analysis is essential because balloon valvuloplasty is the most widely used procedure to treat MS and produces a commissurotomy identical to closed commissurotomy (hemicommissurotomy in most cases). Therefore, balloon valvuloplasty is not indicated in (1) mitral valve obstructions without commissural fusion, (2) heavily calcified mitral valves, (3) MS with nodular calcification involving both commissures (high risk of splitting the leaflet and not the commissures),[155] and (4) MS associated with more than mild mitral regurgitation. In such cases, the best treatment is surgical valve replacement. Thus an essential component of the

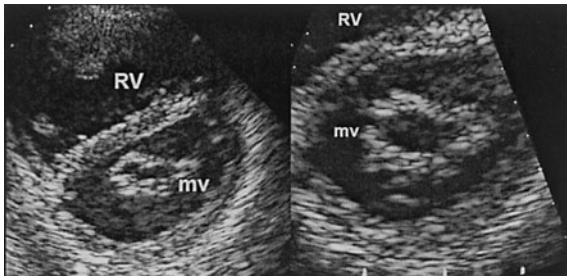

Figure 11-13. Mitral valve (mv) area of a patient with mitral stenosis (MS) before (*left*) and after (*right*) commissurotomy. Note in the panel on the right the narrow orifice and in the panel on the left the large orifice with wide opening of the medial commissure. Note also in the panel on the left the right ventricular (RV) enlargement with signs of pulmonary hypertension manifested by a flat septum and D-shaped left ventricle. In the panel on the right, the position of the septum and the shape of the left ventricle have normalized.

echocardiographic assessment of MS is the short-axis view to ascertain the presence of commissural fusion and the severity and location of leaflet calcifications.[155] Another important component of decision making is alteration of the subvalvular apparatus.[29,156] Very short chordae or direct insertion of papillary muscle on the leaflets may lead to poor results with balloon valvuloplasty but may allow good surgical splitting of the commissures and the papillary muscles. MS severity is assessed using two variables: the transvalvular gradient, representing the pressure overload to the LA and pulmonary circulation, and the mitral valve area (MVA) (Fig. 11-13). The gradient measured is the mean gradient (Fig. 11-14) and not only is affected by the severity of the stenosis but also is increased by tachycardia and increased transvalvular flow (e.g., anemia, pregnancy, hyperthyroidism, and

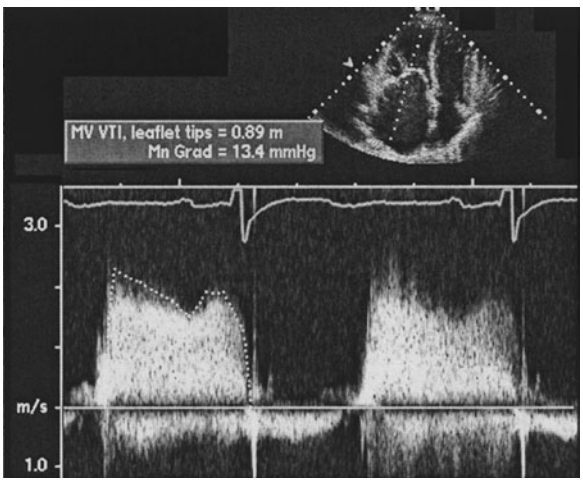

Figure 11-14. Continuous-wave Doppler recording of the mitral gradient in a patient with severe mitral stenosis (MS). Note the high velocity (≥2 m/s) with a mean gradient of more than 13 mm Hg. Note also the flat slope of deceleration of the early diastolic velocity consistent with severe MS.

associated mitral regurgitation) and decreased by bradycardia and low cardiac output. Mild MS is associated with a resting mean diastolic Doppler gradient (measured by continuous-wave Doppler) of 5 mm Hg or less; moderate, with a gradient of 5 to 10 mm Hg; and severe, with a gradient of 10 mm Hg or greater. The normal MVA is 4 to 6 cm^2, and guidelines for MS severity suggest thresholds of 2.0 cm^2 for mild MS, 1.5 cm^2 for moderate MS, and 1.0 cm^2 for severe MS. However, most patients undergoing interventions for MS are in the range of 1 to 1.2 cm^2 and symptomatic, so in our institution, an MVA of less than 1.5 cm^2 is considered severe MS. MS severity assessment also involves LA enlargement and elevation of pulmonary pressure and in time also may involve right-sided heart enlargement and failure and tricuspid regurgitation, whereas the levt ventricle remains of normal size but may show reduced ejection fraction. MVA measurement can be obtained by several methods that are combined because all methods have limitations, and averaging reduces the risk of error. The pressure half-time (PHT) method is the simplest, where the PHT is measured from the Doppler mitral signal using the deceleration from the peak early velocity and calculates MVA using the empirical formula 220/PHT.[157] However, this method may not be accurate in the presence of changes in LV or LA compliance and has a wide range of error with short diastole.[158] Other methods of MVA measurement are (1) direct planimetry of the orifice in short-axis view (technically demanding), (2) a continuity equation in which MVA is calculated as the ratio of flow measured on the aortic valve to mitral velocity (false if mitral regurgitation or atrial regurgitation is present), and (3) the PISA method, imaging of mitral inflow with color using baseline shift (requires an angle correction for the funnel shape of the mitral valve with potential for error).[159,160] Important issues in MS severity assessment are (1) the essential combination of methods of MVA assessment to minimize the potential for error and (2) the need for exercise hemodynamic assessment (with bike allowing continuous hemodynamic monitoring) in patients who present with a low gradient and doubt on MS severity. Thus TTE should provide definite assessment of MS severity and in most cases is the procedure most suited for treatment.[161] Outpatient TEE is systematic in patients considered for balloon valvuloplasty to assess the presence of LA thrombus and mitral regurgitation. If surgery is definitely indicated, TEE can be performed intraoperatively.

INTRAOPERATIVE ASSESSMENT: Intraoperative assessment in patients with MS is most often that of mitral replacement, but in patients suited for open commissurotomy, it provides anatomic and mitral regurgitation reassessment before bypass and repair assessment postoperatively. A high gradient or moderate mitral regurgitation may lead to consideration of a second pump run after mitral valve repair. Mobile element dysfunction or periprosthetic regurgitation suggest consideration of further correction after valve replacement. Although decisions with regard to repair of tricuspid regurgitation should be made preoperatively, IO TEE allows

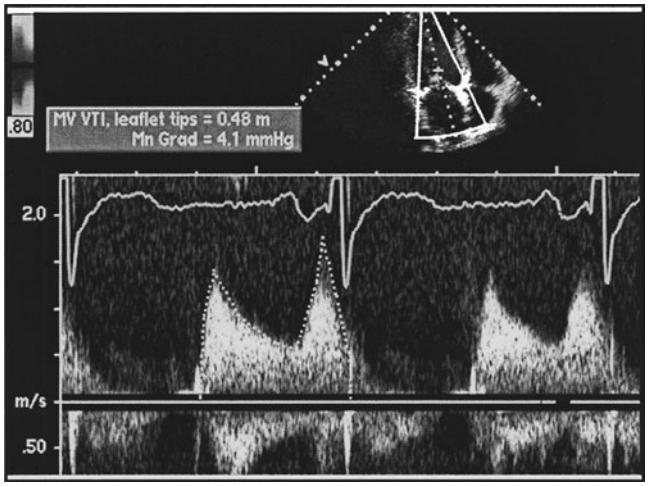

Figure 11-15. Continuous-wave Doppler in the same patient as in Fig. 11-13 after commissurotomy. The mean gradient is now low, with rapid deceleration of early diastolic velocity consistent with mild MS.

reassessment, rarely discovery of organic tricuspid lesions, and consideration of repair of associated moderate or severe regurgitation.

POST-PROCEDURE ASSESSMENT: Postprocedure assessment follows the usual postoperative and 1-year assessments (Fig. 11-15). MS remains a progressive lesion even after valve repair, and there is the potential for recurrence of severe MS and also for progressive scarring and retraction of the mitral valve, leading to progression of mitral regurgitation.[162] Depending on the severity of the mitral lesions, age, and mitral regurgitation, a notable proportion of patients will need reoperation between 5 and 10 years after the original intervention (balloon valvuloplasty or valve repair). Patients should be monitored carefully to avoid progressive heart failure and pulmonary hypertension. After surgery, pulmonary hypertension owing to MS regresses almost uniformly unless chronic pulmonary disease has developed, LV dysfunction usually normalizes with normalization of preload unless coronary artery disease is present, but LA enlargement persists, and patients with atrial fibrillation remain at substantial risk for stroke.

MIXED MITRAL VALVE DISEASE: Mixed mitral valve diseases are those with substantial components of stenosis and regurgitation, and most are due to rheumatic disease. Therefore, this type of situation is rare in Western countries but continues to be prevalent in developing countries.

PREOPERATIVE ASSESSMENT: Preoperative assessment recognizes the rheumatic valve lesions and the combination of stenosis and regurgitation precluding the possibility of valve repair. The major challenge is to evaluate the severity of the mitral valve disease. Often the stenosis and regurgitation are both moderate, and criteria for severe valve diseases are difficult to establish. A transvalvular gradient higher than expected on the basis of MVA alone reflects the severity of the combined disease.

INTRAOPERATIVE ASSESSMENT: Intraoperative assessment confirms the rheumatic features and analyzes the absence of postoperative complications after valve replacement. Tricuspid regurgitation is frequent in mixed valve disease and often requires associated repair.

POST-OPERATIVE ASSESSMENT: This is important not only to monitor the mitral prosthesis but also to assess LV function. LV dysfunction is a frequent complication of the mitral regurgitation of mixed mitral valve diseases, so aggressive detection and treatment of this complication are essential to obtain the best outcome.

AORTIC VALVE DISEASES: These are now dominated by aortic stenosis. The aortic valve normally is formed by three cusps and is bicuspid in 1 to 2% of the population, but the physiology of the aortic valve is poorly understood irrespective of the number of cusps.

AORTIC STENOSIS

PREOPERATIVE ASSESSMENT: Preoperative assessment focuses on the etiology and mechanism, although assessment usually is simplified as compared with assessment of the mitral valve. Most aortic stenoses are due to degenerative disease irrespective of the number of cusp. Indeed, recent data have shown the association of aortic stenosis (AS) with atherosclerosis and the importance of cholesterol deposition with lipid oxidization as the initial step in aortic sclerosis and stenosis, but bicuspid valves tend to calcify more frequently than tricuspid valves for unknown reasons. Rheumatic AS is now rare and is characterized by commissural fusion, whereas commissures are open in degenerative diseases. However, clinically, the various etiologies of AS in the adult are difficult to recognize because with advanced AS, valves are uniformly calcified. Therefore, morphologically, 2-D echocardiography recognizes the valvular calcification associated with AS in the adult (Fig. 11-16). Absence of aortic valve calcification makes AS unlikely and makes a systolic gradient most likely to originate from the sub- or supravalvular region. In children, calcification is inconsistent and not indispensable to a diagnosis of AS. The degree of valvular calcification is difficult to analyze by echocardiography[163] and is measured more precisely with high-resolution computed tomography.[164] The volume or score of calcification is linked to AS severity in a nonlinear manner, so both measures are complementary in assessing AS.[164] The fact that most aortic stenoses are due to valve rigidity caused by calcification and not to commissural fusion explains the lack of efficacy of balloon valvuloplasty in AS.[3] The left ventricle responds to the pressure overload by increasing wall thickness and LV mass.[165] The hypertrophic response is variable, and its absence does not rule out severe AS. LV hypertrophy regresses after aortic valve replacement,[166–168] which is the only effective treatment of AS currently available. [82,166,169] Recent attempts at percutaneous

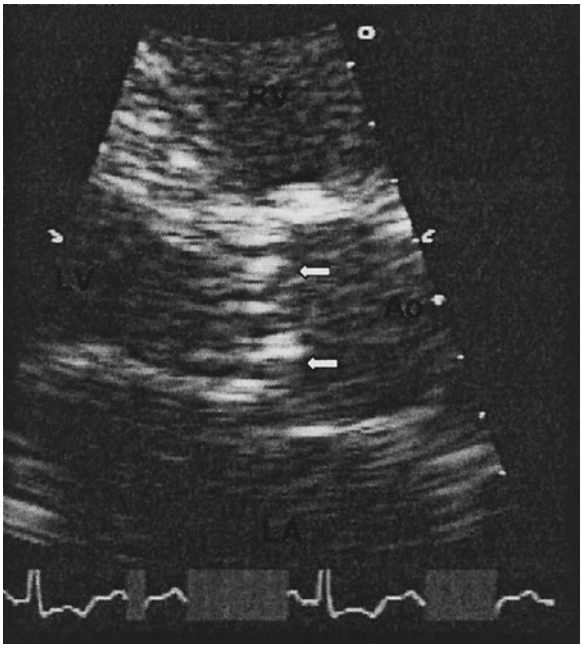

Figure 11-16. Two-dimensional echocardiography of a patient with aortic stenosis (AS). The aortic valve (*arrows*) is heavily calcified (dense nodules). LV = left ventricle; LA = left atrium; Ao = aorta, RV = right ventricle.

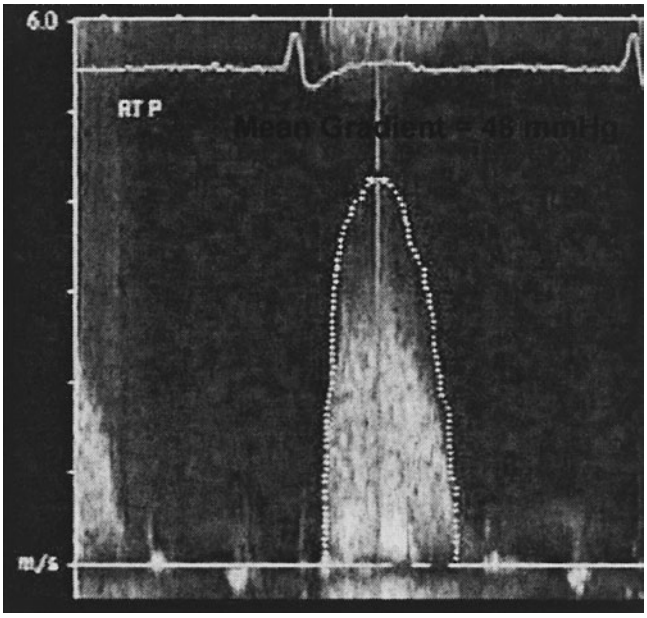

Figure 11-17. Continuous-wave Doppler obtained from the right parasternal window (RT P) in a patient with severe aortic stenosis (AS). The paek velocity is more than 4 m/s, and the mean gradient is 48 mm Hg.

aortic valve replacement have been reported, but the safety of this approach remains to be determined. Moreover, morphologic criteria to indicate such an approach have not yet been developed.[170] Another morphologic component of AS is poststenotic aortic dilatation, which rarely requires repair.

Assessment of AS severity is the major goal of TTE. Opening of even just one aortic leaflet to the aortic wall is usually a marker for nonsevere AS, but AS severity should be assessed quantitatively by measuring mean systolic gradient[8] as a marker of pressure overload and aortic valve area (AVA) to assess lesion severity.[12,13] Normal aortic valve opening area is 2.5 to 4.5 cm^2 . AS is considered present with an AVA of 2 cm^2 or less and a pressure gradient developing across the aortic valve, and AS is considered severe (Fig. 11-17) with an AVA of 1.0 cm^2 or less (using the continuity equation) and a mean gradient of 40 mm Hg or greater (using the Doppler velocity).[82] Other criteria of AS are peak velocity of 4 m/s or more[171,172] and velocity ratio (LV outflow tract to jet) of 0.25 or less.[13] Indeed, in patients with LV outflow tract obstruction, the AVA may not be measurable, and velocity may be the only available criterion to diagnose severe AS (Fig. 11-18). AS is progressive because of progressive calcium deposition, with gradient progression by 5 to 7 mm Hg per year and AVA decline by 0.1 cm^2 per year.[173–175] The major pitfall of gradient measurement is underestimation owing to excessive flow ultrasonic beam angle, so systematic multiwindow Doppler is the key to appropriate assessment of AS severity. Another pitfall is underestimation of the LV outflow tract diameter, which is necessary to the measurement of stroke volume and valve area. Such underestimation leads to underestimation of valve area. Thus the triad of normal LV function, low gradient, and low AVA is not physiologically consistent, is suggestive of inadequate echocardiographic measurements, and should lead to comprehensive reassessment in a reference laboratory. Conversely, coexistence of low gradient and low valve area is possible physiologically in patients with reduced LV function.[176–178] This combination may be due to severe AS and low gradient owing to low output secondary to poor LV function,[179] but the AVA also simply may be measured low owing to insufficiently forceful ejection to overcome a mildly stenotic valve inertia. Diagnosis of severe

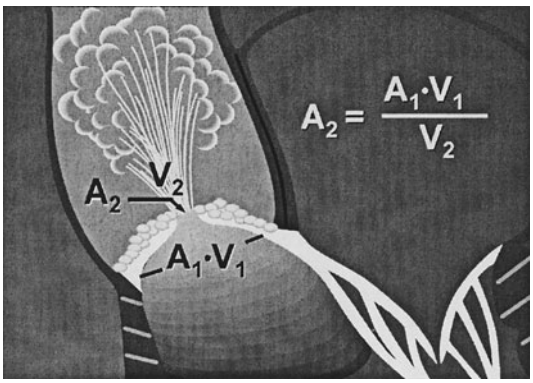

Figure 11-18. Schematics of the measurement of aortic valve area in aortic stenosis (AS). Because blood is incompressible, flow is constant through the left ventricular outflow tract (area A_1) through the aortic orifice (area A_2). Thus the aortic stenosis manifests itself by increased velocity ($V_2 > V_1$). Because flow is equal to area multiplied by velocity, aortic valve area $A_2 = (A_1^* \times V_1)/V_2$. (*Courtesy of Dr. F. A. Miller.*)

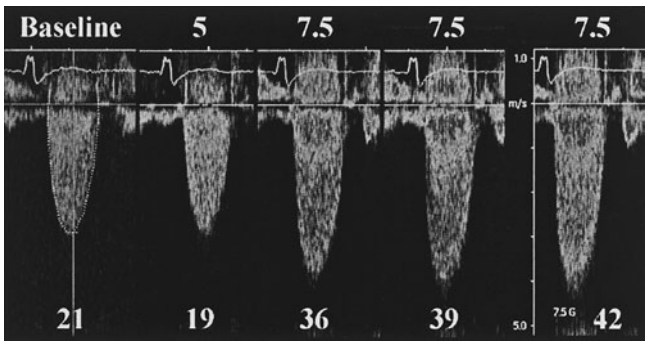

Figure 11-19. Measurement of aortic velocity by continuous wave Doppler in a patient with severe Aortic stenosis, low ejection fraction, low output and low gradient. The baseline (*left*) mean gradient was 21 mm Hg and increased (*bottom line*) with increasing doses of dobutamine (*top line*). The peak dose was 7.5 μg/min, and the mean gradient was 42 mm Hg (*Courtesy of Dr. Messika-Zeitoun.*)

AS in such patients requires additional testing with high-resolution computed tomography to measure a high calcium load[164] and with dobutamine echocardiography to increase myocardial contraction and aortic flow.[180] The classic response is an increased gradient with severe AS (Fig. 11-19) and an increased AVA with cardiomyopathy and mild AS.[176,178] However, this test may not be conclusive in patients lacking contractile response.[177]

While classically asymptomatic severe AS was considered well tolerated, recent data demonstrated excess mortality during follow-up and noted that a large proportion of patients were never offered surgery.[171] Therefore, surgery in asymptomatic patients based on echocardiographic criteria is debated. Asymptomatic patients with rapid decline in AVA and a large calcification load display poor clinical outcome under medical management[163,164] and may be considered for surgery, whereas those with reduced LV function are definitely at high risk and should be offered prompt surgery if the AS is severe.[181]

INTRAOPERATIVE ASSESSMENT: This examines the valve morphology, confirms the large calcification load, and can measure the orifice area by direct planimetry before institution of bypass.[182,183] AVA measurement by 2-D echocardiography is difficult because one has to ascertain measurement at the leaflet tip and cannot replace an appropriate Doppler hemodynamic measurement before surgery.[184] Determination of aortic annulus size may be helpful for early surgical sizing of allografts destined for the aortic position[185] or homografts[186] and may play a role in preventing patient-prosthesis mismatch, which is a cause of postoperative mortality and morbidity[187,188] and may be prevented by sizing taking into account the patient's body surface area.[189] Another important goal of IO TEE is examination of the ascending aorta and, for patients with aneurysmal dilatation, consideration of ascending aortic repair. IO TEE in patients undergoing aortic valve replacement for severe AS may alter the planned surgical procedure in approximately 10% of patients[190] for unexpected severe mitral regurgitation, patent foramen ovale, mass, or thrombus. After bypass, specific issues examined are lack of signs of dysfunction of the prosthesis and potential changes in LV function and functional mitral regurgitation. In patients with prominent LV hypertrophy, LV outflow tract obstruction may occur after aortic valve replacement and should be detected by color imaging or Doppler and verified by simultaneous intraventricular pressure measurement. Myectomy associated with valve replacement may prevent or treat the LV outflow obstruction. Attempts at measuring prosthetic gradient using a transgastric approach are of uncertain reliability, and lack of patient-prosthesis mismatch cannot be ascertained by intraoperative Doppler echocardiography currently.

POSTOPERATIVE ASSESSMENT: Postoperative assessment focuses on prosthetic, LV, and aortic evaluation. Prosthetic function is not entirely predictable on the basis of patient and prosthesis size, and the postoperative Doppler echocardiogram is essential in detecting obstruction, particularly thrombosis,[191] and in following mismatch. Reoperation, considered in limited cases for mismatch,[187] is the mainstay of treatment for prosthetic thrombosis or panus formation, all manifested by prosthetic obstruction.[192] In the diagnosis of prosthetic obstruction, it is important to consider the role of pressure recovery, which may lead to (usually slight) gradient overestimation by Doppler. The 2-D examination rarely discriminates between causes of obstruction for which the context of occurrence is more specific. Degeneration of bioprostheses is rarely observed in elderly patients currently affected by AS but is part of the yearly prosthetic monitoring. LV function usually is maintained after valve replacement for AS. Changes are observed in two circumstances. First, patients with LV dysfunction owing to critical AS generally display improvement in ejection fraction and sometimes normalization after aortic valve repair.[179] Even small improvements have important beneficial impact on outcome, but persistence of LV dysfunction requires active medical therapy. Second, patients with associated coronary artery disease may display a postoperative decline in LV function owing to the coronary artery disease despite successful aortic valve surgery. Such patients also need active echocardiographic follow-up to ensure appropriate medical treatment.[193] Ascending aortic dilatation generally stabilizes postoperatively, but the rare possibility of continued enlargement and need for repair also requires regular echocardiographic follow-up. A particularly difficult group of patients for follow-up is those with postradiation heart disease,[194] in whom cardiac disease is only part of postradiation lesions that affect the lungs with frequent persistence of postoperative symptoms. The valve disease is only part of the cardiac disease, often involving coronary lesions, conduction abnormalities, pericardial constriction, and myocardial fibrosis. These complex lesions lead to an often complex follow-up.

AORTIC REGURGITATION

PREOPERATIVE ASSESSMENT: This focuses on the etiology and mechanism in that it determines the possibility of repair.[195]

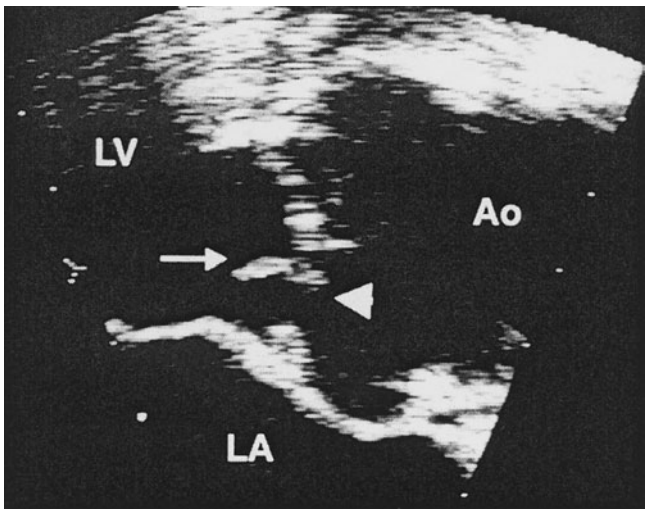

Figure 11-20. Imaging of the aortic valve in a patient with endocarditic aortic regurgitation (AR). The long arrow denotes a vegetation, whereas the arrowhead denotes a perforation of the noncoronary cusp. LA = left atrium; LV = left ventricle; Ao = aorta.

Most frequently, aortic regurgitation in Western countries is due to degenerative disease.[196,197] Minor calcifications may be noted but rarely with thickened myxomatous tissue. The aortic regurgitation is due to annular enlargement and sometimes to valve prolapse. Bicuspid aortic valve is the second cause of aortic regurgitation and leads to regurgitation by malcoaptation and sometimes prolapse of the largest cusp. Aortic root disease more often involves annuloaortic ectasia than Marfan syndrome or aortitis (such as syphilis). Rheumatic aortic regurgitation is recognized by retraction of the leaflet, leaving a central regurgitant orifice, and is rarely repairable. Endocarditis is recognized by echocardiography when vegetations are present and may require TEE (Fig. 11-20). Repair is predictable with detection of a perforation but is not possible with a calcified or retracted leaflet. Repair is also particularly feasible with a prolapsed leaflet, especially if the valve is bicuspid, or with dystrophic leaflets and moderate aortic regurgitation, where resuspension of commissures may be sufficient. Therefore, morphologic assessment should be focused on clearly defining the mechanism of aortic regurgitation.[198]

Aortic regurgitation results in both volume and pressure overload of the left ventricle, which adapts by both concentric and eccentric remodeling until a point of afterload mismatch when LV systolic function fails.[199] Assessment of LV size and systolic function by echocardiography is essential. The recommended approach is M-mode 2-D guided, but with increasing frequency, LV volumes are calculated particularly with use of contrast material injection.[200] Moderate LV dysfunction (defined as an ejection fraction of 50%) and severe LV dysfunction (ejection fraction of 35% or less) justify rescue surgery but result in decreased postoperative survival.[197] No lower limit of ejection fraction firmly contraindicates surgery. Even patients with ejection fractions of 35% or less may benefit from valve replacement. An ejection fraction of less than 55% is associated with reduced survival under medical treatment and should be strong indication for surgery before LV dysfunction affects postoperative survival. Marked LV enlargement is another indication for surgery and is uncovered by LV dimensions of 75 mm or more (end-diastolic) or 55 mm or more (end-systolic)[201] or, better, 25 mm/m^2 or more (end-systolic adjusted to body surface area)[196] because women with smaller body sizes almost never reach absolute LV sizes comparable with those of men.[202] These LV size differences lead to worse postoperative outcomes in women, emphasizing the importance of adjusting LV measures to body size.[202] Exercise changes in LV function may be helpful, but monitoring of complex variables such as wall stress limits applicability.[203]

Assessment of aortic regurgitation severity is key to the surgical indication and should be based on comprehensive integration of all signs.[16] Among qualitative approaches, color Doppler (Fig. 11-21) detects the presence of aortic regurgitation and provides simple measures of severity[204] (Fig 11-22). Vena contracta of 0.6 cm or more and a ratio of jet width to left ventricular outflow tract width of 65% or greater in parasternal long-axis view suggest severe aortic regurgitation (Fig. 11-23), but jet length does not correlate with aortic regurgitation severity.[205,206] Color Doppler has many limitations when assessing aortic regurgitation severity and is used as a gross estimation. Eccentric jet direction leads to underestimation of aortic regurgitation, and jets arising from the entire coaptation line of bicuspid valves may be overestimated. Holodiastolic flow reversal in the abdominal or descending thoracic aorta is consistent with severe aortic regurgitation[207] (Fig. 11-24). Maximum aortic regurgitation velocity (measured by continuous-wave Doppler) deceleration suggest severe aortic regurgitation with fast

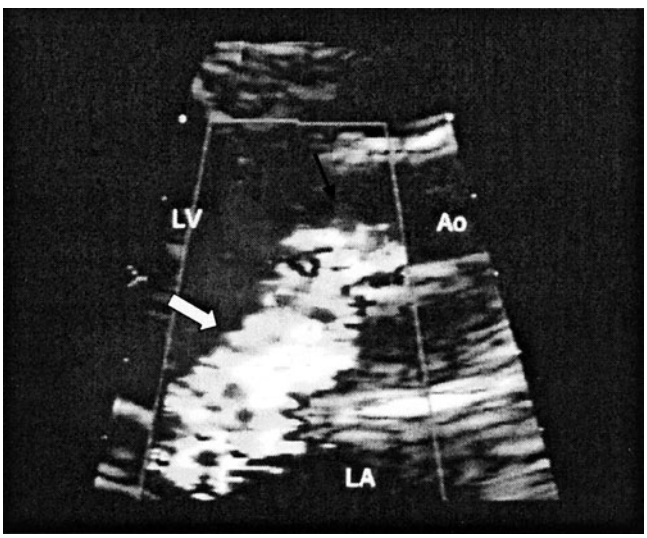

Figure 11-21. Parasternal view of aortic regurgitation (AR) using color-flow imaging. The flow convergence (*thin arrow*) and jet (*thick arrow*) are well seen. Note the limited expansion of the jet owing to its eccentricity.

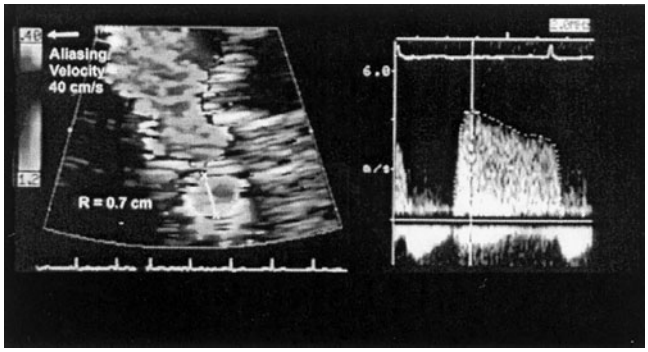

Figure 11-22. Quantitation of aortic regurgitation (AR) using the proximal isovelocity surface area (PISA) method. Note that the color baseline is shifted upward. (*Left*) Analysis of the flow convergence allows measurement of the regurgitant flow. (*Right*) AR velocity is measured using continuous-wave Doppler to calculate the regurgitant volume (RVol) as flow multiplied by the ratio of regurgitant time velocity integral (RTVI) to regurgitant velocity (RVel).

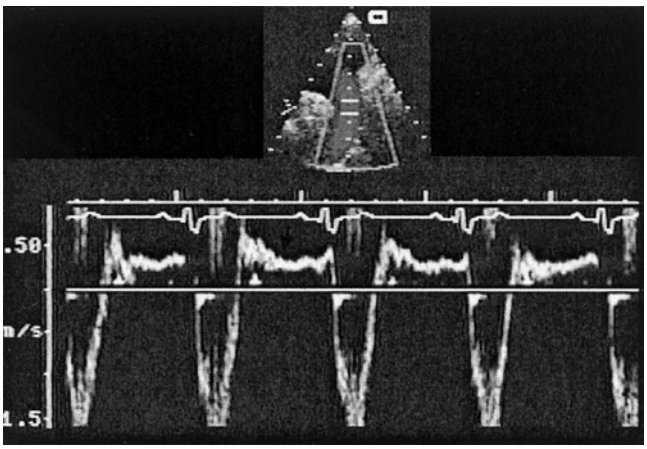

Figure 11-24. Recording of pulsed-wave Doppler in the high descending aorta in a patient with severe aortic regurgitation. Note during diastole the holodiastolic reversal of flow with high velocity (*arrow*).

pressure half-time (<200 ms) (Fig. 11-25). However, aortic regurgitation velocity deceleration is also influenced by LV compliance and reflects elevated LV end-diastolic pressure. Quantitative aortic regurgitation assessment is essential for patients with moderate or severe aortic regurgitation.[16] Regurgitant volume and ERO can be calculated by PISA,[208] quantitative Doppler (mitral and aortic stroke volumes), or the LV volumetric method.[79] While a regurgitant volume of 60 mL/beat, similarly to mitral regurgitation, is consistent with severe regurgitation, a smaller ERO ($\geq$30 mm^2) than in mitral regurgitation is consistent with severe aortic regurgitation[209] because the longer diastolic than systolic time allows larger volume overload for a smaller orifice size.[16]

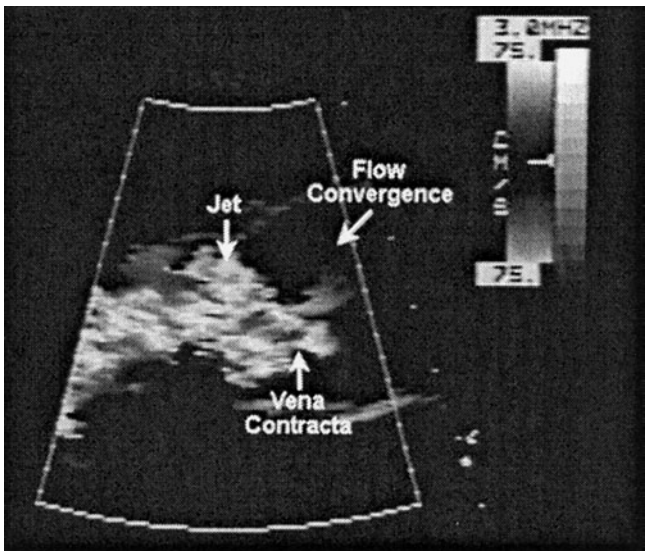

Figure 11-23. Parasternal view of aortic regurgitant flow used to delineate and measure the vena contracta (narrow neck) of the aortic regurgitation.

Quantitative methods are not as consistently applicable in aortic regurgitation than in mitral regurgitation but have relatively few limitations and should be used in clinical practice, similarly to in aortic regurgitation.[208]

INTRAOPERATIVE ASSESSMENT: Before bypass, IO TEE verifies the aortic valve lesions and the extent of aortic aneurysmal dilatation. Aortic valve repair is a safe alternative to valve replacement in selected patients with aortic regurgitation and requires detailed assessment of the mechanism of aortic

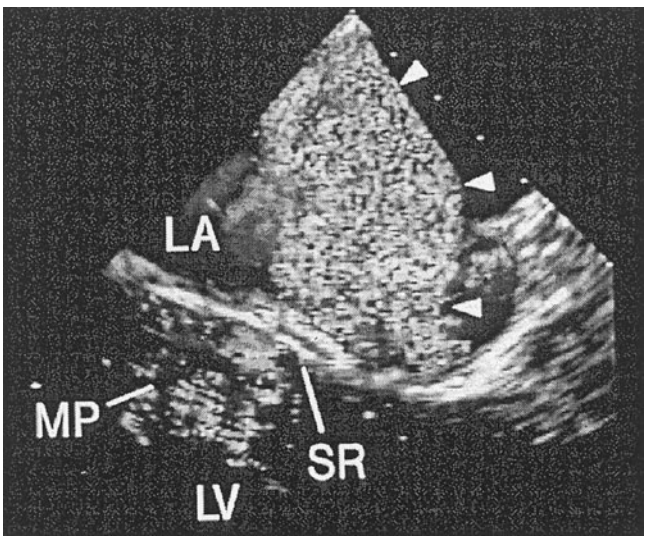

Figure 11-25. Continuous-wave Doppler recording in a patient with endocarditic aortic regurgitation (AR). The rapid deceleration of AR velocity in diastole is quite different from that noted in Fig. 11-22 and is consistent with acute and severe AR revealing a low end-diastolic gradient between the low aortic diastolic pressure and the high left ventricular end-diastolic pressure. The pressure half-time of 154 ms is shorter than the 200-ms threshold for severe AR.

regurgitation.[195,210] Assessment of the mechanism of aortic regurgitation by IO TEE is accurate and reliable compared with surgical findings.[198] Rarely, IO TEE notes aortic dissection or wall hematoma not previously diagnosed, and IO TEE can assist in identifying patients likely to benefit from aortic valve repair.[211] Quantitation of aortic regurgitation is challenging by TEE, and although deep transgastric views may show the flow convergence of aortic regurgitation,[209] imaging usually is poor using this view. A broad jet width on color-flow imaging in central aortic regurgitation is suggestive of severe regurgitation, but a simple, more reliable method by TEE is measurement of the vena contracta width,[206] a surrogate measure of the ERO.[212] Vena contracta assessment by TEE is feasible and has been validated for aortic regurgitation.[206]

After bypass, IO TEE verifies the functional result, anatomically, and for residual aortic regurgitation. This early assessment is important because aortic valve repair is a technique in progress, and results that appear mediocre should lead to consideration of a second pump run. After valve replacement for aortic regurgitation, mismatch is unusual because the annulus is in general dilated with aortic regurgitation and often allows insertion of a sufficiently sized prosthesis. Residual periprosthetic regurgitation is a notable problem in patients with endocarditis, particularly recent, and should be actively evaluated with appropriate loading conditions.

POST-OPERATIVE ASSESSMENT: This focuses on prosthetic or repair function. In patients with allograft replacement of the aortic valve and homograft replacement of the pulmonary valve, calcification of the pulmonary homograft may develop and requires a systematic examination of the pulmonary outflow tract. Failure of valve repair most often involves recurrent prolapse, and timely diagnosis requires regular echocardiographic follow-up.[195,210] Patients with aortic regurgitation are younger than those with AS, and bioprosthetic or homograft aortic valve replacement is associated with notable rates of primary failure depending on age. In patients with dystrophic aortic valves, late aortic dissection may develop and requires careful examination of the aorta, and progressive aortic dilatation should lead to consideration of TEE or computed tomography. LV function is of particular concern if patients were operated with an ejection of less than 50%.[197] In general, given the high preoperative wall stress, aortic valve replacement is associated with improvement in LV function, but the effect is usually modest, and the need for vasoactive treatment aimed at improving LV function and clinical outcome should be assessed postoperatively.

MIXED AORTIC VALVE DISEASE: Mixed aortic valve disease is often rheumatic or associated with aortic valve calcifications, precluding valve repair.[213] The essential step in preoperative evaluation is severity assessment of the valve disease. A composite of moderate AS (with valve area $> 1.0\ cm^2$) and moderate aortic regurgitation (with regurgitant volume $< 60\ mL$) may represent severe valve disease and is diagnosed by a higher mean gradient than the AS severity would justify. IO TEE and postoperative monitoring are similar to those of AS and aortic regurgitation.

TRICUSPID VALVE DISEASES: These are dominated by functional tricuspid regurgitation, but salient issues are the numerous etiologies that may result in notable tricuspid disease and the frequency with which these lesions may be ignored.

TRICUSPID VALVE STENOSIS: This is mostly rheumatic, associated with mitral stenosis and rarely pure. It is difficult to diagnose because there are no absolute morphologic criteria. The essential diagnostic step is to perform a continuous-wave Doppler examination of the tricuspid valve when the morphology is unusual. Mean gradients of 5 mm Hg or more are significant for the tricuspid valve, and the degree of inferior vena cava dilatation reflects the hemodynamic consequences of the stenosis. IO TEE also can examine obstruction of the tricuspid valve if the preoperative hemodynamic assessment was insufficient. Tricuspid valve replacement usually is required, and postoperative echocardiography focuses of the appropriate function of the prosthesis. Other causes of organic tricuspid valve disease such as carcinoid heart disease produce in general mixed tricuspid valve disease with dominant regurgitation.

TRICUSPID VALVE REGURGITATION

PREOPERATIVE ASSESSMENT: Tricuspid regurgitation (TR) is called functional when the valve is structurally normal and regurgitation ensues from incomplete coaptation. Functional TR is the usual consequence of right ventricular dilatation owing to pulmonary hypertension of left-sided heart disease or pulmonary disease but also can be due to primary right ventricular dysfunction or primary atrial and annular dilatation seen in chronic atrial fibrillation. Organic causes of TR include myxomatous valve degeneration with or without ruptured chordae.[214] TR owing to excessive valve movement also can be caused by endocarditis with destructive lesions, blunt chest trauma with chordal or papillary muscle rupture, and iatrogenic trauma after myocardial biopsy. Echocardiography establishes the mechanism more definitely than the etiology of these types of TR and thus is essential in planning valve repair, which is often highly successful.[214] Organic TR with restricted valve motion includes serotoninergic lesions such as carcinoid heart disease, diet-drug valve diseases, ergot valve disease, postradiation valve disease rarely, or more frequently, leaflet impingement (or perforation) by pacemaker or defibrillator leads.[215] The degree of valve thickening or rigidity is an essential guide to predicting repair versus replacement. Congenital causes such as Ebstein anomaly are uncommonly diagnosed in adulthood but may cause severe TR and may be missed easily by a cursory echocardiogram.

There is growing appreciation of tricuspid valve regurgitation as an independent predictor of long-term outcome irrespective of the original cause of this heterogeneous valve disease.[214,216,217] The important consequence of this recognition is that surgery for isolated TR is more common, that in

left-sided valve disease the coexistence of TR should not be ignored because simultaneous correction often is required, and that high-quality echocardiographic assessment of TR severity is warranted because the clinical signs of TR are often ignored. Assessment of TR severity uses mainly (1) the size of the jet in the right atrium (larger is more severe) but with the usual limitation of jets (underestimated with eccentricity and overestimated with high ventricular pressure), (2) vena contracta width of 7 mm or more as a sign of severe TR[218] (useful but limited by lateral resolution issues), (3) the presence of systolic flow reversal in hepatic veins (specific for severe TR but not sensitive), and (4) quantitation of TR by the PISA method.[219,220] For TR quantitation, since the right- versus the left-sided circulatory system is a lower-pressure system, thresholds for severe TR compared with MR are similar for ERO ($\geq$0.40 cm^2) but lower for regurgitant volume ($\geq$45 mL/beat).[220] Severe TR can lead to right-sided volume overload with right ventricular and right atrial enlargement and right ventricular systolic dysfunction.[214] There are no quantitative criteria to assess these changes yet, but qualitative assessment provides useful information. With right ventricular volume overload, the septum may display paradoxical motion and affect LV function and ultimately exercise capacity. With advanced cases, inferior vena cava and hepatic vein dilatation reflects elevated right atrial pressure.

INTRAOPERATIVE ASSESSMENT: TR is often overlooked at left-sided valve surgery,[221] so it is essential that TR assessment be performed without sedation in the outpatient setting.[222] IO TEE before initiation of bypass requires restoration of preload conditions to assess TR. Quantitative assessment of TR by TEE has limitations and cannot replace preoperative assessment. Annular enlargement is important to assess because it is associated with recurrence of TR[221,223] or even development of severe TR in patients with no or mild TR preoperatively.[223] Annulus diameter of more than 70 mm has been considered as markedly enlarged,[223] but there is no consensus on specific annular diameters (absolute or adjusted for body size) that should indicate tricuspid repair.[221] After bypass, it is importance to assess residual TR, although its absence is not invariably synonymous with operative success. Persistent right ventricular enlargement and dysfunction tend to improve later. IO TEE in patients in whom tricuspid surgery is considered results in alteration of the surgical plan in approximately 10% of patients.[224] Rarely is surgery converted to tricuspid replacement because it is considered a predictor of worse survival.

POSTOPERATIVE ASSESSMENT: This focuses mostly on recurrent TR, which, unfortunately, is not uncommon.[221] TR recurrence depends on the surgical techniques used, such as lack of ring annuloplasty[224,225] on lesions (leaflet tethering or thickening),[226] on severe TR at baseline,[225–227] on IO residual TR,[227] and on persistence of pulmonary hypertension of left-sided disease. Right ventricular enlargement and dysfunction improve but often incompletely, particularly if pressure or volume overload persists.

PULMONARY VALVE DISEASES: These are mostly congenital but also can be acquired owing to carcinoid heart disease (now exceptionally rheumatic heart disease) and endocarditis.

PREOPERATIVE ASSESSMENT: This requires proactive examination of the pulmonary valve because the usual examination tends to record few views of the valve, and TEE may be particularly helpful. Knowledge of a disease likely to affect the pulmonary valve is essential in focusing attention to this valve.[228] The valve morphology is difficult to analyze and requires unusual views, elongating the subvalvular, valvular, and supravalvular regions. Thickening can be observed and, more rarely, prolapse, retraction, or vegetation. Morphologically, the pulmonary annulus can be constricted in carcinoid disease in association to intrinsic valve thickening.[229,230] Dilatation of pulmonary artery is important to assess and may require TEE. Hemodynamic assessment is somewhat simpler. Continuous-wave Doppler assesses pulmonary stenosis appropriately. Mild pulmonary regurgitation is frequent in normal individuals. Severe pulmonary regurgitation is rare, detected by color-flow Doppler, but ascertaining severe regurgitation is difficult because the jet may be of limited extent and duration owing to equalization of pulmonary and right ventricular pressures. In such cases, rapid deceleration of the regurgitant jet is suggestive of severe regurgitation.

IO ASSESSMENT: Since pulmonary stenosis is usually treated by balloon valvuloplasty, operative treatment is reserved for regurgitant or mixed lesions. Measurement of the pulmonary annulus and assessment of sub- or supravalvular stenosis are important to operative management. Postoperative assessment of pulmonary regurgitation intends to avoid more than moderate residual regurgitation but is more difficult than outpatient evaluation because restoration of the normal hemodynamic condition is inconsistent. Careful examination of color-flow and continuous-wave Doppler is important in this regard.

POSTOPERATIVE ASSESSMENT: This focuses on assessing function of the native repaired or prosthetic pulmonary valve. Degeneration, stenosis, and regurgitation may develop over time and should be diagnosed early with a combination of color-flow and continuous-wave Doppler. Right ventricular dilatation and dysfunction may persist after surgery or recur with dysfunction of the treated pulmonary valve.[231]

Bacterial endocarditis

Bacterial endocarditis has remained of unchanged incidence despite the decline in rheumatic valve disease and, despite effective antibiotics, continues to carry considerable mortality and morbidity. Since the risk associated with endocarditis drops precipitously with therapy, prompt diagnosis and treatment are essential to improve diagnosis.

PREOPERATIVE ASSESSMENT: This is centered on diagnosis and assessment of complications. Echocardiography aids in the rapid diagnosis of endocarditis and provides one of two

major Duke diagnostic criteria by demonstrating the presence of typical vegetations.[232] Less typical but suspicious lesions represent a minor diagnostic criterion. Vegetations vary in size or shape and are mobile masses attached to endocardium or are implanted material and frequently showing high-frequency oscillations.[233] Vegetations are made of fibrin and are of low density when recent, but there are no definitive criteria to differentiate them from thrombi, particularly on foreign material, or from Lambl's excrescences when small.[234–236] Therefore, diagnosis of vegetation implies contextual interpretation. TEE is superior to TTE in detecting vegetations (sensitivity 95% versus 65 to 80%, respectively), especially in prosthetic valve endocarditis, where TTE may miss vegetations because of shadowing.[237,238] Right-sided vegetations are usually bigger than those on the left, and TEE does not improve diagnostic accuracy.[239]

Apart from diagnosis, TTE and TEE evaluate the presence and severity of endocarditic lesions. Endocarditis is destructive to valves and cardiac tissue and may lead to abscess formation. Valve lesions are perforations or rupture of supportive structures. Perforations are voids, often difficult to visualize directly by TTE or TEE, but observation by the color of the regurgitating flow with flow convergence in the center of a valve leaflet is strongly supportive of a perforation.[105] Ruptures of chordae have nonspecific features unless a vegetation is attached to their tip. Aortic valve prolapse may result from destruction of the central coaptation zone or of the supporting commissural area. Abscesses may involve any region of the myocardium but often involve the fibrosa between the mitral and aortic annuli. Expansion of annular abscesses may lead to conduction abnormalities and to cavity (aneurysm) formation when the abscess ruptures in a cardiac cavity, most often the LV, with sometimes secondary rupture and fistula formation. These complex lesions are better identified by TEE than by TTE. Of note, abscess cavities are seen rarely around the mitral and tricuspid annuli, and abscesses are more prone to be present in patients with prosthetic valve endocarditis. Nevertheless, in all cases of endocarditis, comprehensive assessment of all possible abscesses and fistulous tracts is indispensable. Assessment of the severity of valve lesions is particularly difficult because regurgitations owing to the destructive valve lesions form and progress acutely as sudden tissue loss. Thus clinical signs of regurgitation, particularly murmur intensity, and, similarly, color-flow jets may not be impressive owing to rapid equalization of pressure (e.g., in acute endocarditic aortic regurgitation, LV diastolic pressure is markedly elevated and early in diastole equalizes the aortic pressure so that the murmur and jet are brief and of low energy). This acuteness makes quantitation of regurgitation, particularly measures of effective regurgitant orifice, essential in assessing regurgitation severity.[16] Also, heart failure owing to valve regurgitation may progress rapidly, particularly in patients with acute endocarditic aortic regurgitation, and surgery may be indicated urgently. In patients with mitral or tricuspid regurgitation, heart failure may be controllable with medical treatment, and this may offer some opportunity for sufficient antibiotic therapy.[241,242] Nevertheless, even in clinically stable patients with endocarditis, monitoring of lesions and valvular regurgitation severity by regular echocardiography is essential. Vegetations can be complicated rarely by accumulation and valvular obstruction and more frequently by embolism. Characteristics of vegetations, size (>10 mm), and marked mobility are predictors of the risk of embolism,[243] which led to controversy regarding intervention for ablation of vegetations. While this controversy is unresolved, the precipitous decline in vegetation size with antibiotic treatment and the risk of embolism associated with surgery should be taken into account in this discussion.[235,243] Over time, endocarditic lesions become chronic, and vegetations heal, leaving fibrotic lesions that offer more solid suturing possibilities.

INTRAOPERATIVE ASSESSMENT: This confirms the lesions, assesses the possibility of silent progression and unexpected abscess cavity or fistulous tract, and reassess regurgitations that may have appeared moderate on preoperative assessment. Of particular importance is careful examination of moderate lesions that may require interventional treatment simultaneously with that of severe lesions.

After bypass, it is essential to examine the surgical correction of complex abscesses and fistulous tracts. Also, since recently infected valvular and annular tissue may not offer a solid basis for suturing, examination of all reparative procedures and of the seating of prosthetic valves is particularly important.

POSTOPERATIVE ASSESSMENT: This usually demonstrates that acute LV dysfunction is reversible. With appropriate antibiotic treatment, recurrence of endocarditis is rare, and development of echocardiographic signs may be delayed in contrast to fever and positive blood cultures. A possible complication is the occurrence of aseptic perivalvular regurgitation developing with some delay after the intervention. Low intensity of murmurs may contrast with symptoms, and early detection by systematic TTE and, if necessary, TEE is paramount to appropriate care. Repeated prosthetic dehiscence owing to tissue friability is not uncommon and makes such situations difficult to manage.

Prosthetic valves

Prosthetic valves require specific approaches, and comparison with early postoperative assessment is essential to detect dysfunction.

ECHOCARDIOGRAPHY OF PROSTHETIC VALVES: Although valve repair generally is preferred, valve replacement remains the leading way to correct severe valvular disease. Echocardiography currently is the best approach to evaluate prosthetic valves, but it has limitations that must be recognized for appropriate interpretation. All prostheses are responsible for acoustic shadowing behind them, so examination of all aspects of a prosthesis often requires both TTE and TEE. Morphologically, mechanical prostheses also have specific characteristics that influence their imaging.[189] For example,

in a ball-cage prosthesis, the ball transmits ultrasound slower than blood, so its distal limit appears beyond the prosthetic seating. In bileaflet prostheses, leaflets may be placed in an angle to the thoracic wall, preventing their visualization. Struts of bioprostheses may prevent imaging of leaflets. With Doppler, the presence of a restrictive orifice may create pressure recovery, so gradients may be somewhat overestimated, particularly with small aortas. In prostheses that have no clinical signs of dysfunction, it is important to obtain early and serial hemodynamic assessments that serve as reference points if the clinical issue of dysfunction arises. Each prosthesis is characterized by its gradient, effective orifice area, and physiologic regurgitation. The gradient is measured by continuous-wave Doppler, from apical views for mitral and tricuspid prostheses and from multiple views for aortic prostheses. Mean and peak gradients are measured using the same $4V^2$ formula used in native valves. Each type and size of prosthesis has a range of expected gradients that should be used as a guide to assessment of normal function. Effective orifice area (EOA) is measurable for aortic prostheses, similar to the valve area of AS, as the ratio of stroke volume (LV outflow tract) to time-velocity integral of prosthetic jet velocity. For mitral and tricuspid prostheses, measuring orifice area relies on aortic stroke volume, which is not adequate if aortic regurgitation or prosthetic regurgitation is present. Lack of mitral or tricuspid prosthetic stenosis beyond the normal range is defined by a rapidly declining velocity (and gradient) in early diastole. Physiologic regurgitation of prostheses is common and constant in appearance in mechanical prostheses but rare in bioprostheses. Readily visible for aortic prostheses, it is more difficult to detect with TTE for mitral or tricuspid prostheses owing to prosthetic shadowing and may be observable only by color with TEE. However, physiologic regurgitation is detectable by continuous-wave Doppler and is usually brief, faint, and central. In normally functioning prostheses clinically and as visualized by TTE, TEE is not necessary unless other lesions (e.g., aortic dilatation or aneurysm) are suspected.

MECHANICAL PROSTHESIS DYSFUNCTION: There is no primary failure of mechanical prostheses components because ball variance of Starr-Edwards prostheses and strut ruptures of Bjork-Shiley prostheses have been eliminated. The mechanism of failure of mechanical prostheses is either by tissue interposition rarely[244] or more frequently by obstruction owing to thrombosis or its chronic equivalent, panus formation, or by periprosthetic regurgitation.[245] Tissue interposition usually is detected early and is characterized mostly by regurgitation owing to lack of closure of the mobile element, but it can have a component of stenosis.[113] Incomplete movement of the mobile element can be detected by TTE, TEE, and fluoroscopy with angle-of-movement measurement. Hemodynamic dysfunction is detected by Doppler. Increased flow velocities beyond the normal range (and beyond previous measurements) suggest increased pressure gradients and prosthetic obstruction. However, with increased flow (e.g., from pregnancy, anemia, hyperthyroidism, and sepsis), gradients may increase, so stenosis should be characterized, if possible, by measuring effective orifice area using continuity equations.[246] A ratio of valvular to subvalvular velocity of 3 or more suggests aortic prosthesis stenosis, whereas a slow decline in diastolic velocity suggest stenosis of mitral or tricuspid prostheses.[247] A stenotic prosthesis should lead the clinician to rule out patient-prosthesis mismatch by comparison of prosthesis size and previous measurements.[188] Sudden obstruction suggests acute thrombosis,[191] whereas progressive obstruction suggests panus formation. However, the mechanism of obstruction is rarely defined directly by echocardiography, although a thrombus may be seen by TEE in acute thrombosis.[248] Thrombus size affects the potential efficacy of thrombolysis.[249,250] If thrombolysis is elected as treatment because the prosthesis is in a tricuspid location or because reoperation presents a high risk, monitoring of the prolonged thrombolysis administration requires daily echocardiography with subsequent frequent measurements because recurrence is common, affecting around half the successfully treated patients.[251] Panus obstruction is organized and not affected by thrombolysis.[192] Postoperatively, recurrence of prosthetic thrombosis should be monitored by Doppler. Periprosthetic regurgitation is, if large enough, usually associated with hemolysis and heart failure or progression of symptoms but inconsistently with a murmur. TTE easily detects the regurgitant jet on aortic prostheses, and determination of jet origin requires complete prosthesis scanning to observe periannular flow (Fig. 11-26). For mitral and tricuspid prostheses, shadowing often prevents TTE from recording the color jet, but detection of periprosthetic regurgitation is possible by continuous-wave Doppler, leading to TEE for assessing the severity of regurgitation.

BIOLOGIC PROSTHESIS DYSFUNCTION: Although thrombus (exceedingly rare) and periprosthetic regurgitation (rare) may occur on bioprostheses, primary tissue failure is the most frequent failure mode.[252] The specific mechanism can be early, owing to tears often close to struts, or late, owing to

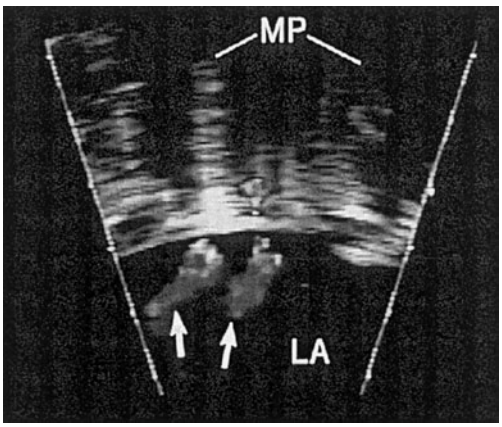

Figure 11-26. Transesophageal imaging of a severe periprosthetic regurgitation (*arrowheads*) around the sewing ring (SR) of a mitral prosthesis (MP). LA = left atrium; LV = left ventricle.

calcification or rupture of cusps. The diagnosis of valve stenosis owing to calcification is based on standard Doppler criteria of excessive gradient, decreased effective orifice area, persistence of end-diastolic high velocity in mitral and tricuspid prostheses, and direct visualization of calcifications by TTE or TEE, if necessary. The diagnosis of tissue failure with regurgitation is suspected by murmur and confirmed by color imaging, but severity often is difficult to confirm because of eccentric jets (even by TEE). In this circumstance, observations of a severe lesion such as a torn cusp and of a large flow convergence proximal to the intraprosthetic regurgitant orifice are important clues to severe regurgitation. With primary tissue failure, it is important to exclude prosthetic endocarditis by blood cultures and by searching for vegetations by TEE.

Coronary Artery Diseases

Coronary artery disease is the most frequent indication for cardiac surgery. Echocardiography does not allow direct observation of coronary artery lesions unless intravascular ultrasound is used for proximal coronary artery segments but reveals the consequences of coronary artery disease. Echocardiography is pivotal to lay the suspicion of coronary artery disease on the basis of stress-induced ischemia, to assess myocardial viability, and to diagnose myocardial infarction and its complications requiring surgical intervention.[22]

Diagnosis of coronary artery diseases

Echocardiography allows visualization of multiple tomographic planes to assess regional wall motion.[22] The American Society of Echocardiography recommends 16-segment analysis of the left ventricle for regional wall motion evaluation.[253] A wall thickness increase in systole of 40% or more characterizes normal LV contractility, whereas less than 30% characterizes reduced contractility (hypokinetic) and less than 10% indicates absent contractility (akinetic). Myocardial segment outward motion during systole (dyskinesis) usually is associated with thinning, whereas an aneurysm is a permanent outwardly bulging wall with or without dyskinesis. LV segments are scored from 1 to 5, with 1 being normal, 2 being hypokinetic, 3 being akinetic, 4 being dyskinetic, and 5 being aneurysmal, and the wall motion score index is the sum of scores divided by the number of segments visualized.[22] A wall motion score index of 1 is normal, and 2 or greater is associated with poor outcome following myocardial infarction. Resting scar (i.e., wall akinetic, dyskinetic, or aneurysmal and dense with thinning) is a resting abnormality diagnostic of myocardial infarction and coronary artery disease (wall motion abnormalities without scar are seen in cardiomyopathies). Stress echocardiography can identify coronary artery disease by inducing new regional wall motion abnormalities.[23] There are many stress modalities, including exercise treadmill or bicycle; pharmacologic with dobutamine, adenosine, or dipyridamole; and rarely TEE atrial pacing.[25] Pharmacologic or pacing stress testing is reserved for patients who are unable to exercise enough to reach maximum effort.[254] With stress, normal LV response is hyperdynamic with increased ejection fraction and decreased LV end-systolic dimension. Resting regional wall motion abnormalities unchanged with stress are consistent with coronary artery disease (previous myocardial infarction) but without ischemia. Increased LV end-systolic dimension or decreased ejection fraction with stress suggest severe coronary artery disease. The diagnostic value of stress echocardiography for coronary artery disease is imperfect, with acceptable sensitivity but mediocre specificity, not notably different from other stress modalities.[255] Once angiography referral bias is accounted for, the sensitivity of stress testing is less impressive.[256] The indications of stress echocardiography for diagnosing coronary artery disease should be weighed according to the pretest probability of disease and are most contributive in the intermediate probability range. The prognostic value of stress echocardiography is considerable in patients presenting with chest pain, justifying its widespread use.[24,257,258]

In evaluating chest pain, echocardiography may reveal resting regional wall motion abnormalities consistent with acute coronary syndrome, but if the findings are normal, this is usually associated with a good prognosis.[259] Stress echocardiography is safe in patients with no sign of myocardial infarction or ischemia and a normal baseline echocardiogram. In overt acute coronary syndromes, a wall motion score index 1.7 or greater suggests a large area at risk.[260]

Postoperatively, stress echocardiography is most useful when chest pain is moderate or atypical to weigh the indication for repeat coronary angiogram. The localizing value of regional wall motion abnormalities for a specific coronary artery bed is mediocre and cannot imply that a specific graft may be dysfunctioning.

Myocardial viability

Myocardial contraction declines when 20% or more of the myocardial wall is ischemic or infracted.[261] Thus, resting hypokinesis or akinesis does not rule out viability (myocardial hibernation) and may improve with revascularization. Dobutamine stress echocardiography is the preferred stress method to assess viability in patients with LV dysfunction (with or without regional wall motion abnormalities).[262] With increasing infusion rates of dobutamine, initially improved contractility of an akinetic segment at low dose suggests viability, and worsening with higher doses (biphasic response) suggests ischemia.[263] This biphasic pattern is typical of viable myocardium that will improve with revascularization.[264] Sustained improvement with increasing dobutamine (monophasic response) often predicts functional recovery after revascularization. Scarred or unresponsive myocardium tends not to improve with revascularization.[265] Strain-rate imaging with low-dose dobutamine may increase the ability to detect viability.[266]

Complications of coronary artery diseases

Heart failure with cardiogenic shock complicating acute myocardial infarction is the leading cause of hospital death

in patients hospitalized for myocardial infarction and may result from various causes that demand specific interventions.[267] Echocardiography can identify the mechanism of circulatory failure and in patients with LV dysfunction identify those at higher risk based on markedly reduced LV ejection fraction and moderate to greater mitral regurgitation.[268]

FREE WALL RUPTURE: This is an important cause of death.[269] There are no predictive echocardiographic features that define a high risk of rupture, but echocardiography provides early and rapid diagnosis in patients with this fatal complication. In patients who are hemodynamically unstable, free wall rupture should be suspected with pericardial effusion, particularly gelatinous-appearing pericardial clot, and with thin-walled myocardium.[270] An incomplete free wall rupture results in a "subepicardial aneurysm" contained by the epicardial layer.[271] The pericardial effusion, even if compressive and with signs of tamponade, should not be tapped for evacuation because this may precipitate catastrophic rupture, but a minimal echocardiography-guided tap to confirm the presence of blood may help in surgical decision making. Rarely, color-flow Doppler detects flow in the pericardial cavity, but the absence of such flow does not rule out rupture. Intramyocardial hematoma is consistent with impending rupture. A pseudoaneurysm is a contained rupture bordered by organized clot and is diagnosed on the basis of a narrow neck with to-and-fro flow and carries a considerable risk of delayed rupture. Detection of early free wall rupture allows surgical repair. Postoperatively, since the infarct often is limited in size, excellent long-term result can be obtained.

VENTRICULAR SEPTAL RUPTURE: Ventricular septal rupture complicating myocardial infarction occurs in the first weeks after infarction. Echocardiography shows the ventricular septal defect, but it is important to use multiple views to identify it because those associated with inferior infarction may be elusive. The defect borders are ragged, different from those of a congenital defect, and fall of myocardial eschars tends to increase the defect size progressively.[272] Color-flow Doppler is critical to diagnosis by demonstrating directly a left-to-right shunt at the ventricular level, and TEE is rarely needed. Surgery is preferable before hemodynamic compromise is intractable, but a shunt may recur postoperatively owing to progressive septal necrosis, which should be monitored. Closure with an endovascular device is possible but entails the possibility of recurrent shunt after the procedure.

PAPILLARY MUSCLE RUPTURE: Mitral regurgitation associated with acute myocardial infarction may be functional or organic owing to papillary muscle rupture, but both frequently are silent, so mitral regurgitation revealed by echocardiography ofter is indicated by hemodynamic compromise or pulmonary edema. Papillary muscle rupture may be incomplete (i.e., one head partially separated but remaining attached to papillary muscle) or complete (i.e., head detachment from the papillary muscle resulting in a flail leaflet). The morphologic abnormality is diagnosed by TTE, but TEE may be necessary.[273] Color-flow imaging detects mitral regurgitation but may underestimate it because of rapid and severe increase in LA pressure. Confirmation by echocardiography of papillary muscle rupture leads to prompt surgical correction. Repair often is feasible with IO TEE monitoring, and rarely, mitral regurgitation recurs postoperatively.[274]

RIGHT VENTRICULAR MYOCARDIAL INFARCTION: Right ventricular myocardial infarction typically is associated with an inferior infarct but rarely is isolated.[275] Patients present with elevated jugular venous pressure contrasting with clear lungs or may present with hypotension or shock. TTE provides rapid diagnosis, showing an enlarged and hypokinetic right ventricle, commonly associated with LV inferior wall motion abnormalities. Color-flow Doppler reveals tricuspid regurgitation with normal pulmonary pressure and low peak velocity. High right atrial pressure may lead to right-to-left shunting via a patent foramen ovale, manifested clinically as hypoxemia and diagnosed by agitated saline contrast material injection showing the shunt as contrast material passing from the right to the left atrium. TEE is useful for diagnosing shunt and supporting closure of a patent foramen ovale percutaneously, which results in marked clinical improvement. Right ventricular function almost universally improves over time, but residual tricuspid regurgitation may be observed and may require surgical correction.[276]

Pericardial, Endocardial, and Myocardial Diseases

Pericardial effusion was the first clinical application of echocardiography and remains, with other pericardial diseases, one of the most important indications for the test.

Pericardial effusion

Pericardial effusion is diagnosed as an echo-free space around the heart. This fluid collection follows the anatomic landmarks of the pericardium, covering both ventricles and most of the right atrium, whereas a small portion of the LA wall is surrounded by pericardium.[277] Pericardial effusion should be differentiated from left pleural effusion, an echo-free space that extends posterior to the descending aorta, and from increased pericardial fat content, of typical granular appearance, that does not deserve medical attention. Pericardial effusion is more often compressive if large (with a swinging heart within the effusion), but tamponade may occur in small acute effusions. Diagnosis of tamponade relies on inferior vena cava dilatation, invagination of right atrial wall in diastole, expiratory collapse of the right ventricle, and marked Doppler and respirometer variability (of opposite timing) of mitral and tricuspid inflows.[277,278] While classically large effusions required surgical drainage, an echocardiography-directed pericardial tap with prolonged catheter drainage is now the mainstay of treatment and is particularly useful in postoperative effusions. Approaches most are often para-apical and rarely subcostal. Effusions of aortic dissection or myocardial infarction should not be drained

percutaneously because full rupture may ensue. The other indications for surgical drainage are purulent effusions, pericardial thrombi, and loculated effusions that cannot be reached safely.[279] Postoperatively, echocardiography monitors the recurrence of effusions and the possible occurrence of constriction.[280]

Pericardial constriction

Pericardial constriction can occur while fluid remains in the pericardium but is mostly due to thickened, rigid pericardium.[281] The classic tuberculous pericarditis is now rare, and most constrictive pericardites are idiopathic, postoperative, and rarely, due to hemopericardium, purulent pericarditis, radiation, or inflammatory disease of the pericardium.[282] Diagnosis should be suspected when heart failure with dilatation of the inferior vena cava is associated with normal LV function. Doppler signs that are specific for pericardial constriction are increased pericardial thickness (difficult to measure),[283] ventricular interaction indicating fixed intrapericardial space diagnosed by leftward septal shift, decreased mitral inflow and pulmonary venous flow and increased tricuspid inflow during inspiration, atrial interaction with diastolic hepatic venous flow reversal with expiration,[284] and isolation from thoracic pressure changes with stable superior vena caval flow with respiration.[285] Pericardial constriction should be differentiated from restrictive cardiomyopathy, which is not associated with ventricular interaction and is associated with reduced myocardial velocity by tissue Doppler, whereas it is normal in pericardial constriction. Pericardial constriction and chronic obstructive pulmonary disease share the respiratory variation of flow, but subtle differences allow diagnosis.[285] Thus Doppler is the mainstay of the preoperative diagnosis of constriction. IO TEE shows the thickened pericardium and monitors the sudden hemodynamic changes after pericardectomy. Postoperatively, echocardiography monitors the persistence of constrictive signs that may be due to a severe epicarditis or insufficient pericardectomy.

Endomyocardial fibrosis

Endomyocardial fibrosis starts as an endomyocarditis with thrombosis that becomes organized and fibrotic, resulting in elevated filling pressures. Imaging shows early the apical obliterative thrombosis that invades the region below the posterior mitral leaflet and encases it. Eosinophilia is observed generally. The fibrosis also can be observed later and results in mitral and tricuspid regurgitation. IO TEE allows monitoring of potential aggravation of valve regurgitations during endomyocardectomy. Postoperatively, persistence of signs of elevated pressures is common.

Cardiomyopathies

Cardiomyopathies usually are diagnosed easily when presenting with congestion owing to LV dysfunction. Regional wall motion abnormalities may be present and are not synonymous with coronary artery diseases. It is not possible to rule out myocarditis by echocardiography. IO TEE during cardiac transplantation excludes dysfunction of the donor heart and monitors tolerance of frequent residual pulmonary hypertension. Posttransplantation assessment notes atrial enlargement, a feature of the atrial connection, with dual atrial activity. Myocardial biopsy may result over time in severing of tricuspid chordae and flail tricuspid valve that require tricuspid repair. Restrictive cardiomyopathy is exemplified by amyloidosis, which characteristically displays wall thickening of the levt and right ventricles, mild valvular regurgitation, pericardial effusion, and restrictive LV filling. Occurrence of LV systolic dysfunction or irreversible diastolic dysfunction is associated with a poor prognosis. Rarely, these patients undergo cardiac transplantation. Hypertrophic cardiomyopathy may be mostly basal and obstructive. LV outflow tract obstruction results from the characteristic septal bulge with systolic anterior motion of the mitral valve and is diagnosed by typical late peaking systolic acceleration by Doppler. These patients benefit from myectomy guided by measures of depth and thickness of the septal bulge to be removed by IO TEE.[286] Elimination of the obstruction and mitral regurgitation are the IO measures of success, as well as absence of iatrogenic ventricular septal defect. Midventricular and apical hypertrophic cardiomyopathy can be missed easily and have complex intracardiac flows but rarely require surgery.

Diseases of the Aorta

The entire thoracic aorta can be visualized by combined TTE and TEE,[31,287,288] but TEE provides complete and detailed imaging of the aorta and should be preferred if a disease of the aorta is suspected.

Aortic dissection

TEE allows rapid visualization of the entire thoracic aorta and proximal abdominal aorta and diagnosis of aortic dissection, whereas TTE provides a more limited view but one that is sometimes sufficient to direct patients to the operating room, where TEE is performed. TTE has limited sensitivity (79%) compared with TEE (99%) in diagnosing aortic dissection,[289] and a negative TTE should be followed by a TEE study is patients in whom aortic dissection is suspected.[289–292] Aortic dissection is seen as an undulating intimal flap and should be distinguished from artifacts often seen in the aorta, using particularly color-flow imaging. The proximally extent of the dissection, dislocation of the intima of the sinus of Valsalva, prolapsed or aortic cusp, and presence and severity of aortic regurgitation should be defined but should not delay access to the operating room if the ascending aorta is involved, where these issues can be examined further. Involvement of the origins of the coronary arteries (particularly the right) may cause myocardial infarction but is not easily visualized, even by TEE. The presence of a pericardial effusion that may cause tamponade is particularly of concern for imminent aortic rupture and should lead to prompt surgery. IO TEE helps to define the presence and

extent of residual dissection involving the aortic arch and descending aorta and of pleural effusion. Postoperatively, TEE evaluates residual aortic regurgitation if the aortic valve has been preserved and LV function if myocardial infarction is suspected, as well as the progression of residual aortic dissection.

Aortic hematoma and rupture

Intramural hematoma precedes aortic dissection in 15 to 20% of patients who present with aortic dissection.[287,293] It results from blood collection between the intima and adventitia and appears as increased echocardiographic density along the aortic wall visible by TEE but usually not by TTE. Aortic perforation can be caused by aortic ulcers complicating atherosclerosis. Its diagnosis is raised in older patients with upper chest pain, but such a diagnosis is difficult even using TEE. Aortic rupture complicates deceleration injury and can be diagnosed by multiplane TEE.[294] Despite the trauma, TEE is feasible in the vast majority of patients and is rarely complicated. TEE is sensitive to detect isthmic rupture. Pseudoaneurysm resulting from containment of rupture by surrounding tissue can be differentiated from true aneurysm by the sharply demarcated rupture site and the narrow communication between the aorta and the pseudoaneurysm.

Aortic aneurysm

Aortic dilatation and aneurysms are visualized and measurable by TTE and TEE, but the extent of the entire aneurysm is better determined by TEE (Fig. 11-27). Rupture rates increase with aneurysm size, and the risk is considerable if the aneurysm is 6 cm or larger but also is notable if the aneurysm is between 5.5 and 6 cm in size. Smaller aneurysms can be followed serially with echocardiography. Patients with Marfan syndrome and those with bicuspid aortic valve are at risk for aortic dilatation and potentially dissection. Prophylactic beta blockers are helpful in delaying progressive aorta dilatation detected by echocardiography and possibly dissection.[295] Sinus of Valsalva aneurysm is best assessed from parasternal long- and short-axis views. Sinus of Valsalva aneurysm may cause compression of adjacent structures or rupture into the cardiac chambers, most commonly the right atrium or right ventricle.[296,297]

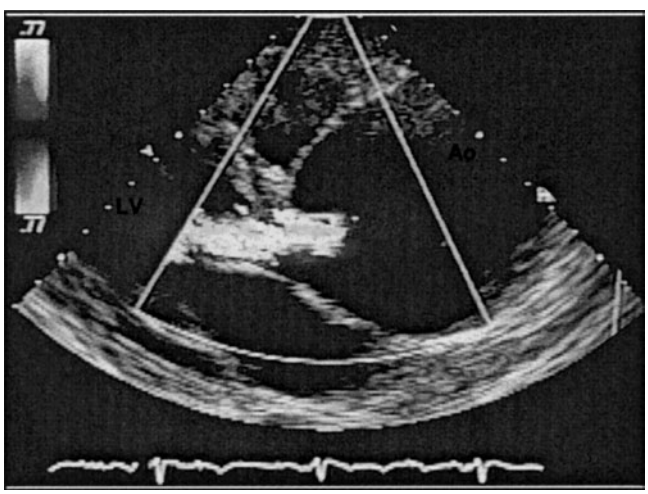

Figure 11-27. Annuloaortic ectasia associated with aortic regurgitation diagnosed by transthoracic echocardiography. Ao = aorta; LV = left ventricle.

Aortic artherosclerosis

Aortic atherosclerosis causes plaques and debris within the aorta, particularly in the elderly. Plaques of higher thickness, irregular surface (ulceration), and with mobile components have higher embolic potential[298–301] Intraoperatively, the presence of severe aortic plaques is of particular importance when an intra-aortic balloon pump is considered. The role of cholesterol embolism in postoperative strokes and decline of renal function is uncertain.

Aortic coarctation

Coarctation of the aorta can be diagnosed by TTE with suprasternal imaging, and Doppler gradient can be measured at rest and with exercise. TEE shows the narrowing of the descending thoracic aorta. TTE and TEE also show the frequently associated bicuspid aortic valve. Postoperatively, echocardiography follows the residual stenosis and the progression of aortic valve dysfunction and ascending aortic enlargement.

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CHAPTER 12

Extracorporeal Circulation

John W. Hammon

Cardiac surgery is unique in that a special perfusion system is required for open cardiac surgery and many other examples of closed surgery. It is remarkable that in this new millennium, only 50 years after the first use of extracorporeal circulation, hundreds of thousands of patients a year undergo successful surgery augmented by extracorporeal circulation at a very low risk and with superb clinical outcomes. These occur despite the fact that blood exposed to nonendothelial cell surfaces is collected and continuously recirculated throughout the entire body. This contact with synthetic surfaces in the perfusion circuit and multiple tissues within the wound triggers a defense reaction that involves at least five plasma protein systems and five blood cells. This reaction—the inflammatory response to cardiopulmonary bypass—initiates a powerful thrombotic stimulus and the production, release, and circulation of vasoactive and cytotoxic substances that affect every organ and tissue within the body. Cardiopulmonary bypass and open heart surgery are simply not possible without heparin; thus the inflammatory response to cardiopulmonary bypass describes the consequences of exposing heparinized blood to nonendothelial cell–covered surfaces.

Much has been learned about the inflammatory response since early pioneers first described hemolysis, thrombocytopenia, and production of emboli during and after open heart surgery. Still, much remains to be learned and the goal of a truly nonthrombogenic synthetic surface remains beyond the horizon. This chapter summarizes applications of extracorporeal circulation as used in adult cardiac surgery. The presentation is divided into three sections. Section 12A describes the components and operation of perfusion systems and related special topics. The humoral response to cardiopulmonary bypass, including the reaction of blood elements and the inflammatory response, are presented in section 12B. The consequences of extracorporeal perfusion in terms of organ damage are summarized in section 12C.

Perfusion System

COMPONENTS

During cardiopulmonary bypass (CPB) for clinical cardiac surgery, blood is typically drained by gravity into the venous reservoir of the heart-lung machine via cannulas placed in the superior and inferior venae cavae or a single cannula placed in the right atrium. Blood from this reservoir is pumped through a membrane oxygenator into the systemic arterial system, usually through a cannula placed in the distal ascending aorta (Fig. 12-1). This basic extracorporeal perfusion system can be adapted to provide partial or total circulatory and respiratory support or partial support for the left or right heart or for the lungs separately.

The complete heart-lung machine includes many additional components (Fig. 12-2).[1] Most manufacturers consolidate a *membrane oxygenator, venous reservoir,* and *heat exchanger* into one unit. A *microfilter-bubble trap* is added to the arterial outflow. Depending on the operation, various suction systems are used to return blood from the surgical field, cardiac chambers, and/or the aorta. Aspirated blood passes through a *cardiotomy reservoir* and *microfilter* before returning to the venous reservoir. Optionally, but increasingly recommended, field blood is washed in a *cell saver system* and returned to the perfusate as packed red cells. In addition to adjusting pump flow, partial and occluding *clamps* on venous and arterial lines are used to direct and

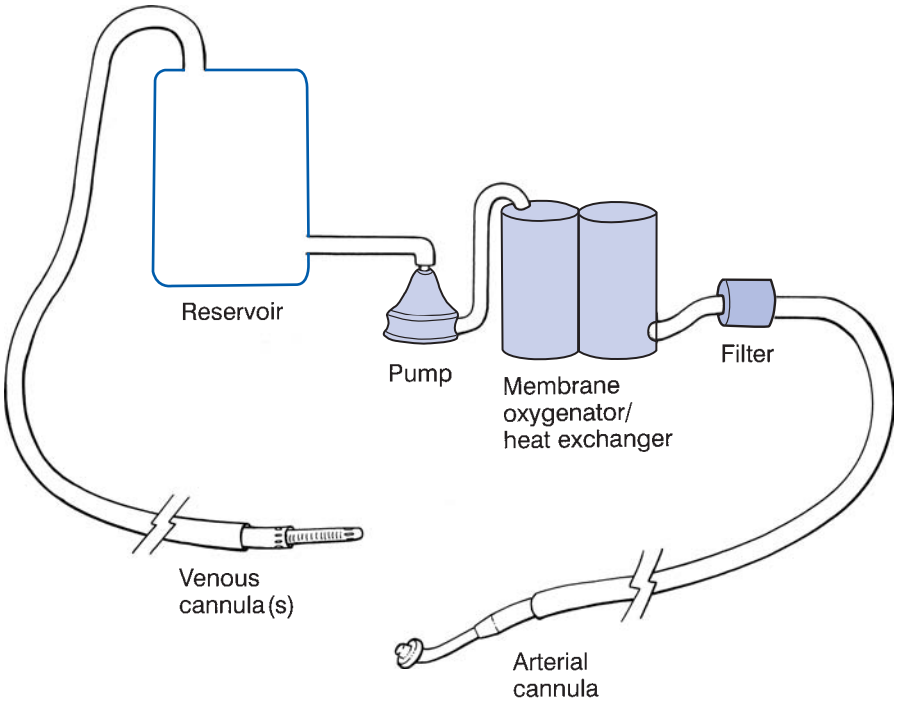

Figure 12-1. Basic cardiopulmonary bypass circuit with membrane oxygenator and centrifugal pump.

regulate flow. *Sites* for obtaining blood samples and *sensors* for monitoring pressures, temperatures, oxygen saturation, blood gases, and pH are included, as are various safety devices.

A separate circuit for administering *cardioplegic* solutions at controlled composition, rate, and temperature is usually included in the system. Often a *hemoconcentrator* (for removal of water and small molecules) is added to the primary circuit.

Venous Cannulation and Drainage

Principles of venous drainage

Venous blood usually enters the circuit by gravity or siphonage into a venous reservoir placed 40 to 70 cm below the level of the heart. The amount of drainage is determined by central venous pressure; the height differential; resistance in cannulas, tubing, and connectors; and absence of air within the system. Central venous pressure is determined by intravascular volume and venous compliance, which is influenced by medications, sympathetic tone, and anesthesia. Inadequate blood volume or excessive siphon pressure may cause compliant venous or atrial walls to collapse against cannular intake openings to produce "chattering" or "fluttering." This phenomenon is corrected by adding volume to the patient.

Venous cannulas and cannulation

Venous cannulas are usually made out of flexible plastic, which may be stiffened against kinking by wire reinforcement. Tips are straight or angled and often are constructed of thin, rigid plastic or metal. Size is determined by patient size, anticipated flow rate, and an index of catheter flow characteristics and resistance (provided by the manufacturer). For an average adult with 60-cm negative siphon pressure, a 30F cannula in the superior vena cava (SVC) and 34F in the inferior vena cava (IVC) or a single 42F cavoatrial catheter suffices. Catheters are typically inserted through purse-string guarded incisions in the right atrial appendage, lateral atrial wall, or directly in the SVC and IVC.

Three basic approaches for central venous cannulation are used: bicaval, single atrial, or cavoatrial ("two stage") (Fig. 12-3). *Bicaval cannulation* and caval tourniquets are necessary to prevent bleeding and air entry into the system when the right heart is entered during CPB. Because of coronary sinus return, caval tourniquets should not be tightened without decompressing the right atrium. Bicaval cannulation without caval tapes is often preferred to facilitate venous return during exposure of the left atrium and mitral valve.

Single venous cannulation is adequate for most aortic valve and coronary artery surgery; however, usually a cavoatrial cannula ("two-stage") is employed (see Fig. 12-3B). This catheter is typically introduced via the right atrial appendage. Its narrowed distal end is threaded into the IVC while the wider proximal portion has side holes designed to rest within the right atrium. It tends to be more stable and provide better drainage than a single cannula, but proper positioning is critical.[2] With single cannulas, elevation of the heart may kink the junction of the SVC with the atrium and partially obstruct venous drainage and more importantly, block venous outflow from the cerebral circulation.

At times, venous cannulation is accomplished via the femoral or iliac vein. This either open or percutaneous

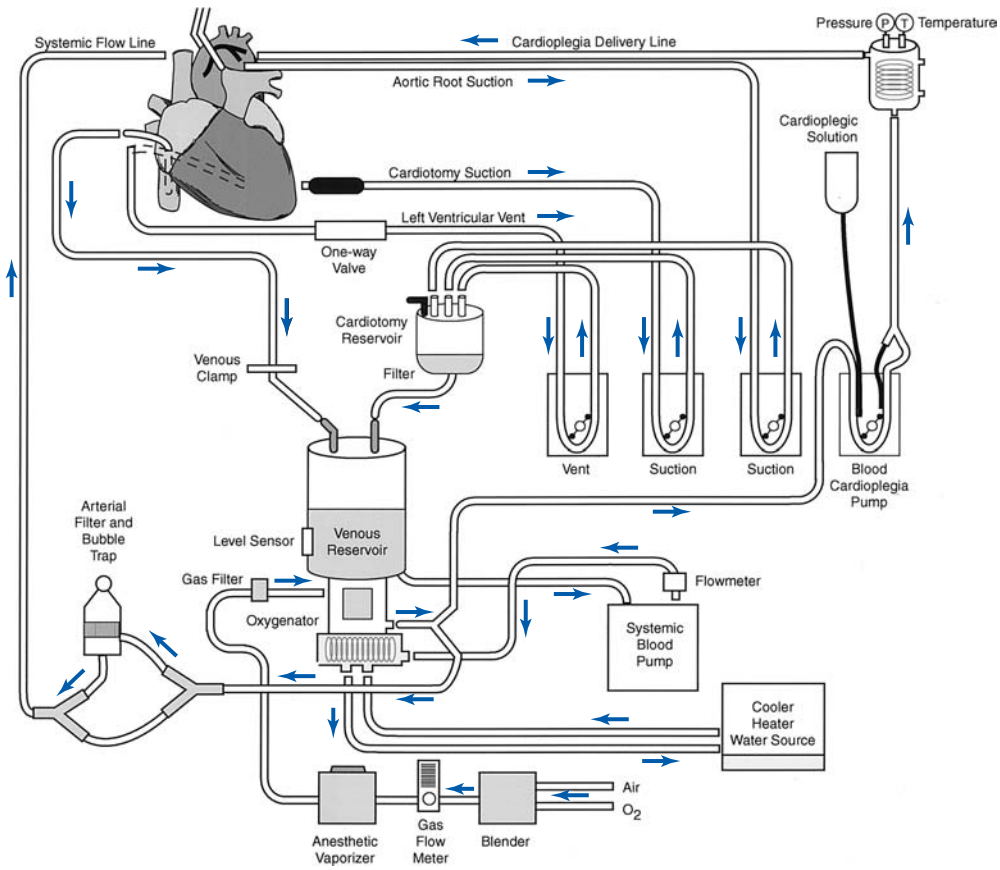

Figure 12-2. Diagram of a typical cardiopulmonary bypass circuit with vent, field suction, aortic root suction, and cardioplegic system. Blood is drained from a single "two-stage" catheter into the venous reservoir, which is part of the membrane oxygenator/heat exchanger unit. Venous blood exits the unit and is pumped through the heat exchanger and then the oxygenator. Arterialized blood exits the oxygenator and passes through a filter/bubble trap to the aortic cannula, which is usually placed in the ascending aorta. Blood aspirated from vents and suction systems enters a separate cardiotomy reservoir, which contains a microfilter, before entering the venous reservoir. The cardioplegic system is fed by a spur from the arterial line to which the cardioplegic solution is added and is pumped through a separate heat exchanger into the antegrade or retrograde catheters. Oxygenator gases and water for the heat exchanger are supplied by independent sources.

cannulation is used for emergency closed cardiopulmonary assist, for support of particularly ill patients before induction of anesthesia, for prevention or management of bleeding complications during sternotomy, for reoperations,[3] for certain types of aortic and thoracic surgery, and for applications of CPB that do not require thoracotomy. Adequate flow rates require using a cannula that is as large as possible and advancing the catheter into the right atrium guided by transesophageal echocardiography (TEE). Specially designed commercially manufactured long, ultra-thin, wire-reinforced catheters are available for this purpose.

Persistent left superior vena cava

A persistent left superior vena cava (PLSVC) is present in 0.3 to 0.5% of the general population and usually drains into the coronary sinus; however, in about 10% of cases it drains into the left atrium.[4–6] The presence of a PLSVC should be suspected when the (left) innominate vein is small or absent, and when a large coronary sinus or the PLSVC itself is seen on baseline TEE.[7,8]

A PLSVC may complicate retrograde cardioplegia or entry into the right heart.[9] If an adequate sized innominate vein is present (30% of patients), the PLSVC can simply be occluded during CPB, if the ostium of the coronary sinus is present.[10] If the right SVC is not present (approximately 20% of patients with PLSVC), the left cava cannot be occluded. If the innominate vein is absent (40% of patients) or small (about 33% of patients), occlusion of the PLSVC may cause venous hypertension and possible cerebral injury. In these patients a cannula is passed retrograde into the PLSVC through the coronary sinus ostium and secured. Alternatively, a cuffed endotracheal tube may be used as a cannula.[11]

Augmented or assisted venous return

Negative pressure is sometimes applied to the venous lines to provide assisted venous drainage using a roller pump or

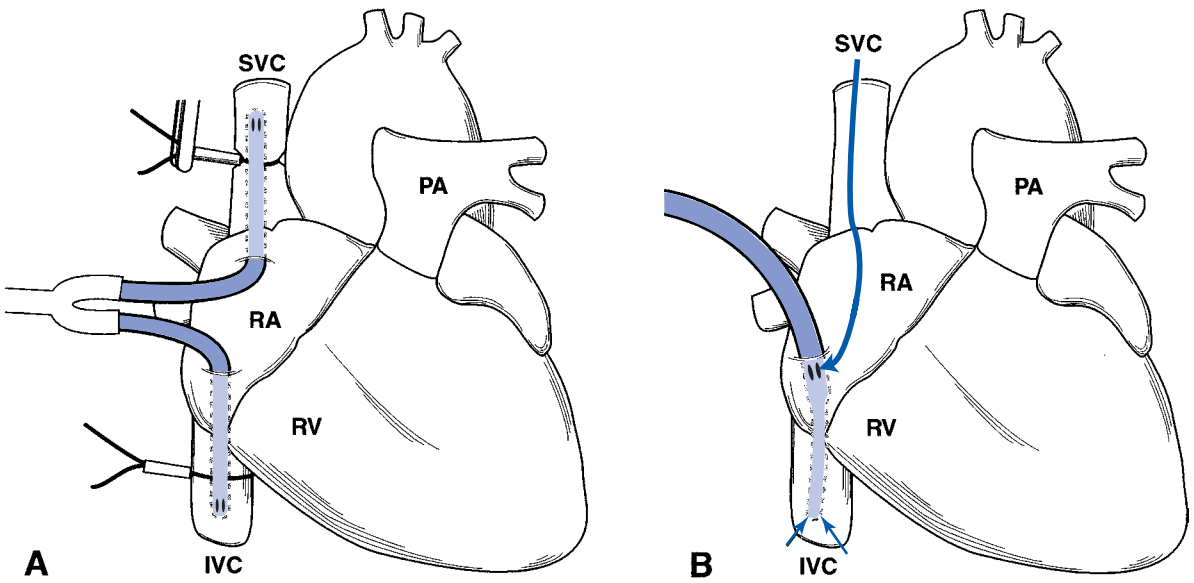

Figure 12-3. Placement of venous cannulas. (A) Cannulation of both cavae from incisions in the right atrium. (B) Cannulation using the "two-stage cannula." Blood in the right atrium is captured by vents in the expanded shoulder several inches from the narrower IVC catheter tip. IVC = inferior vena cava; PA = pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

centrifugal pump,[12] or by applying a regulated vacuum to a closed hard-shell venous reservoir (vacuum-assisted venous drainage).[13] This may permit use of smaller diameter catheters,[14] and may be helpful when long peripheral catheters are used. Augmented negative pressure in the venous line increases the risk of aspirating gross or microscopic air and causing cerebral injury,[15–18] hemolysis, or aspiration of air into the blood compartment of membrane oxygenators. Positive pressure in the venous reservoir can cause air to enter the venous lines and right heart.[19] These potential complications require special safety monitors and devices and adherence to detailed protocols.[19,20]

Complications associated with venous cannulation and drainage

These include atrial arrhythmias, atrial or caval tears and bleeding, air embolization, injury or obstruction due to catheter malposition, reversing arterial and venous lines, and unexpected decannulation. Placing tapes around the cavae may lacerate branches, nearby vessels (e.g., the right pulmonary artery), or the cava itself. Before or after CPB, catheters may compromise venous return to the right atrium from the body. Venous catheters and/or caval tapes may displace or compromise central venous or pulmonary arterial monitoring catheters; conversely, monitoring catheters may compromise the function of caval tapes.

Any intracardiac catheter may be trapped by sutures, which may impede removal before or after the wound is closed. Any connection between the atmosphere and cannula intake ports may entrain air to produce an air lock or gaseous microembolism. Assisted venous drainage increases the risk of air entrainment.[21,22] Finally, improperly placed purse-string sutures may obstruct a cava when tied.[23]

Causes of low venous return

Low venous pressure, hypovolemia, drug- or anesthetic-induced venous dilatation, inadequate differential height between heart and reservoir, too small cannula size, cannula obstruction from any cause, air locks, or excessive flow resistance in the drainage system are possible causes of reduced venous return. Partial obstruction of the venous line may distend the right ventricle and impair later contractility.

Arterial Cannulation

Arterial cannulas

The tip of the arterial cannula is usually the narrowest part of the perfusion system and at required flows small aortic and arterial catheters produce high pressure differentials, jets, turbulence, and cavitation. Most arterial catheters are rated by a performance index, which relates external diameter, flow, and pressure differential.[24] High-velocity jets may damage the aortic wall, dislodge atheroemboli, produce dissections, disturb flow to nearby vessels, and cause cavitation and hemolysis. Pressure differences that exceed 100 mm Hg cause excessive hemolysis and protein denaturation.[25] Weinstein[26] attributed a predominance of left-sided stroke following cardiac surgery to the sand-blasting effect of end-hole aortic cannulas directing debris into the left carotid artery. Aortic catheters with only side ports[27] are designed to minimize jet effects and better distribute arch vessel perfusion and pressure[28] and may be associated with fewer strokes.[26]

Recently a dual-stream aortic perfusion catheter has been developed that features an inflatable horizontal streaming baffle that is designed to protect the arch vessels from atherosclerotic and other emboli and permits selective cerebral

hypothermia.[29,30] Another novel aortic cannula features a side port that deploys a 120-μm mesh filter to remove particulate emboli beyond the ascending aorta.[31] Although this catheter increased the pressure gradient by 50%,[32] it removed an average of 8 emboli in 99% of 243 patients and cerebral injuries were less than expected.[33]

Connection to the patient

Anatomic sites available for arterial inflow include the proximal aorta, innominate artery and distal arch, and femoral, external iliac, axillary, and subclavian arteries. The choice is influenced by the planned operation[34] and distribution of atherosclerotic disease.[35]

Atherosclerosis of the ascending aorta

Dislodgment of atheromatous debris from the aortic wall from manipulation,[36] cross-clamping, or the sand-blasting effect of the cannula jet is a major cause of perioperative stroke[37,38] and a risk factor for aortic dissection[39] and postoperative renal dysfunction.[40] Simple palpation during transient hypotension or TEE is less sensitive and accurate for detecting severe atherosclerosis than epiaortic ultrasonic scanning.[36,41,42] TEE views of the middle and distal ascending aorta are often inadequate,[41–44] but some recommend this method for screening.[44,45] Epiaortic scanning is preferred for all patients who have a history of transient ischemic attack, stroke, severe peripheral vascular disease, palpable calcification in the ascending aorta, calcified aortic knob on chest radiograph, age older than 50 to 60 years, or TEE findings of moderate aortic atherosclerosis.[36] Calcified aorta ("porcelain aorta"), which occurs in 1.2 to 4.3% of patients,[46,47] is another indication for changing the location of the aortic cannula.[48,49] Alternative sites include the distal aortic arch[46,50] and innominate, axillary-subclavian, or femoral arteries.

Ascending aortic cannulation

The distal ascending aorta is the preferred cannulation site because of ease and fewest complications. Most surgeons place two sutures, full- or partial-thickness, through the aortic wall, followed by a 4- to 5-mm, full-thickness stab wound, and insert the cannula under a finger while the mean arterial pressure is approximately 60 to 80 mm Hg. Usually the cannula is inserted 1 to 2 cm with a whiff of back bleeding, rotated to ensure that the tip is completely within the lumen, and positioned to direct flow to the mid-transverse aorta. A few surgeons prefer a long catheter with the tip placed beyond the left subclavian artery.[51] Proper cannula placement is critical[28] and is confirmed by noting pulsatile pressure in the aortic line monitor and equivalent pressure in the radial artery. Once inserted the cannula must be adequately secured in place.

COMPLICATIONS OF ASCENDING AORTA CANNULATION: Complications include difficult insertion; bleeding; tear in the aortic wall; intramural or malposition of the cannula tip (in or against the aortic wall, toward the valve, or in an arch vessel)[52]; atheromatous emboli; failure to remove all air from the arterial line after connection; injury to the aortic back wall; high line pressure indicating obstruction to flow; inadequate or excessive cerebral perfusion[53]; inadvertent decannulation; and aortic dissection.[54,55] It is essential to monitor aortic line and radial artery pressures and to carefully observe the aorta for possible cannula-related complications during onset of CPB and during placement of aortic clamps. Asymmetric cooling of the face or neck may suggest a problem with cerebral perfusion. Late bleeding and infected or noninfected false aneurysms are delayed complications of aortic cannulation.

Aortic dissection occurs in 0.01 to 0.09% of aortic cannulations[39,55–58] and is more common in patients with aortic root disease. The first clues may be discoloration beneath the adventia near the cannula site, an increase in arterial line pressure, or a sharp reduction in return to the venous reservoir. TEE may be helpful in confirming the diagnosis,[59] but prompt action is necessary to limit the dissection and maintain perfusion. The cannula must be promptly transferred to a peripheral artery or uninvolved distal aorta. Blood pressure should be controlled pharmacologically and perfusion cooling to temperatures less than 20°C initiated. During hypothermic circulatory arrest, the aorta is opened at the original site of cannulation and repaired by direct suture, patch, or circumferential graft.[57,58] When recognized early, survival rates range from 66 to 85%, but when discovered after operation, survival is approximately 50%.

Cannulation of the femoral or iliac artery

These vessels are usually the first alternative to aortic cannulation, but are also indicated for initiating CPB quickly for severe bleeding, cardiac arrest, acute intraoperative dissection or severe shock, limited access cardiac surgery, and selected reoperative patients.[3] Femoral or iliac cannulation limits cannula size, but the retrograde distribution of blood flow is similar to antegrade flow.[60]

Femoral cannulation is associated with many complications[3,61] that include tears, dissection, late stenosis or thrombosis, bleeding, lymph fistula, infection in the groin, or cerebral and coronary atheroembolism. In patients with prior aortic dissections femoral perfusion may cause malperfusion; thus some surgeons recommend alternative cannulation sites for these patients.[62,63] Ischemic complications of the distal leg may occur during prolonged (3 to 6 hours) retrograde perfusions[64,65] unless perfusion is provided to the distal vessel. This may be provided by a small Y catheter in the distal vessel[65] or a side graft sutured to the artery.[66]

Retrograde arterial dissection is the most serious complication of femoral or iliac arterial cannulation and may extend to the aortic root and/or cause retroperitoneal hemorrhage. The incidence is between 0.2 and 1.3%[67–70] and is associated with a mortality of about 50%. This complication is more likely in diseased arteries and in patients over 40 years old. The diagnosis is similar for an aortic cannula dissection and may be confirmed by TEE of the descending thoracic aorta.[59] Antegrade perfusion in the true lumen must be immediately resumed by either the heart itself or by cannulation in

the distal aorta or axillary-subclavian artery. It is not always necessary to repair the dissected ascending aorta unless it affects the aortic root.[67–69]

Other sites for arterial cannulation

The axillary-subclavian artery is increasingly used for cannulation.[71–75] Advantages include freedom from atherosclerosis, antegrade flow into the arch vessels, and protection of the arm and hand by collateral flow. Because of these advantages and the dangers of retrograde perfusion in patients with aortic dissection, some surgeons prefer this cannulation site for these patients.[63,75,76] Brachial plexus injury and axillary artery thrombosis are reported complications.[71] The axillary artery is approached through a subclavicular incision; the intrathoracic subclavian artery may be cannulated through a thoracotomy.[77]

Occasionally the innominate artery may be cannulated through a purse-string suture without obstructing flow around a 7F to 8F cannula to the right carotid artery.[34,49] The ascending aorta can also be cannulated by passing a cannula through the aortic valve from the left ventricular apex.[78,79] Coselli and Crawford[80] also describe retrograde perfusion through a graft sewn to the abdominal aorta.

Venous Reservoir

The venous reservoir serves as volume reservoir and is placed immediately before the arterial pump when a membrane oxygenator is used (see Fig. 12-1). This reservoir serves as a high-capacitance (i.e., low-pressure) receiving chamber for venous return; facilitates gravity drainage; is a venous bubble trap; provides a convenient place to add drugs, fluids, or blood; and adds storage capacity for the perfusion system. As much as 1 to 3 L of blood may be translocated from patient to circuit when full CPB is initiated. The venous reservoir also provides several seconds of reaction time if venous return is suddenly decreased or stopped during perfusion.

Reservoirs may be rigid (hard) plastic canisters ("open" types) or soft, collapsible plastic bags ("closed" types). The rigid canisters facilitate volume measurements and management of venous air, often have larger capacity, are easier to prime, permit suction for vacuum-assisted venous drainage, and may be less expensive. Some hard-shell venous reservoirs incorporate macrofilters and microfilters and can serve as cardiotomy reservoirs and to receive vented blood.

Disadvantages include the use of silicon antifoam compounds, which may produce microemboli,[81,82] risk of microembolism, and increased activation of blood elements.[83] Soft bag reservoirs eliminate the blood-gas interface and by collapsing reduce the risk of pumping massive air emboli.

Oxygenators

Membrane oxygenators imitate the natural lung by interspersing a thin membrane of either microporous polypropylene (0.3- to 0.8-μm pores) or silicone rubber between the gas and blood phases. Compared to bubble oxygenators, membrane oxygenators are safer, produce less particulate and gaseous microemboli,[84,85] are less reactive to blood elements, and allow superior control of blood gases.[86,87] With microporous membranes, plasma-filled pores prevent gas from entering blood, but facilitate transfer of both oxygen and carbon dioxide. Because oxygen is poorly diffusible in plasma, blood must be spread as a thin film (approximately 100 μm) over a large area with high differential gas pressures between compartments to achieve oxygenation. Areas of turbulence and secondary flow enhance diffusion of oxygen within blood and thereby improve oxyhemoglobin saturation.[88] Carbon dioxide is highly diffusible in plasma and easily exits the blood compartment despite small differential pressures across the membrane.

The most popular design uses sheaves of hollow fibers (120 to 200 μm) connected to inlet and outlet manifolds within a hard-shell jacket (Fig. 12-4). The most efficient configuration creates turbulence by passing blood between fibers and oxygen within fibers. Arterial partial carbon dioxide pressure ($PaCO_2$) is controlled by gas flow, and arterial partial oxygen pressure (PaO_2) is controlled by the fraction of inspired oxygen (FIO_2) produced by an air-oxygen blender. Modern membrane oxygenators add up to 470 mL of O_2 and remove up to 350 mL CO_2 per minute at 1 to 7 L of flow with priming volumes of 220 to 560 mL and resistances of 12 to 15 mm Hg per liter blood flow. Most units combine a venous reservoir, heat exchanger, and hollow fiber membrane oxygenator into one compact unit.

Oxygen and CO_2 diffuse across thin silicone membranes, which are made into envelopes and wound around a spool to produce a spiral coil oxygenator. Gas passes through the envelope and blood passes between the coil windings. Because of protein leakage, which degrades membrane function, these spiral coil oxygenators are preferred over hollow fiber microporous oxygenators for the prolonged perfusions (days) used in respiratory support.

A new membrane oxygenator features a very thin (0.05 μm), solid membrane on the blood side of a highly porous support matrix. This membrane reduces the risk of gas emboli and plasma leakage during prolonged CPB, but may impair transfer of volatile anesthetics.[89]

Flow regulators, flow meters, gas blender, oxygen analyzer, gas filter, and moisture trap are parts of the oxygenator gas supply system used to control the ventilating gases within membrane oxygenators. Often an anesthetic vaporizer is added, but care must be taken to prevent volatile anesthetic liquids from destroying plastic components of the perfusion circuit.

Bubble oxygenators are obsolete in the United States, but are used elsewhere for short-term CPB because of cost and efficiency. Because each bubble presents a new foreign surface to which blood elements react, bubble oxygenators cause progressive injury to blood elements and entrain more gaseous microemboli.[90,91] In bubble oxygenators, venous blood drains directly into a chamber into which oxygen is infused through a diffusion plate (sparger). The sparger

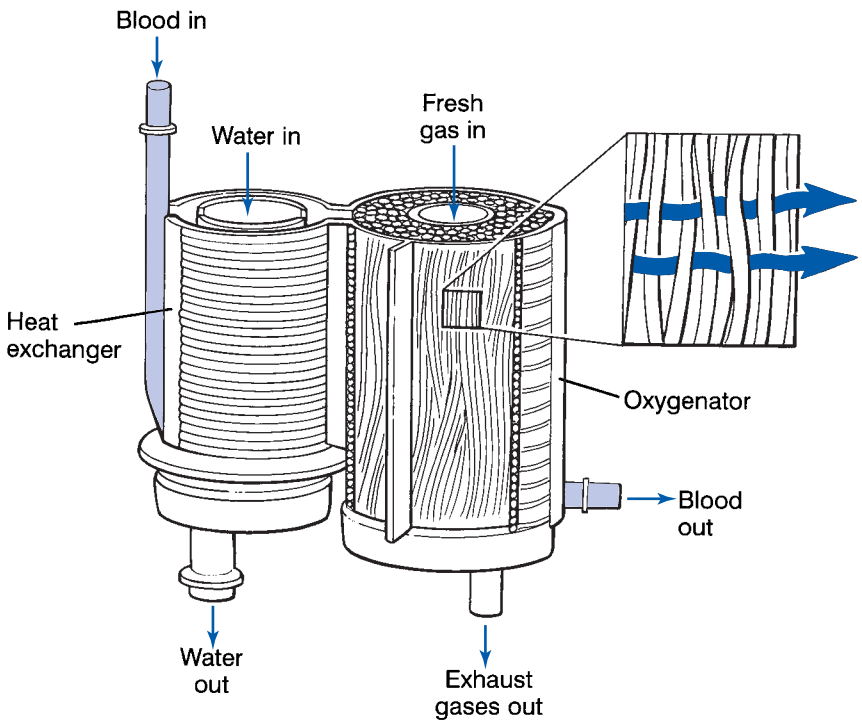

Figure 12-4. Diagram of a hollow fiber membrane oxygenator and heat exchanger unit. Blood enters the heat exchanger first and flows over water-cooled or -warmed coils and then enters the oxygenator to pass between woven strands of hollow fibers. Oxygen enters one end of the bundles of hollow fibers and exits at the opposite end. The hollow fiber bundles are potted at each end to separate the blood and gas compartments. Oxygen and carbon dioxide diffuse in opposite directions across the aggregate large surface of the hollow fibers.

produces thousands of small (approximately 36 μm) oxygen bubbles within the blood. Gas exchange occurs across a thin film at the blood-gas interface around each bubble. Carbon dioxide diffuses into the bubble and oxygen diffuses outward into blood. Small bubbles improve oxygen exchange by effectively increasing the surface area of the gas-blood interface,[92] but are difficult to remove. Large bubbles facilitate CO_2 removal. Bubbles and blood are separated by settling, filtration, and defoaming surfactants in a reservoir. Bubble oxygenators add 350 to 400 mL of oxygen to blood and remove 300 to 330 mL of CO_2 per minute at flow rates from 1 to 7 L/min.[86,93] Priming volumes are less than 500 mL. Commercial bubble oxygenators incorporate a reservoir and heat exchanger within the same unit and are placed upstream to the arterial pump.

Oxygenator malfunction requiring change during CPB occurs in 0.02 to 0.26% of cases,[94–96] but the incidence varies between membrane oxygenator designs.[97] Development of abnormal resistant areas in the blood path is the most common cause,[96] but other problems include leaks, loss of gas supply, rupture of connections, failure of the blender, and deteriorating gas exchange. Blood gases need to be monitored to ensure adequate CO_2 removal and oxygenation. Heparin coating may reduce development of abnormally high resistance areas.[95]

Heat Exchangers

Heat exchangers control body temperature by heating or cooling blood passing through the perfusion circuit. Hypothermia is frequently used during cardiac surgery to reduce oxygen demand or to facilitate operative exposure by temporary circulatory arrest. Gases are more soluble in cold than in warm blood; therefore, rapid rewarming of cold blood in the circuit or body may cause formation of bubble emboli.[98] Most membrane oxygenator units incorporate a heat exchanger upstream to the oxygenator to minimize bubble emboli. Blood is not heated above 40°C to prevent denaturation of plasma proteins, and temperature differences within the body and perfusion circuit are limited to 5 to 10°C to prevent bubble emboli. The heat exchanger may be supplied by hot and cold tap water, but separate heater/cooler units with convenient temperature-regulating controls are preferred. Leakage of water into the blood path can cause hemolysis and malfunction of heater/cooler units may occur.[94]

Separate heat exchangers are needed for cardioplegia. The simplest system is to use bags of precooled cardioplegia solution. More often cardioplegia fluid is circulated through a dedicated heat exchanger or tubing coils placed in an ice- or warm-water bath.

Pumps

Most heart-lung machines use two types of pumps, although roller pumps can be used exclusively (Table 12-1). Centrifugal pumps are usually used for the primary perfusion circuit for safety reasons and for a possible reduction in injury to blood elements. However, this latter reason remains highly controversial and unproven.[99–104]

Centrifugal pumps (Fig. 12-5) consist of a vaned impeller or nested, smooth plastic cones, which when rotated rapidly, propel blood by centrifugal force.[105] An arterial flowmeter is required to determine forward blood flow, which varies with the speed of rotation and the afterload of the arterial line. Unless a check valve is used,[106] the

Table 12–1.

Roller Versus Centrifugal Pump

	Roller pump	Centrifugal pump
Description	Nearly occlusive Afterload independent	Nonocclusive Afterload sensitive
Advantages	Low prime volume Low cost No potential for backflow Shallow sine-wave pulse	Portable, position insensitive Safe positive and negative pressure Adapts to venous return Superior for right or left heart bypass Preferred for long-term bypass Protects against massive air embolism
Disadvantages	Excessive positive and negative pressure Spallation Tubing rupture Potential for massive air embolism Necessary occlusion adjustments Requires close supervision	Large priming volume Requires flowmeter Potential passive backward flow Higher cost

arterial line must be clamped to prevent backward flow when the pump is off. Centrifugal blood pumps generate up to 900 mm Hg of forward pressure, but only 400 to 500 mm Hg of negative pressure, and therefore less cavitation and fewer gaseous microemboli. They can pump small amounts of air, but become "deprimed" if more than 30 to 50 mL of air enters the blood chamber. Centrifugal pumps are probably superior for temporary extracorporeal assist devices and left heart bypass, and for generating pump-augmented venous return.

Roller pumps consist of a length of $^{1}/_{4}$- to $^{5}/_{8}$-inch (internal diameter) polyvinyl, silicone, or latex tubing, which is compressed by two rollers 180° apart inside a curved raceway. Forward flow is generated by roller compression and flow rate depends on the diameter of the tubing, rate of rotation, the length of the compression raceway, and completeness of compression. Compression is adjusted before use to be barely nonocclusive against a standing column of fluid that produces 45 to 75 mm Hg back pressure.[107–110] Hemolysis and tubing wear are minimal at this degree of compression.[107] Flow rate is determined from calibration curves for each pump for different tubing sizes and rates of rotation. Roller pumps are inexpensive, reliable, safe, insensitive to afterload, and have small priming volumes, but can produce high negative pressures and microparticles shed from compressed tubing (spallation).[111] Roller pumps are vulnerable to careless operation that results in propelling air, inaccurate flow calibration, backflow when not in use if rollers are not sufficiently occlusive, excessive pressure with rupture of connections if arterial inflow is obstructed, tears in tubing, and changing roller compression settings during operation. Roller pumps, but not centrifugal pumps, are used for sucker systems and for delivering cardioplegic solutions.

Centrifugal pumps produce pulseless blood flow and standard roller pumps produce a sine wave pulse around 5 mm Hg. The arterial cannula dampens the pulse of pulsatile pumps, and it is difficult to generate pulse pressures above 20 mm Hg within the body during full CPB.[112,113] To date no one has conclusively demonstrated the need for pulsatile perfusion during short-term or long-term CPB or circulatory assistance.[114–117]

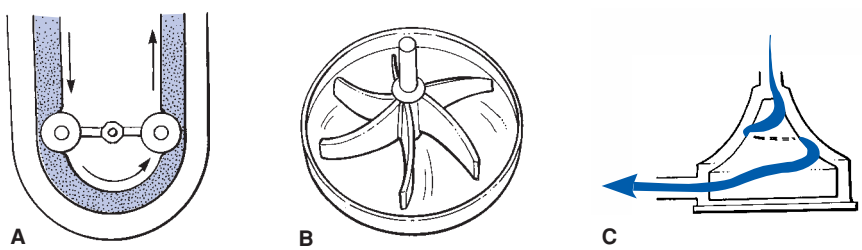

Figure 12-5. Diagrams of blood pumps. (A) Roller pump with two rollers, 180° apart. The compression of the rollers against the raceway is adjustable and is set to be barely nonocclusive. Blood is propelled in the direction of rotation. (B) The impeller pump uses vanes mounted on a rotating central shaft. (C) The centrifugal pump uses three rapidly rotated, concentric cones to propel blood forward by centrifugal force.

Complications that may occur during operation of either type of pump include loss of electricity, loss of the ability to control pump speed, which produces "runaway pump" or "pump creep" when turned off, loss of the flow meter or RPM indicator, rupture of tubing in the roller pump raceway, and reversal of flow by improper tubing in the raceway. A means to manually provide pumping in case of electrical failure should always be available.

Filters and Bubble Traps

Microemboli

During clinical cardiac surgery with CPB the wound and the perfusion circuit generate gaseous and biologic and nonbiologic particulate microemboli (<500 μm diameter).[31,118–123] Microemboli produce much of the morbidity associated with cardiac operations using CPB (see section 12C). Gaseous emboli contain oxygen or nitrogen and may enter the perfusate from multiple sources and pass through other components of the system.[18,21] Potential sources of gas entry include stopcocks, sampling and injection sites,[122] priming solutions, priming procedures, intravenous fluids, vents, the cardiotomy reservoir, tears or breaks in the perfusion circuit, loose purse-string sutures (especially during augmented venous return),[18] rapid warming of cold blood,[98] cavitation, oxygenators, venous reservoirs with low perfusate levels,[21,82] and the heart and great vessels. Bubble oxygenators produce many gaseous emboli; membrane oxygenators produce very few.[84–86] Aside from mistakes (open stopcocks, empty venous reservoir, or air in the heart) the cardiotomy reservoir is the largest source of gaseous emboli in membrane oxygenator perfusion systems.

Blood produces a large number of particulate emboli related to thrombus formation (clots), fibrin, platelet and platelet-leukocyte aggregation, hemolyzed red cells, cellular debris, and generation of chylomicrons, fat particles, and denatured proteins.[124] Stored donor blood is also an important source of blood-generated particles.[125] Other biologic emboli include atherosclerotic debris and cholesterol crystals and calcium particles dislodged by cannulation, manipulation for exposure, or the surgery itself. Both biologic and nonbiologic particulate emboli are aspirated from the wound. Bits of muscle, bone, and fat are mixed with suture material, talc, glue, and dust and aspirated into the cardiotomy reservoir.[125,126] Materials used in manufacture, spallated material, and dust may also enter the perfusate from the perfusion circuit[125] if it is not first rinsed by recirculating saline through a prebypass microfilter, which is discarded.

In vivo microemboli larger than 100 μm are detected by transcranial Doppler ultrasound,[127] fluorescein angiography,[84] TEE, and retinal inspection. In the circuit, microemboli are monitored by arterial line ultrasound[128] or monitoring screen filtration pressure. Microfilter weights and examination, histology of autopsy tissues, and electron particle size counters of blood samples[125] verify microemboli beyond the circuit.

PREVENTION AND CONTROL OF MICROEMBOLI: Table 12-2 outlines methods to reduce microembolism. Major methods include using a membrane oxygenator and cardiotomy reservoir filter, minimizing and washing blood aspirated from the field,[129] and preventing air entry into the circuit and using left ventricular vents when the heart is opened.[130,131]

The brain receives 14% of the cardiac output and is the organ most sensitive to microembolic injury.[132] Strategies to selectively reduce microembolism to the brain include reducing Pa_{CO_2} to cause cerebral vasoconstriction,[133] hypothermia,[134] placing aortic cannulas downstream to the cerebral vessels,[50,51,122] and using special aortic cannulas with[29–31,33] or without[26] special baffles or screens designed to prevent cannula-produced cerebral atherosclerotic emboli.

Two types of blood microfilters are available for use within the perfusion circuit: depth and screen.[135–137] Depth filters consist of packed fibers or porous foam; have no defined pore size; present a large, tortuous, wetted surface; and remove microemboli by impaction and absorption. Screen filters are usually made of woven polyester or nylon

Table 12–2.

Minimizing Microemboli

Membrane oxygenator, centrifugal arterial pump
Cardiotomy reservoir filter (≤40 μm)
Arterial line filter/bubble trap (≤40 μm)
Keep temperature differentials <8–10°C
Prime with carbon dioxide flush; recirculate with saline and filter (5 μm)
Prevent air entry into the circuit Snug purse-string sutures Three-way stopcocks on all sampling ports Meticulous syringe management Adequate cardiotomy reservoir volume (for debubbling) Avoid excessive suction on vents One-way valved purge lines for bubble traps Use transesophageal echocardiography to locate trapped intracardiac air; de-air thoroughly
Wash blood aspirated from the surgical field
Prevent thrombus formation with adequate anticoagulation
Assess inflow cannulation site by epiaortic ultrasound imaging
Cannulate distal aorta or axillary artery
Consider use of special aortic cannulas

thread, have a defined pore size, and filter by interception. Screen filters vary in pore size and configuration and block most air emboli; however, as pore size decreases, resistance increases. As compared to no filter, studies indicate that all commercial filters effectively remove gaseous and particulate emboli.[138–141] Most investigations find that the Dacron wool depth filter is most effective, particularly in removing micro- and macroscopic air. Pressure differences across filters vary between 24 and 36 mm Hg at 5 L/min flow. Filters cause slight hemolysis and tend to trap some platelets; nylon filters may activate complement.[135,136]

The need for microfilters in the cardiotomy suction reservoir is universally accepted,[126] and most commercial units contain an integrated micropore filter. The need for a filter in the cardioplegia delivery system, however, is questionable,[142] and while almost always used, the need for an arterial line filter is unsettled.[137] In vitro studies demonstrate that an arterial filter reduces circulating microemboli[139–141] and clinical studies are confirmatory.[140,141] However, these filters do not remove all microemboli generated by the extracorporeal circuit.[18,122,126,143] When bubble oxygenators are used, studies show equivocal or modest reductions in microemboli[84,144–146] and neurologic outcome markers.[146–150] In contrast, membrane oxygenators produce far fewer microemboli, and when used without an arterial filter, the numbers of microemboli are similar to those found with bubble oxygenators plus arterial line filters.[85,137]

Although efficacy of arterial line microfilters remains unsettled, use is almost universal.[151] Filters are effective bubble traps, but increase costs, occasionally obstruct during use, are difficult to de-air during priming, and should be used with a bypass line and valved purge line to remove air.

Other sources of biologic microemboli may be more important. Cerebral microemboli are most numerous during aortic cannulation,[152–154] application and release of aortic clamps,[153,154] and at the beginning of cardiac ejection after open heart procedures.[155] Furthermore, as compared to perfusion microemboli, surgically induced emboli are more likely to cause postoperative neurologic deficits.[156]

Leukocyte-depleting filters

Leukocyte-depleting filters are discussed in section 12B and have been recently reviewed.[157–160] These filters reduce circulating leukocyte counts in most studies,[161–163] but fail to produce convincing evidence of clinical benefit.[164–166]

Tubing and Connectors

The various components of the heart-lung machine are connected by polyvinyl tubing and fluted polycarbonate connectors. Medical grade polyvinyl chloride tubing is universally used because it is flexible, compatible with blood, inert, nontoxic, smooth, nonwettable, tough, transparent, resistant to kinking and collapse, and can be heat sterilized. To reduce priming volume, tubing connections should be short; to reduce turbulence, cavitation, and stagnant areas, the flow path should be smooth and uniform without areas of constriction or expansion. Wide tubing improves flow rheology, but also increases priming volume. In practice $^{1}/_{2}$- to $^{5}/_{8}$-inch (internal diameter) tubing is used for most adults, but until a compact, integrated, complete heart-lung machine can be designed and produced as a unit, the flow path produces some turbulence. Careless tubing connections are sources of air intake or blood leakage and all connections must be secure. For convenience and safety, most tubing and connectors are prepackaged and disposable.

Heparin-Coated Circuits

Heparin can be attached to blood surfaces of all components of the extracorporeal circuit by ionic or covalent bonds. The Duraflo II heparin coating ionically attaches heparin to a quaternary ammonium carrier (alkylbenzyl dimethyl-ammonium chloride), which binds to plastic surfaces (Edwards Lifesciences, Irvine, Calif). Covalent attachment is produced by first depositing a polyethylenimine polymer spacer onto the plastic surface, to which heparin fragments bind (Carmeda Bioactive Surface, Medtronic Inc., Minneapolis, Minn). Ionic-bound heparin slowly leaches, but this is irrelevant in clinical cardiac surgery. The use of heparin-coated circuits during CPB has spawned an enormous literature[167–172] and remains controversial largely because studies are contaminated by patient selection, reduced doses of systemic heparin, and washing or discarding field-aspirated blood.[172] There is no credible evidence that heparin-coated perfusion circuits reduce the need for systemic heparin or reduce bleeding or thrombotic problems associated with CPB (see section 12B). Although the majority of studies indicate that heparin coatings reduce concentrations of C3a and C5b-9,[173] the inflammatory response to CPB is not reduced (see section 12B), and the evidence for clinical benefit is not convincing.[174,175]

Other surface modifications and coatings in development[168] include a phosphorylcholine coating,[176] surface-modifying additives,[179] a trillium biopassive surface,[177,178] and a synthetic protein coating[180] (see also section 12B).

Cardiotomy Reservoir and Field Suction

Blood aspirated from the surgical wound may be directed to the cardiotomy reservoir for defoaming, filtration, and storage before it is added directly to the perfusate. A sponge impregnated with a surfactant removes bubbles by reducing surface tension at the blood interface and macrofilters, microfilters, or combined filters remove particulate emboli. Negative pressure is generated by either a roller pump or by a vacuum applied to the rigid outer shell of the reservoir. The degree of negative pressure and blood level must be monitored to avoid excessive suction or introducing air into the perfusate.

The cardiotomy suction and reservoir are major sources of hemolysis, particulate and gaseous microemboli, fat globules, cellular aggregates, platelet injury and loss, thrombin generation, and fibrinolysis.[82,118,126,181,182] Air aspirated with wound blood contributes to blood activation and destruction and is difficult to remove because of the high proportion of nitrogen, which is poorly soluble in blood. High suction volumes and admixture of air are particularly destructive of platelets and red cells.[181,183] Commercial reservoirs are designed to minimize air entrainment and excessive injury to blood elements. Air and microemboli removal are also facilitated by allowing aspirated blood to settle within the reservoir before it is added to the perfusate.

An alternative method for recovering field-aspirated blood is to dilute the blood with saline and then remove the saline to return only packed red cells to the perfusate. Two types of centrifugal cell washers automate the process. Intermittent centrifugation (e.g., Haemonetics Cell Saver, Haemonetics Corp., Braintree, Mass) removes air, thrombin, and many biologic and nonbiologic microemboli from the aspirate at the cost of discarding plasma. Continuous centrifugation (e.g., Fresenius Continuous AutoTransfusion System, distributed in the U.S. by Terumo Corp., Ann Arbor, Mich) in addition removes fat and activated leukocytes.[184] A third alternative is to discard all field-aspirated blood, although most surgeons would find this practice unacceptable if it increased allogeneic blood transfusion. Increasingly, field-aspirated blood is recognized as a major contributor to the thrombotic, bleeding, and inflammatory complications of CPB (see section 12B).

Venting the Heart

If the heart is unable to contract, distention of either ventricle is detrimental to subsequent contractility.[185] Right ventricular distention during cardiac arrest or ventricular fibrillation is rarely a problem, but left ventricular distention can be insidious in that blood can enter the flaccid, thick-walled chamber from multiple sources during this period. During CPB blood escaping atrial or venous cannulas and from the coronary sinus and thebesian veins may pass through the unopened right heart into the pulmonary circulation. This blood plus bronchial arterial and venous blood, blood regurgitating through the aortic valve, and blood from undiagnosed abnormal sources (e.g., patent foramen ovale or patent ductus) may distend the left ventricle unless a vent catheter is used (Fig. 12-6). During CPB bronchial blood and noncoronary collateral flow average approximately 140 ± 182 and 48 ± 74 mL/min, respectively.[186]

There are several methods for venting the left heart during cardiac arrest. Few surgeons vent the left ventricular apex directly because of inconvenience and myocardial injury. Most often a multihole, soft-tip catheter (8F to 10F) is inserted into the junction of the right superior pulmonary vein and left atrium (see Fig. 12-6B) or left atrial appendage and may or may not be passed into the left ventricle. Others prefer to place a small suction catheter into the pulmonary artery.[187] The ventricle can also be vented by passing a catheter retrograde across the aortic valve when working on the mitral valve. Vent catheters are drained to the cardiotomy reservoir by a roller pump, vacuum source, or gravity drainage,[188,189] but must be carefully monitored for malfunction. If connected to a roller pump, the system should be carefully tested before use to ensure proper operation. Although inspection and palpation may detect ventricular distention, TEE monitoring or direct measurements of left atrial or pulmonary arterial pressures are more reliable. The heart is no longer vented for most myocardial revascularization operations, but the ventricle must be protected from distention.[190–192] If the heart cannot remain decompressed during distal anastomoses, a vent should be inserted. Often the cardioplegia line inserted into the aortic root is used for venting when not used for cardioplegia.[193]

The most common and serious complication of left heart venting is residual air when the heart is filled and begins to contract. De-airing maneuvers and TEE are important methods for ensuring removal of all residual air. In addition, many surgeons aspirate the ascending aorta via a small metal or plastic cannula to detect and remove any escaping air as the heart begins to eject.[194,195] Bleeding

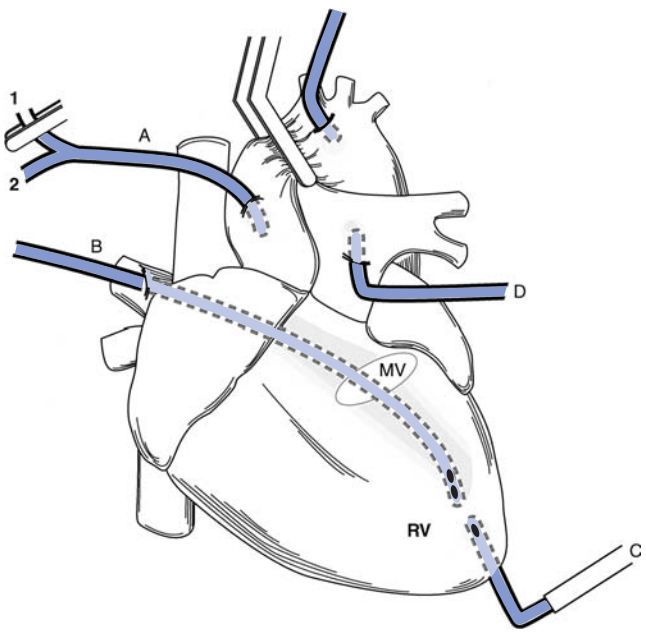

Figure 12-6. Diagram shows locations used to vent (decompress the heart). (A) Aortic root vent, which can also be used to administer cardioplegic solution after the ascending aorta is clamped. (B) A catheter placed in the right superior pulmonary vein/left atrial junction can be passed through the mitral valve into the left ventricle. (C) Direct venting of the left ventricle at the apex. (D) Venting the main pulmonary artery, which decompresses the left atrium because pulmonary veins lack valves.

problems or direct injury to the myocardium are other complications associated with left ventricular vents.

Cardioplegia Delivery Systems

Cardioplegic solutions contain 8 to 20 mEq/L potassium, magnesium, and often other components and are infused into the aortic root proximal to the aortic cross-clamp or retrograde into the coronary sinus to arrest the heart in diastole. The carrier may be crystalloid or preferably blood and is infused at temperatures around 4°C or 37°C, depending upon surgeon preference. Normothermic cardioplegia must be delivered almost continuously to keep the heart arrested; cold cardioplegia is infused intermittently. Cardioplegic solutions are delivered through a separate perfusion system that includes a reservoir, heat exchanger, roller pump, bubble trap, and perhaps microfilter (see Fig. 12-2). Temperature and infusion pressure are monitored. The system may be completely independent of the main perfusion circuit or branch from the arterial line. The system also may be configured to vent the aortic root when between infusions.

Antegrade cardioplegia is delivered through a small cannula in the aortic root or via cannulas directly into the coronary ostia when the aortic valve is exposed. Retrograde cardioplegia is delivered through a cuffed catheter inserted blindly into the coronary sinus.[196] Proper placement of the retrograde catheter is critical, but not difficult, and is verified by palpation, TEE, color of the aspirated blood, or pressure waveform of a catheter pressure sensor.[197] Complications of retrograde cardioplegia include rupture or perforation of the sinus, hematoma, and rupture of the catheter cuff.[198,199]

Hemoconcentrators (Hemofiltration/Ultrafiltration)

Hemoconcentrators, like oxygenators, contain one of several available semipermeable membranes (typically hollow fibers) that transfer water, electrolytes (e.g., potassium), and molecules up to 20 kD in size out of the blood compartment.[200] Hemoconcentrators may be connected to either venous or arterial lines or a reservoir in the main perfusion circuit, but require high pressure in the blood compartment to effect fluid removal. Thus a roller pump is needed unless connected to the arterial line. Suction may or may not be applied to the air side of the membrane to facilitate filtration. Up to 180 mL/min of fluid can be removed at flows of 500 mL/min.[201] Hemoconcentrators conserve platelets and most plasma proteins as compared to centrifugal cell washers, and may allow greater control of potassium concentrations than diuretics.[202] Aside from cost, disadvantages are few and adverse effects are rare.[201]

Perfusion Monitors and Safety Devices

Table 12-3 lists monitors and safety devices that are commonly used during CPB. Pressure in the arterial line between

Table 12–3.

Safety Devices and Procedures

Device or procedure	Usage (%)*
Low venous blood level alarm	60–100
With pump cut-off	34–80
High arterial line pressure alarm	84–94
With pump cut-off	35–75
Macrobubble detector	42–88
With pump cut-off	62–63
Arterial line filter	44–99
Pre-bypass recirculation/filtration	75–81
Oxygen supply filter	81–95
In-line venous oxygen saturation	75–76
In-line arterial oxygen saturation	12–13
Oxygenator gas supply oxygen analyzer	43–53
One-way valved intracardiac vent lines	18–73
Batteries in heart-lung machine	29–85
Alternate dedicated power supply	36
Electrical generator	28
Back-up arterial pump head	80
Back-up heater-cooler	97
Back-up oxygen supply	88–91
Emergency lighting	62–91
Pre-bypass activated clotting time	74–99
Activated clotting time during cardiopulmonary bypass	83
Pre-bypass check list	74–95
Written protocols	49–75
Log of perfusion incidents	46
Log of device failures	52

**Usage data represent ranges from various surveys, in references 94, 151, 354, 363, and 364.*

pump and arterial line filter is monitored continuously to instantly detect any increased resistance to arterial inflow into the patient. This pressure should be higher than radial arterial pressure because of resistance of the filter (if used) and cannula. The arterial pressure monitor may be connected to an audible alarm or the pump switch to alert the perfusionist of abrupt increases.

An *arterial line flowmeter* is essential for centrifugal pumps and may be desirable to confirm flow calculations with roller pumps.

Flow-through devices are available to continuously measure *blood gases, hemoglobin/hematocrit, and some electrolytes.*[203] These devices in the venous line permit rapid assessment of oxygen supply and demand.[204–206] In the arterial line the devices offer better control of blood gases.[207] The need for these devices is unproven and because reliability is still uncertain, use may distract operative personnel and spawn unnecessary laboratory measurements.[208–211] The use of automated analyzers by the perfusion team in the operating room is an alternative if frequent measurement of blood gases, hematocrit, and electrolytes is desirable.[203]

The *flow and concentration of oxygen* entering the oxygenator should be monitored.[212] Some teams also monitor exit gases to indirectly estimate metabolic activity and depth of anesthesia.[212] Some manufacturers recommend monitoring the *pressure gradient across membrane oxygenators,* which may be an early indication of oxygenator failure.[95–97]

Temperatures of the water entering heat exchangers must be monitored and carefully controlled to prevent blood protein denaturation and gaseous microemboli.[98] During operations using deep hypothermia, changes in venous line temperatures reflect rates of temperature change in the patient, and arterial line temperatures help protect against brain hyperthermia during rewarming.

A *low-level sensor* with alarms on the venous reservoir and a bubble detector on the arterial line are desirable safety devices. A *one-way valve* is recommended in the purge line between an arterial filter/bubble trap and cardiotomy reservoir to prevent air embolism. Ultrasound transducers embedded in the arterial perfusion tubing distal to the filter are now available to monitor low-level air entry into the circulation. Valves in the venous and vent lines protect against retrograde air entry into the circulation or in the arterial line to prevent inadvertent exsanguination.[106]

Automatic data collection systems are available for preoperative calculations and to process and store data during CPB.[213,214] Computer systems for operating CPB are in development.[215]

CONDUCT OF CARDIOPULMONARY BYPASS

The Perfusion Team

Although the surgeon is directly responsible to the patient for the outcome of the operation, he or she needs a close working relationship with the anesthesiologist and perfusionist. These three principals must communicate freely, often, and candidly. Their overlapping and independent responsibilities relevant to CPB are best defined by written policies that include protocols for various types of operations and emergencies and by periodic multidisciplinary conferences. This teamwork is not unlike the communication advocated for the cockpit crew of commercial and military aircraft.

The surgeon determines the planned operation, target perfusion temperatures, methods of cardioplegia, cannulations, and anticipated special procedures. During operation the surgeon communicates the procedural steps involved in connecting and disconnecting the patient to CPB and interacts with the other principals to coordinate perfusion management with surgical exposure and working conditions. The perfusionist is responsible for setting up and priming the heart-lung machine, performing safety checks, operating the heart-lung machine, monitoring the conduct of bypass, monitoring anticoagulation, adding prescribed drugs, and maintaining a written perfusion record.

The anesthesiologist monitors the operative field, anesthetic state and ventilation of the patient, the patient's physiology, and conduct of perfusion. A vigilant anesthesiologist is the safety officer and often "troubleshooter" of these complex procedures and along with the surgeon is in the best position to anticipate, detect, and correct deviations from desired conditions. In addition the anesthesiologist provides TEE observations before, during, and immediately after bypass.

Assembly of the Heart-Lung Machine

The perfusionist is responsible for setting up and preparing the heart-lung machine and all components necessary for the proposed operation. Most perfusionists use commercial, sterile, pre-packaged customized tubing packs that are connected to the various components that constitute the heart-lung machine. This dry assembly takes about 10 to 15 minutes, and the system can be kept in standby for up to 7 days. Once the system is primed with fluid, which takes about 15 minutes, it should be used within 8 hours. After assembly the perfusionist conducts a safety inspection and completes a written pre-bypass checklist.

Priming

Adult extracorporeal perfusion circuits require 1.5 to 2.0 L of balanced electrolyte solution (lactated Ringer solution, Normosol-A, or Plasma-Lyte). Before connections are made to the patient, the prime is recirculated through a micropore filter to remove particulate matter and air. The priming volume represents approximately 30 to 35% of the patient's blood volume and reduces the hematocrit to about two-thirds of the preoperative value. The addition of crystalloid cardioplegia causes further dilution. Thus sometimes a unit of banked blood is added to raise the

perfusate hematocrit to a predetermined minimum (e.g., 25% or more). Porcine heparin (2000 units) is added to each unit of banked whole blood to ensure anticoagulation. There is no consensus regarding the optimal hematocrit during CPB; most perfusates have hematocrits between 20 and 25% when used with moderate hypothermia (25 to 32°C). Dilution reduces perfusate viscosity, which is not a problem during clinical CPB, but also reduces oxygen-carrying capacity; mixed venous oxygen saturations below 60% usually prompt either transfusion or increased pump flow.[204,205] Sometimes 12.5 to 50 g of mannitol is added to stimulate diuresis and possibly minimize postoperative renal dysfunction.

Efforts to avoid the use of autologous blood include reducing the priming requirement of the machine by using smaller-diameter and shorter tubing lengths and operating the machine with minimal perfusate in the venous and cardiotomy reservoirs. This latter practice increases the risk of air embolism, the risk of which can be reduced by using collapsible reservoirs and reservoir level sensors that stop the pump. Autologous blood prime is another method, which displaces and then removes crystalloid prime by bleeding the patient into the circuit just before beginning CPB.[216,217] This method reduces perfusate volume, but phenylephrine may be required to maintain stable hemodynamics.[216,217] The method reduces transfusions and does not affect clinical outcome.

The use of colloids (albumin, gelatins, dextrans, and hetastarches) in the priming volume is controversial.[218] Colloids reduce the fall in colloid osmotic pressure[219,220] and may reduce the amount of fluid entering the extracellular space. The question is whether or not clinical outcome is improved. Prospective clinical studies have failed to document significant clinical benefits with albumin,[219–224] which is expensive and may have adverse effects.[225,226] Hetastarch may contribute to postoperative bleeding.[227] McKnight and colleagues found no influence of prime composition on postoperative nitrogen balance.[228] Because of possible adverse effects, including neurologic deficits, the addition of glucose and/or lactate to the prime is avoided.[229,230]

Anticoagulation and Reversal

Porcine heparin (300 to 400 U/kg IV) is given before arterial or venous cannulas are inserted. CPB is not started until anticoagulation is confirmed by either an activated clotting time (ACT) or the Hepcon test. Although widely used, bovine heparin is more antigenic in inducing antiplatelet IgG antibodies than is porcine heparin.[231] The anticoagulation effect is measured about 3 minutes after heparin administration. However, groups differ in the minimum ACT that is considered safe for CPB. The minimum ACT is 400 seconds; many groups recommend 480 seconds[232] because heparin only partially inhibits thrombin formation during CPB (see section 12B). In patients who have received aprotinin, ACT should be measured using kaolin as opposed to celite, because celite artifactually and erroneously increases ACT. Failure to achieve a satisfactory ACT may be due to inadequate heparin or to low concentrations of antithrombin. If a total of 500 U/kg of heparin fails to adequately prolong ACT, fresh frozen plasma (or recombinant antithrombin when available[233]) is needed to increase antithrombin concentrations to overcome "heparin resistance." Antithrombin is a necessary cofactor that binds circulating thrombin; heparin accelerates this reaction a thousandfold. See section 12B for management of patients with suspected or proven heparin-induced antiplatelet IgG antibodies and alternative anticoagulants to heparin.

During CPB, ACT or the Hepcon test is measured every 30 minutes. If ACT goes below the target level, more heparin is given. Usually one-third of the initial heparin bolus is given every hour even when the ACT is within the normal range. The Hepcon test titrates the heparin concentration and is more reproducible than ACT, but ACT provides satisfactory monitoring of anticoagulation. Although excessively high concentrations of heparin (ACT >1000 s) may cause remote bleeding away from operative sites, low concentrations increase circulating thrombin concentrations and risk clotting within the extracorporeal perfusion circuit.

One milligram of protamine (not to exceed 3 mg/kg) is given for each 100 units of heparin injected in the initial bolus dose. The heparin-protamine complex activates complement and often causes acute hypotension, which may be attenuated by adding calcium (2 mg/1 mg protamine). After a third of the planned protamine dose, blood must not be returned to the cardiotomy reservoir from the surgical field. Rarely, protamine may cause an anaphylactic reaction in patients with antibodies to protamine insulin.[234] Neutralization of heparin is usually confirmed by an ACT or Hepcon test and more protamine (50 mg) is given if either test remains prolonged and bleeding is a problem. Heparin rebound is the term used to describe a delayed heparin effect due to release of tissue heparin after protamine is cleared from the circulation. Although protamine is a mild anticoagulant, one or two supplemental 25- to 50-mg doses can be given empirically if heparin rebound is suspected. In most instances the heart-lung machine should be available for immediate use until the patient leaves the operating room.

Starting Cardiopulmonary Bypass

CPB is started at the surgeon's request with concurrence of the anesthesiologist and perfusionist. As venous return enters the machine, the perfusionist progressively increases arterial flow while monitoring the patient's blood pressure and volume levels in all reservoirs. Six observations are critical:

1. Is venous drainage adequate for the desired flow?
2. Is pressure in the arterial line acceptable?
3. Is arterial blood adequately oxygenated?

4. Is systemic arterial pressure acceptable?
5. Is systemic venous pressure acceptable?
6. Is the heart adequately decompressed?

Once full stable cardiopulmonary bypass is established for at least 2 minutes, lung ventilation is discontinued, perfusion cooling may begin, and the aorta may be clamped for arresting the heart.

Cardioplegia

Antegrade blood or crystalloid cardioplegia is administered directly into the aortic root at 60 to 100 mm Hg pressure proximal to the aortic cross-clamp by a dedicated cardioplegia roller pump (see Fig. 12-2). Blood entering the coronary sinus is captured by the right atrial or unsnared caval catheters; right ventricular distention is prevented. Usually the heart is cooled to a prespecified myocardial temperature range. The heart usually arrests within 30 to 60 seconds; delay indicates problems with delivery of the solution or unrecognized aortic regurgitation. Some surgeons monitor myocardial temperature or pH via direct needle sensors.[235]

The usual flow of retrograde cardioplegia is 200 to 400 mL/min at coronary sinus pressures between 30 and 50 mm Hg.[236] Higher pressures may injure the coronary venous system;[198] low pressures usually indicate inadequate delivery due to malposition of the catheter or leakage around the catheter cuff, but may indicate a tear in the coronary sinus.[199] Induction of electrical arrest is slower (2 to 4 minutes) than with antegrade, and retrograde cardioplegia may provide incomplete protection of the right ventricle.[196,237]

Key Determinants of Safe Perfusion

The following offers rational guidelines for management of CPB, which uses manipulation of temperature, hematocrit, pressure, and flow rate to adequately support cellular metabolism during nonphysiologic conditions.

Blood flow rate

Normally, basal cardiac output is determined by oxygen consumption, which is approximately 250 mL/min. It is impractical to measure oxygen consumption during cardiac surgery; therefore, the generally accepted flow rate at 35 to 37°C and hematocrit of 25% is approximately 2.4 L/min/m^2 in deeply anesthetized and muscle-relaxed patients. Hemodilution reduces blood oxygen content from approximately 20 mL/dL to 10 to 12 mL/dL; consequently flow rate must increase over resting normal cardiac output or oxygen demand must decrease. The resistance of venous catheters, turbulence, and loss of physiologic controls of the vasculature are reasons venous return and maximum pump flows are limited.

Hypothermia reduces oxygen consumption by a factor of 0.5 for every 10°C decrease in temperature. However, at both normothermia and hypothermia maximal oxygen consumption falls with decreasing flow as described in the following equation:

$$V_{O_2} = 0.44\,(Q - 62.7) + 71.6$$

This relationship at various temperatures is depicted in Fig. 12-7. For this reason Kirklin and Barrett-Boyes[238] recommend that flows be reduced only to levels that permit at least 85% of maximal oxygen consumption. At 30°C this

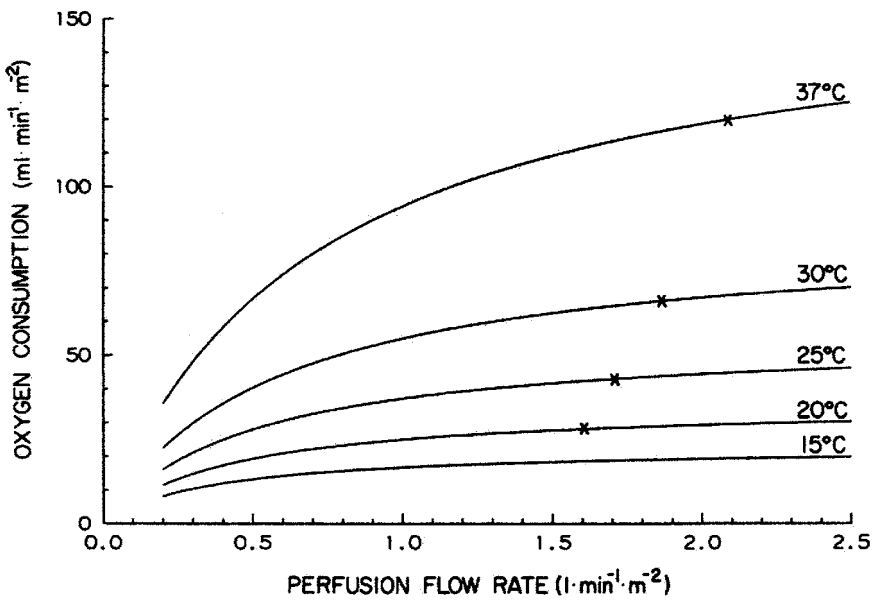

Figure 12-7. Nomogram relating oxygen consumption to perfusion flow rate and temperature. The small x's indicate clinical flow rates used by Kirklin and Barrett-Boyes. (*Reproduced with permission from Kirklin JW, Barrett-Boyes BG: Hypothermia, circulatory arrest, and cardiopulmonary bypass, in Kirklin JW, Barrett-Boyes BG [eds]: Cardiac Surgery, 2nd ed. New York, Churchill Livingstone, 1993; p 91.*)

flow rate is approximately 1.8 L/min/m^2; at 25°C, 1.6 L/min/m^2; and at 18°C, 1.0 L/min/m^2.

As long as mean arterial pressure remains above 50 to 60 mm Hg (i.e., above the autoregulatory range), cerebral blood flow is preserved even if systemic flow is less than normal. However, there is a hierarchical reduction of flow to other organs as total systemic flow is progressively reduced. First skeletal muscle flow falls, then abdominal viscera and bowel, and finally kidneys.

Pulsatile flow

Theoretical benefits of pulsatile blood flow include transmission of more energy to the microcirculation, which reduces critical capillary closing pressure, augments lymph flow, and improves tissue perfusion and cellular metabolism. Pulsatile flow theoretically also reduces vasocontrictive reflexes and neuroendocrine responses and may increase oxygen consumption, reduce acidosis, and improve organ perfusion. However, despite extensive investigation no one has convincingly demonstrated a benefit of pulsatile blood flow over nonpulsatile blood flow for short- or long-term CPB.[112,115,116,239–243] Two studies reported the association of pulsatile flow with lower rates of mortality, myocardial infarction, and low cardiac output syndrome,[244,245] but others failed to detect clinical benefits.[246–251]

Pulsatile CPB, which actually reproduces the normal pulse pressure within the body, is expensive, complicated, and requires a large-diameter aortic cannula. Higher nozzle velocities increase trauma to blood elements,[252] and pulsations may damage micromembrane oxygenators.[253] Thus for clinical CPB, nonpulsatile blood flow is an acceptable, nonphysiologic compromise with few disadvantages.

Arterial pressure

Systemic arterial blood pressure is a function of flow rate, blood viscosity (hematocrit), and vascular tone. Perfusion of the brain is normally protected by autoregulation, but autoregulation appears to be lost somewhere between 55 and 60 mm Hg during CPB at moderate hypothermia and a hematocrit of 24%.[133,254–256] Cerebral blood flow may still be adequate at lower arterial pressures,[257,258] but the only prospective randomized study found a lower combined major morbidity/mortality rate when mean arterial pressure was maintained near 70 mm Hg (average 69 $\pm$ 7) rather than below 60 (average 52 mm Hg).[259] In older patients, who may have vascular disease[260] and/or hypertension, mean arterial blood pressure is generally maintained between 70 and 80 mm Hg at 37°C. Higher pressures are undesirable because collateral blood flow to the heart and lungs increases blood in the operative field.

Hypotension during CPB may be due to low pump flow, aortic dissection, measurement error, or vasodilatation. Phenylephrine is most often used to elevate blood pressure, but arginine vasopressin (0.05 to 0.1 U/min) has recently been introduced. If anesthesia is adequate, hypertension can be treated with nitroprusside, an arterial dilator, or nitroglycerin, which predominately dilates veins and pulmonary vessels.

Hematocrit

The ideal hematocrit during CPB remains controversial because of competing advantages and disadvantages. Low hematocrits reduce blood viscosity and hemolysis, reduce oxygen-carrying capacity, and reduce the need for autologous blood transfusion. In general, viscosity remains stable when percent hematocrit and blood temperature (in degrees centigrade) are equal (i.e., viscosity is constant at hematocrit 37%, temperature 37°C, or at hematocrit 20%, temperature 20°C). Hypothermia reduces oxygen consumption and permits perfusion at 26 to 28°C with hematocrits between 18 and 22%, but at higher temperatures limits on pump flow may not satisfy oxygen demand.[261–263] Hill[264] and associates found that hematocrit during CPB did not affect either hospital mortality or neurologic outcome, but DeFoe and colleagues observed[265] increasing hospital mortality with hematocrits below 23% during CPB; thus the issue remains unresolved.[266] However, higher hematocrits (25 to 30%) during CPB appear justified[263] in view of the increasing safety of autologous blood transfusion, improved neurologic outcomes with higher hematocrits in infant cardiac surgery,[267] and more frequent operations near normothermia in older sicker patients.

Temperature

The ideal temperature for uncomplicated adult cardiac surgery is also an unsettled question.[263] Until recently nearly all operations reduced body temperature to 25 to 30°C during CPB to protect the brain, support hypothermic cardioplegia, permit perfusion at lower flows and hematocrits, and increase the safe duration of circulatory arrest in case of emergency. Hypothermia, however, interferes with enzyme and organ function, aggravates bleeding, increases systemic vascular resistance, delays cardiac recovery, lengthens duration of bypass, increases the risk of cerebral hyperthermia, and is associated with higher levels of depression and anxiety postoperatively.[268] Since the embolic risk of cerebral injury often is greater than perfusion risk, perfusion at higher temperatures (33 to 35°C), or "tepid" CPB, is recommended, in part because detrimental high blood temperatures are avoided during rewarming.[269] Increasingly, efforts are made to avoid cerebral hyperthermia during and after operation, and one study suggests improved neuropsychometric outcomes if patients are rewarmed to only 34°C.[270]

pH/P_{CO_2} management

There are two strategies for managing pH/P_{CO_2} during hypothermia: pH stat and alpha stat. During deep hypothermia and circulatory arrest (see below) there is increasing evidence that pH-stat management may produce better neurologic outcomes during pediatric cardiac surgery.[267] Alpha stat may be better in adults.[248,271,272] pH stat maintains temperature-corrected pH 7.40 at all temperatures and requires the addition of CO_2 as the patient is cooled. Alpha stat allows the pH to increase during cooling so that blood becomes alkalotic. Cerebral blood flow is higher, and pressure is passive and uncoupled from cerebral oxygen demand with pH

stat. With alpha stat, cerebral blood flow is lower, autoregulated, and coupled to cerebral oxygen demand.[273]

Arterial pao_2

Pao_2 should probably be kept above 150 mm Hg to assure complete arterial saturation. Whether or not high levels (i.e., >200 mm Hg) are detrimental has not been determined.

Glucose

Although Hill and associates[264] found no relationship between blood glucose concentrations during CPB and adverse neurologic outcome, others are concerned that hyperglycemia (>180 mg/dL) aggravates neurologic injury[230] and other morbidity/mortality.[274]

Patient Monitors

Systemic arterial pressure is typically monitored by radial, brachial, or femoral arterial catheter; central venous pressure is routinely monitored by a jugular venous catheter. Routine use of a Swan-Ganz pulmonary arterial catheter is controversial and not necessary for uncomplicated operations in low-risk patients.[275] During CPB the pulmonary artery catheter should be withdrawn into the main pulmonary artery to prevent lung perforation and suture ensnarement.

Transesophageal echocardiography

A comprehensive transesophageal echocardiography (TEE) examination[276] is an important monitor during most applications of CPB[277] to assess catheter and vent insertion and location;[196,278,279] severity of regional atherosclerosis;[43,44] myocardial injury, infarction, dilatation, contractility, thrombi, and residual air; undiagnosed anatomic abnormalities;[276] valve function after repair or replacement; diagnosis of dissection;[59,280] and adequacy of de-airing at the end of CPB.[281]

Temperature

Bladder or rectal temperature is usually used to estimate temperature of the main body mass, but does not reflect brain temperature.[282] Esophageal and pulmonary artery temperatures may be affected by local cooling associated with cardioplegia. The jugular venous bulb temperature is considered the best surrogate for brain temperature, but is difficult to obtain.[283] Nasopharyngeal or tympanic membrane temperatures are more commonly used, but tend to underestimate jugular venous bulb temperature during rewarming by 3 to 5°C.[284] During rewarming, arterial line temperature correlates best with jugular venous bulb temperature.[285]

Neurophysiologic monitoring

The efficacy of neurophysiologic monitoring during CPB is under investigation and not yet established as necessary. Techniques being investigated include jugular venous bulb temperature and saturation, transcranial Doppler ultrasound, near-infrared transcranial reflectance spectroscopy, and the raw or processed electroencephalogram.[286,287]

Adequacy of perfusion

During CPB oxygen consumption (Vo_2) equals pump flow rate times the difference in arterial (Cao_2) and venous oxygen content (Cvo_2). For a given temperature, maintaining Vo_2 at 85% predicted maximum during CPB assures adequate oxygen delivery (see Fig. 12-7).[238] Oxygen delivery (Do_2) equals pump flow times Cao_2 and should be above 250 mL/min/m^2 during normothermic perfusion.[261] Mixed venous oxygen saturation (Svo_2) assesses the relationship between Do_2 and Vo_2; values below 60% indicate inadequate oxygen delivery. Because of differences in regional vascular tone, higher Svo_2 does not assure adequate oxygen delivery to all vascular beds.[210,288] Metabolic acidosis (base deficit) or elevated lactic acid levels also indicate inadequate perfusion.

Urine output

Urine output is usually monitored but varies with renal perfusion, temperature, composition of the pump prime, diuretics, absent pulsatility, and hemoconcentration. Urine production is reassuring during CPB and oliguria requires investigation.

Gastric tonometry and mucosal flow

These Doppler and laser measurements gauge splanchnic perfusion but are rarely used clinically.

Stopping Cardiopulmonary Bypass

Prior to stopping CPB the patient is rewarmed to 34 to 36°C, the heart is defibrillated, and the lungs are re-expanded (40 cm H_2O pressure) and ventilated. Cardiac rhythm is monitored, and hematocrit, blood gases, acid-base status, and plasma electrolytes are reviewed. If the heart has been opened, TEE is recommended for detection and removal of trapped air before ejection begins. Caval catheters are adjusted to ensure unobstructed venous return to the heart. If inotropic drugs are anticipated, these are started at low flow rates. Vent catheters are removed, although sometimes an aortic root vent is placed on gentle suction to remove undiscovered air.

Once preparations are completed, the surgeon, anesthesiologist, and perfusionist begin to wean the patient off CPB. The perfusionist gradually occludes the venous line and simultaneously reduces pump input as cardiac rate and rhythm, arterial pressure and pulse, and central venous pressure are monitored and adjusted. Initially blood volume within the pump is kept constant, but as pump flow approaches zero, volume is added or removed from the patient to produce arterial and venous pressures within the physiologic ranges. During weaning, cardiac filling and contractility is often monitored by TEE, and intracardiac repairs and regional myocardial contractility are assessed. Pulse oximetry saturation near 100%, end-tidal CO_2 greater than 25 mm Hg, and mixed venous oxygen saturation higher than 65% confirm satisfactory ventilation and circulation. When cardiac performance is satisfactory and stable, all

catheters and cannulas are removed, protamine is given to reverse heparin, and blood return from the surgical field is discontinued.

Once the patient is hemodynamically stable, as determined by surgeon and anesthesiologist, and after starting wound closure, the perfusate may be returned to the patient in several ways. The entire perfusate may be washed and returned as packed cells. Excess fluid may be removed by a hemoconcentrator. More often the perfusate, which still contains heparin, is gradually pumped into the patient for hemoconcentration by the kidneys. Occasionally some of the perfusate must be bagged and given later. The heart-lung machine should not be completely disassembled until the chest is closed and the patient is ready for transfer.

SPECIAL TOPICS

Special Applications of Extracorporeal Perfusion

Reoperations, surgery of the descending thoracic aorta, and minimally invasive procedures may be facilitated by surgical incisions other than midline sternotomy. These alternative incisions often require alternative methods for connecting the patient to the heart-lung machine. Some alternative applications of CPB are presented below.

Right thoracotomy

Anterolateral incisions through the fourth or fifth interspaces provide easy access to the cavae and right atrium, adequate access to the ascending aorta, and no direct access to the left ventricle. Adequate exposure of the ascending aorta is available for cross-clamping, aortotomy, and administration of cardioplegia by retracting the right atrial appendage. De-airing the left ventricle (e.g., after mitral valve repair) is more difficult. External pads facilitate defibrillation.

Left thoracotomy

Lateral or posterolateral incisions in the left chest are used for a variety of operations. Venous return may be captured by cannulating the pulmonary artery via a stab wound in the right ventricle, or by retrograde cannulation of the left pulmonary artery or cannulation of the left iliac or femoral vein. With iliac or femoral cannulation, venous return is augmented by threading the cannula into the right atrium using TEE guidance.[289] The descending thoracic aorta or left subclavian, iliac, or femoral arteries are accessible for arterial cannulation.

Left heart bypass

Left heart bypass utilizes the beating right heart to pump blood through the lungs to provide gas exchange.[290] An oxygenator is not used and intake cannulation sites are exposed through a left thoracotomy. The left superior pulmonary vein–left atrial junction is an excellent cannulation site for capturing blood. The left atrial appendage can also be used, but is more friable and difficult. The apex of the left ventricle is infrequently used because of myocardial injury. The tip of the intake catheter must be free in the left atrium and careful technique is required to avoid air entry during cannulation and perfusion. The extracorporeal circuit typically consists only of tubing and a centrifugal pump and does not include a reservoir, heat exchanger, or bubble trap. This reduces the thrombin burden (see section 12B) and may permit reduced or no heparin, if anticoagulation poses an additional risk (e.g., in acute head injury). Otherwise, full heparin doses are recommended. The reduced perfusion circuit precludes the ability to add or sequester fluid, adjust temperature, or intercept systemic air emboli. Intravenous volume expanders may be needed to maintain adequate flows; temperature can usually be maintained without a heat exchanger.[291]

Full left heart bypass may be employed for left-sided coronary artery surgery by draining all of the pulmonary venous return out of the left atrium and leaving no blood for left ventricular ejection. If the heart fibrillates, blood can still passively pass through the right heart and lungs, but often an elevated central venous pressure is required.[292]

Partial left heart bypass is identical in configuration and cannulation to full left heart bypass and is used to facilitate surgery on the descending thoracic aorta. The patient's left ventricle supplies blood to the aorta proximal to aortic clamps, and the circuit supplies blood to the distal body. Typically about two-thirds normal basal cardiac output (i.e., 1.6 L/min/m^2) is pumped to the lower body. Arterial pressure is monitored proximal (radial or brachial) and distal (right femoral or pedal) to the aortic clamps. Blood volume in the body and circuit is assessed by central venous pressure and TEE monitoring of chamber dimensions. Management is more complicated because of the single venous circulation and separated arterial circulations.[290,293]

Partial cardiopulmonary bypass

Partial CPB with an oxygenator is also used to facilitate surgery of the descending thoracic aorta. After left thoracotomy, systemic venous and arterial cannulas are placed as described above. The perfusion circuit includes a reservoir, pump, oxygenator, heat exchanger, and bubble trap. The beating left ventricle supplies the upper body and heart, so lungs must be ventilated and upper body oxygen saturation should be independently monitored. Blood flow to the separate upper and lower circulations must be balanced as described for partial left heart bypass above.

Full cardiopulmonary bypass

Full CPB with peripheral cannulation is used when access to the chest is dangerous because of proximity of the heart, vital vessels (e.g., mammary arterial graft), or pathologic condition (e.g., ascending aortic mycotic aneurysm) abutting the anterior chest wall.[3] The patient is supine and a complete extracorporeal perfusion circuit is prepared and primed. Venous cannulas may be inserted into the right atrium via the iliac or femoral vessels and/or the right jugular vein. The iliac, femoral, or axillary-subclavian arteries may be used for arterial

cannulation. Initiation of CPB decompresses the heart, but cooling is usually deferred to keep the heart beating and decompressed until the surgeon can insert a vent catheter.

Femoral vein to femoral artery bypass

Femoral vein to femoral artery bypass with full CPB is used to initiate bypass outside the operating room for emergency circulatory assistance,[3] supportive angioplasty,[294] and intentional (aneurysm repair) or accidental hypothermia. Femoral vessel cannulation is occasionally used during other operations to facilitate control of bleeding (e.g., cranial aneurysm, tumor invading the inferior vena cava) or ensure oxygenation (e.g., lung transplantation or upper airway reconstruction).

Cannulation for minimally invasive (limited access) surgery

Off-pump coronary artery bypass describes construction of coronary arterial bypass grafts on the beating heart without CPB. Minimally invasive direct coronary artery bypass refers to coronary arterial bypass grafting with or without CPB through small, strategically placed incisions. Peripheral cannulation sites, described above, may be used, but often central cannulation of the aorta, atrium, or central veins is accomplished using specially designed or smaller cannulas placed through the operative incision or through separate small incisions in the chest wall.[295,296] Venous return may be augmented by applying negative pressure (see discussion of venous cannulation above); often soft-tipped arterial catheters are used to minimize arterial wall trauma.[27]

The Port-Access System provides a means for full CPB, cardioplegia administration, and aortic cross-clamping without exposing the heart and can be used for both valvular and coronary arterial operations.[70,279] Through the right internal jugular vein separate transcutaneous catheters are inserted into the coronary sinus for retrograde cardioplegia and the pulmonary artery for left heart venting. A multilumen catheter is inserted through the femoral artery and using TEE and/or fluoroscopy is positioned in the ascending aorta for arterial pump inflow, for balloon occlusion of the ascending aorta, and for administration of antegrade cardioplegia into the aortic root. Venous return is captured by a femoral venous catheter advanced into the right atrium. The system allows placement of small skin incisions directly over the parts of the heart that require surgical attention.

Minimally invasive surgery using CPB is associated with potential complications that include perforation of vessels or cardiac chambers, aortic dissection, incomplete de-airing, systemic air embolism, and failure of the balloon aortic clamp. Because CO_2 is heavier than air and more soluble in blood, the surgical field is sometimes flooded with CO_2 at 5- to 10-L/min flow to displace air when the heart is open. The balloon aortic clamp can leak, prolapse through the aortic valve, or move distally to occlude arch vessels. For safety the position of the occluding balloon is closely monitored by TEE, bilateral radial arterial pressures, and one of the following: transcranial Doppler ultrasound, cerebral near-infrared spectroscopy, or electroencephalogram.[296a]

Deep Hypothermic Circulatory Arrest

Deep hypothermic circulatory arrest (DHCA) is used for operations involving the aortic arch, porcelain aorta, thoracoabdominal aneurysms, pulmonary thromboendarterectomy, selected uncommon cardiovascular and neurologic procedures,[297,298] and certain complex congenital heart procedures. The technology involves reducing body temperature to less than 20°C, arresting the circulation for a short period, and then rewarming to 37°C. Deep hypothermia reduces cerebral oxygen consumption (Fig. 12-8), and attenuates release of toxic neurotransmitters and reactive oxidants during ischemia and reperfusion.[299]

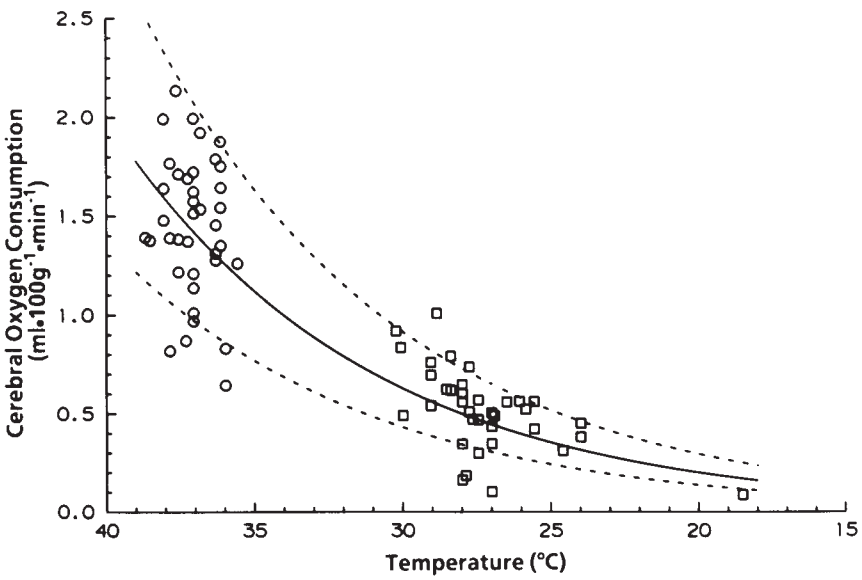

Figure 12-8. Relation between cerebral oxygen consumption and nasopharyngeal temperature during CPB at 2 L/min/m^2. (*Reproduced with permission from Kirklin JW, Barrett-Boyes BG: Hypothermia, circulatory arrest, and cardiopulmonary bypass, in Kirklin JW, Barrett-Boyes BG [eds]: Cardiac Surgery, 2d ed. New York, Churchill Livingstone, 1993; p 91.*)

Because perfusion cooling produces differential temperatures within both the body and brain,[282] more than one temperature is customarily monitored. Bladder, pulmonary artery, esophageal, or rectal temperatures are used to estimate body temperature. Nasopharyngeal and tympanic membrane temperatures are imperfect surrogates for mean brain temperature. Most surgical teams cool to either electroencephalographic silence, jugular venous saturation above 95%, or for at least 30 minutes before stopping circulation at nasopharyngeal or tympanic membrane temperatures below 20°C. Caloric exchange is proportional to body mass, rate of perfusion, and temperature differences between patient and perfusate; however, rates of perfusion cooling and rewarming are restricted (see the section on heat exchangers above). Perfusion cooling is usually supplemented by surface cooling using hypothermia blankets and/or packing the head in ice. Hyperthermia is avoided by keeping arterial inflow temperature below 37°C during rewarming.

Changes in temperature affect acid-base balance, which must be monitored and managed during deep hypothermia. The pH-stat protocol (CO_2 is added to maintain temperature-corrected blood pH at 7.4) may be preferred over the alpha-stat protocol, which allows cold blood to become alkalotic. Compared to alpha stat, pH stat increases the rate and uniformity of brain cooling,[300,301] slows the rate of brain oxygen consumption by 30 to 40% at 17°C,[301–303] and improves neurologic outcomes in animal models[267,304,305] and perhaps in infants,[306–308] but not necessarily in adults.[309] Hyperglycemia appears to increase brain injury and is avoided during deep hypothermia.[310] The value of high-dose corticosteroids or barbiturates remains unproven.

The safe duration of circulatory arrest during deep hypothermia is unknown. In adults arrest times as short as 25 minutes are associated with poor performance on neuropsychologic tests of fine motor function and memory.[311] Ergin and coworkers[312] found duration of arrest was a predictor of temporary neurologic dysfunction, which correlated with long-term neuropsychologic deficits.[313] At 18°C, cerebral metabolism and oxygen consumption are 17 to 40% of normothermia[314–316] and abnormal encephalographic patterns and cerebrovascular responses can be detected after 30 minutes of circulatory arrest.[314,317] Most investigators,[318–322] but not all[323] report increased mortality and adverse neurologic outcomes after 40 to 65 minutes of circulatory arrest. Most surgeons try to keep the period of arrest at less than 45 minutes, and if the operation allows, many perfuse for 10 to 15 minutes between serial arrest periods of 10 to 20 minutes.

Antegrade and Retrograde Cerebral Perfusion

Antegrade cerebral perfusion is used in lieu of DHCA or as a supplement. The cerebral vessels can be cannulated separately and perfused together by a single pump[324] or perfused collectively after a graft with a side branch is sewn to the top of the aortic arch from which the innominate, left carotid, and left subclavian arteries originate. Separate perfusion of separately cannulated vessels is rarely done. Perfusion is usually provided by a separate roller pump that receives blood from the arterial line. Line pressure is monitored and a microfilter may or may not be used. The cerebral vessels are collectively perfused with cold blood between 10 and 18°C and at approximate flows of 10 mL/kg/min; perfusion pressures are restricted to 30 to 70 mm Hg. At the present time each individual surgeon seems to have a preferred protocol between these broad ranges.[325–332] The adequacy of cerebral perfusion can be assessed by monitoring jugular venous saturation or near-infrared spectroscopy. Selective antegrade cerebral perfusion risks dislodging atheromatous emboli or causing air embolism, cerebral edema, or injury from excessive perfusion pressure.

Retrograde cerebral perfusion (RCP) was introduced in 1980 as emergency treatment for massive air embolism.[333] Ueda and associates introduced continuous RCP for cerebral protection as an adjunct to deep hypothermic circulatory arrest during aortic surgery.[334] During RCP and DHCA the superior vena cava is perfused at blood pressures usually between 25 and 40 mm Hg, temperatures between 8 and 18°C, and flows between 250 and 400 mL/min from a spur off the arterial line, which is clamped downstream to the spur. Some surgeons advocate much higher pressures and flows to compensate for runoff and have not shown detrimental effects.[335] A snare is usually placed around the superior caval catheter cephalad to the azygos vein to reduce runoff. The IVC may or may not be occluded.[322,336–339]

Retrograde cerebral perfusion has been widely and safely used,[321,335,339–347] but its effectiveness in protecting the brain is not clear.[322,328,348] The method can wash out some particulate emboli entering from arteries, which is a major cause of brain injury after aortic surgery.[337,349] However, it is not clear how adequately and completely all regions of the brain are perfused.[322,339,348,350] Lin and colleagues[342] found cortical flows to be only 10% of control values. RCP slows but does not arrest the decrease in cerebral oxygen saturation[324,335] and the decay in amplitude of somatosensory evoked potentials.[351] Others from clinical comparisons and animal studies believe RCP provides some cerebral protection over DHCA alone.[321,335,339,341,342,344,345,347,352] A few studies report that antegrade cerebral perfusion provides better protection than retrograde.[324,338,353]

Complications and Risk Management

Life-threatening incidents occur in 0.4 to 2.7% of operations with CPB and the incidence of serious injury or death is between 0.06 and 0.08% (Table 12-4).[94,151,354] Massive air embolism, aortic dissection, dislodgment of cannulas, and clotting within the circuit during perfusion are the principal causes of serious injury or death. Malfunctions of the heater-cooler, oxygenator, pumps, and electrical supply are the most common threatening incidents related to equipment. Other threatening incidents include premature takedown or clotting within the perfusion circuit. Complications related to

Table 12–4.

Adverse Incidents Involving Cardiopulmonary Bypass

	Incidence (events/1000)	Death or serious injury (%)*
Protamine reaction	1.3	10.5
Thrombosis during cardiopulmonary bypass	0.3–0.4	2.6–5.2
Aortic dissection	0.4–0.8	14.3–33.1
Dislodgment of cannula	0.2–1.6	4.2–7.1
Rupture of arterial connection	0.2–0.6	0–3.1
Gas embolism	0.2–1.3	0.2–8.7
Massive systemic gas embolism	0.03–0.07	50–52
Electrical power failure	0.2–1.8	0–0.6
Pump failure	0.4–0.9	0–3.5
Heater-cooler problems	0.5–3	0
Replace oxygenator during cardiopulmonary bypass	0.2–1.3	0–0.7
Other oxygenator problems	0.2–0.9	0
Urgent re-setup after takedown	2.9	13
Early unplanned cessation of cardiopulmonary bypass	0.2	0–0.7

**Percentage of incidents that resulted in death or serious injury. Data derived from references 94 and 151.*

connections to and from the heart-lung machine and perfusion during operation are described above with descriptions of the various components of the perfusion circuit.

Massive Air Embolism

The incidence of massive air embolism is between 0.003 and 0.007% with 50% of outcomes adverse.[94,151] Air can enter any component of the perfusion circuit at any time during operation if the integrity of the circuit is broken.[355] Stopcocks, connections, vent catheters, empty reservoirs, purse-string sutures, cardioplegia infusion catheters, and unremoved air in opened cardiac chambers are the most common sources of air emboli. Uncommon sources include oxygenator membrane leaks; residual air in the circuit after priming; reversal of flow in venous, vent, or arterial lines; and unexpected inspiration by the patient during cannula removal.

Massive air embolism during perfusion is a catastrophe and management guidelines are evolving.[20,333,355–358] Perfusion should stop immediately and clamps should be placed on both venous and arterial lines. Air in the circuit should be rapidly removed by recirculation and entrapment of all air in a reservoir or bubble trap. The patient should be immediately placed in steep Trendelenburg position and blood and air at the site of entry should be aspirated until no air is retrieved. TEE should be rapidly employed to search for air, but perfusion must resume promptly depending on body temperature to prevent ischemic brain damage. Cooling to deep hypothermia should be considered to protect the brain and other organs while air is located and removed. As soon as possible, retrograde perfusion of the brain should be undertaken while the aortic arch is simultaneously aspirated with the patient in steep Trendelenburg position. Corticosteroids and/or barbiturates may be considered. Depending upon circumstances and availability, hyperbaric oxygen therapy may be helpful if patients can be treated within 5 hours of operation.[357,359]

Risk management

Minimizing risks of extracorporeal perfusion requires strict attention to personnel training, preparation and training for emergencies, equipment function, and recordkeeping.[20] All members of the operative team must be trained, certified, and recertified in their respective roles and participate in continuing education programs. A policy manual for the perfusion team and written protocols should be developed

and continuously updated for various types of operations and emergencies. Emergency kits are prepared for out-of-operating-room crises. Adequate supplies are stocked in designated locations with sufficient inventory to support any operation or emergency for a specified period. An inventory of supplies is taken and recorded at regular intervals. Checklists are prepared and used for setting up the perfusion system and connecting to the patient. Equipment is inspected at regular intervals; worn, loose, or outdated parts are replaced; and preventive maintenance is provided and documented. New equipment is thoroughly checked before use and instructions are thoroughly digested by all user personnel. Safety alarms are optional; none replace the vigilance and attention of all OR personnel during an operation. Complete, signed written records are required for every perfusion; adverse events are recorded in a separate log and reviewed by the entire OR team. A continuous quality assurance program is desirable.[360]

During the procedure communication must be open between the surgeon, anesthetist, and perfusionist to coordinate activities. Statements are verbally acknowledged. Distractive conversations are discouraged. The entire OR team is committed to a zero-error policy, which can only be achieved by discipline and attention to details.[354,361,362]

The Response of Humoral and Cellular Elements of Blood to Extracorporeal Circulation

Within the body the endothelial cell, the only surface in contact with circulating blood, simultaneously maintains the fluidity of blood and the integrity of the vascular system. This remarkable cell maintains a dynamic equilibrium by producing anticoagulants to maintain blood in a fluid state and by generating procoagulant substances to enhance gel formation when perturbed. Blood proteins circulate as inert zymogens, which convert to active enzymes when stimulated. Likewise, blood cells remain quiescent until activated to express surface receptors and release proteins and enzymes involved in coagulation and inflammation. The continuous exposure of heparinized blood to the perfusion circuit and to cell tissues and fluid constituents of the wound during clinical cardiac surgery produces an intense thrombotic stimulus that involves both the tissue factor pathway (extrinsic coagulation pathway) in the wound and the contact and intrinsic coagulation pathways in the perfusion circuit. Thrombin is continuously generated and circulated despite massive doses of heparin in all applications of extracorporeal perfusion.[365–369] This powerful enzyme along with tissue factor from the wound and many other cytokines also activate an inflammatory reaction which can damage tissues and ultimately produce cell death by necrosis or apoptosis.

THROMBOSIS AND BLEEDING

Initial Reactions in the Perfusion Circuit

When heparinized blood contacts any biomaterial, plasma proteins are instantly adsorbed (<1 s) onto the surface to form a *monolayer* of selected proteins.[370–372] For each protein the amount adsorbed depends on its bulk concentration in plasma and the *intrinsic surface activity* of the biomaterial. Different biomaterials have different intrinsic surface activities for each plasma protein. The physical and chemical composition of the *biomaterial surface* determine the intrinsic surface activity of the biomaterial, but intrinsic surface activity is not predictable from knowledge of chemical and physical characteristics. Thus intrinsic surface activity differs among biomaterial surfaces, among plasma proteins, and among different bulk concentrations of plasma proteins. Concentrations of plasma proteins on a given biomaterial differ from concentrations in bulk plasma. Similarly, concentrations of surface-adsorbed proteins from the same plasma differ on different biomaterials. The composition of the protein monolayer is specific for the biomaterial and for various concentrations of proteins in the plasma, but the topography of the adsorbed protein layer may not be uniform across the surface of the biomaterial.[373] Thus it is not possible to predict the "thrombogenicity" of any biomaterial except by trial and error.

On most biomaterial surfaces fibrinogen is selectively adsorbed, but the adsorbed concentration of fibrinogen and other proteins may change over time.[372] Surface-adsorbed proteins "compete" for space on the biomaterial surface, but are tightly packed, irreversibly bound, and immobile. The density of surface-adsorbed proteins is 100 to 1000 times greater than the density of proteins in bulk plasma.[373] The complexity of blood-biomaterial interactions is further compounded by the fact that adsorbed proteins often undergo limited conformational changes[374,375] that may expose "receptor" amino acid sequences that are recognized by specific blood cells or bulk plasma proteins. Conformational changes of adsorbed

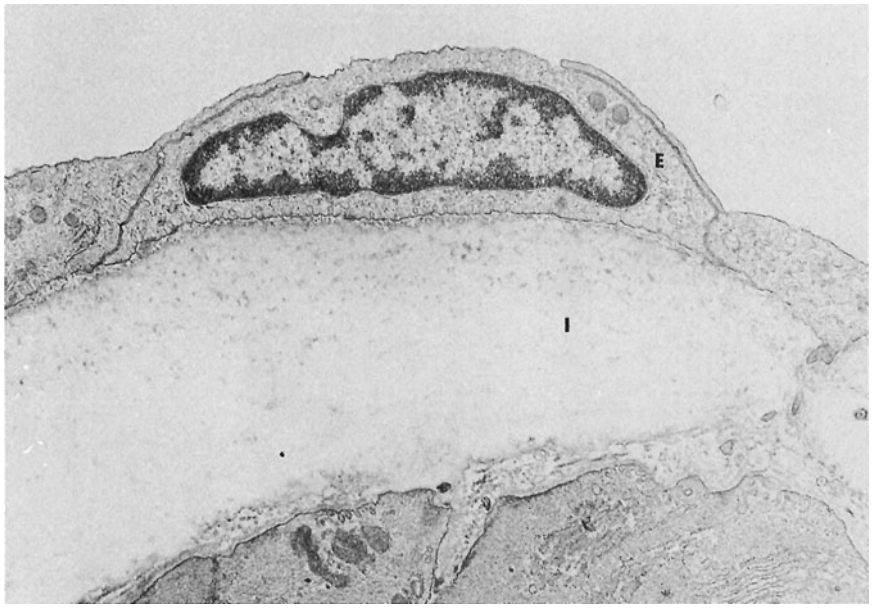

Figure 12-9. Electron micrograph of a rabbit endothelial cell (E), the only known nonthrombogenic surface. Note the overlapping junctions with neighboring endothelial cells. Endothelial cells rest on the internal elastic lamina (I), which abut medial smooth muscle cells. The vessel lumen is at the top. (*Reproduced with permission from Stemerman MB: Anatomy of the blood vessel wall, in Colman RW, Hirsh J, Marder VJ, Salzman E [eds]: Hemostasis and Thrombosis: Basic Principles and Clinical Practice, 2nd ed. Philadelphia, JB Lippincott, 1987; p 775.*)

factor XII and fibrinogen initiate activation of the contact pathway and platelet surface adhesion, respectively; similar changes in complement protein 3 participate in activation of the complement system.[375] For a given adsorbed protein these conformational changes may vary between biomaterial surfaces and in turn vary the reactivity of the adsorbed protein with cells and blood proteins in the bulk phase.

Thus heparinized blood does not directly contact biomaterial surfaces in extracorporeal perfusion circuits, but contacts monolayers of densely packed, immobile plasma proteins arranged in undefined mosaics that differ between locations and possibly across time. All biomaterial surfaces, including heparin-coated surfaces, are *procoagulant*;[367,376] only the endothelial cell is truly nonthrombogenic (Fig. 12-9).

ANTICOAGULATION

Extracorporeal perfusion and CPB are not possible without anticoagulation; the large procoagulant surface quickly overwhelms natural circulating anticoagulants—antithrombin, proteins C and S, tissue factor pathway inhibitor, and plasmin—to produce thrombin and thrombosis within the circuit. Thrombin is produced in extracorporeal perfusion systems with small surface areas and high-velocity flow,[368,377,378] but thrombosis may not be apparent if other procoagulants (e.g., addition of blood from wounds) are absent. Generation of thrombin varies widely between applications of extracorporeal technology (see below), but this powerful and potentially dangerous enzyme is produced whenever blood contacts a nonendothelial cell surface (Fig. 12-10).

During CPB and open heart surgery high concentrations of heparin (3 to 4 mg/kg, initial dose) are needed to maintain the fluidity of blood. Heparin has both advantages and disadvantages; the most notable advantages are parenteral use, immediate onset of action, and rapid reversal by protamine or recombinant platelet factor 4.[379] Heparin does not directly inhibit coagulation, but acts by accelerating the actions of the natural protease, antithrombin.[380] Heparin-catalyzed antithrombin, however, does not inhibit thrombin bound to fibrin[381] or factor Xa bound to platelets within clots;[382] thus heparin only partially inhibits thrombin in vivo. Antithrombin primarily binds thrombin; its action on factors Xa and IXa is much slower. Heparin inhibits coagulation at the end of the cascade after nearly all other coagulation proteins have been converted to active enzymes. In addition, heparin to varying degrees activates several blood constituents: platelets,[383–385] factor XII,[386] complement, neutrophils, and monocytes.[387–389] Heparin increases the sensitivity of platelets to soluble agonists,[385] inhibits binding to

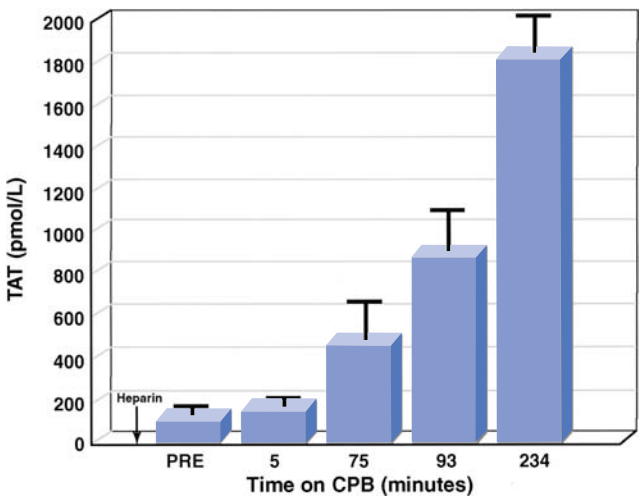

Figure 12-10. Plasma thrombin-antithrombin (TAT) measurements of thrombin generation during CPB and clinical cardiac surgery of varying duration. (*Data from Brister et al.*[366])

von Willebrand factor,[390] and modestly increases template bleeding times.[384] Thrombin concentrations cannot be measured in real time and only insensitive, indirect methods are available to regulate heparin anticoagulation in the operating room.[391–393]

Heparin is also associated with some clinical idiosyncrasies. In some patients recent, prolonged parenteral heparin may reduce antithrombin concentrations and produce *heparin resistance.*[380,394,395] Insufficient antithrombin may also occur due to insufficient synthesis or increased consumption in some cyanotic infants, premature babies, cachectic patients, and patients with advanced liver or renal disease. The deficiency in antithrombin prevents heparin from prolonging activated clotting times to therapeutic levels. In these patients fresh frozen plasma is needed to increase plasma antithrombin concentrations to inhibit thrombin. *Heparin rebound* is a delayed anticoagulant effect after protamine neutralization due to the rapid metabolism of protamine and delayed seepage of heparin into the circulation from lymphatic tissues and other deposits. Heparin is also associated with an allergic response in some patients that produces heparin-induced thrombocytopenia (HIT) with or without thrombosis (see below). Lastly, heparin only partially suppresses thrombin formation during CPB and all applications of extracorporeal perfusion and mechanical circulatory and respiratory assistance despite doses two to three times those used for other indications (see Fig. 12-10).[365–368] Thus heparin is far from an ideal anticoagulant.

Potential alternatives for heparin during extracorporeal perfusion (ECP) include low-molecular-weight heparin, danaparoid (Organan), recombinant hirudin (Lepirudin), and the organic chemical argatroban (Texas Biotechnology Corp., Houston, Texas). All have important drawbacks and are approved for use in HIT and in patients with circulating IgG anti-heparin-PF4 complex antibodies (see below). Low-molecular-weight heparins have long half-lives in plasma (4 to 8 hours), require antithrombin as a cofactor, primarily inhibit factor Xa, and are not reversible by protamine.[396,397] Although less antigenic than standard heparin, low-molecular-weight heparins can stimulate production of IgG anti-heparin-PF4 complex antibodies.[397] Danaparoid is a mixture of heparin sulfate, dermatan sulfate, and chrondroitin sulfate that catalyzes antithrombin to inhibit thrombin and factor Xa. To a lesser extent, danaparoid also catalyzes inhibition of thrombin by heparin cofactor II. The anticoagulant effect is long lasting (plasma half-life 4.3 hours)[398] and is not reversed by protamine.

Recombinant hirudin (Lepirudin) is a direct inhibitor of thrombin, is effective rapidly, does not have an effective antidote, is monitored by the partial thromboplastin time, is cleared by the kidney, and has a relatively short half-life in plasma (40 minutes).[399] This drug has been successfully used during CPB and open heart surgery, but in many instances bleeding after bypass has been troublesome and substantial. A newer drug is a semisynthetic bivalent thrombin inhibitor composed of 12 amino acids from hirudin, which binds to exosite 1 of thrombin linked to an active site-directed moiety, D Phe Pro Arg Pro, by four glycines.[400] This drug, bivalirudin (Angiomax), has a shorter half-life than hirudin and therefore may be safer. In addition, only a small amount is excreted by the kidney. In coronary angioplasty, bivalirudin was as effective as heparin but there was less bleeding. Argatroban is also a direct thrombin inhibitor[401] with rapid onset of action and short plasma half-life (40 to 50 minutes).[402] Argatroban is metabolized in the liver and is without an antidote, but can be monitored with partial thromboplastin times or activated clotting times. At present there is little clinical experience with argatroban or bivalirudin in cardiac surgical patients.

HEPARIN-ASSOCIATED THROMBOCYTOPENIA, HEPARIN-INDUCED THROMBOCYTOPENIA, AND HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS

Heparin-associated thrombocytopenia is a benign, nonimmune, 5 to 15% decrease in platelet count that occurs within a few hours to 3 days after heparin exposure. The etiology is due to mild platelet stimulation from multifactorial causes; bleeding does not occur; and the condition is clinically inconsequential.[403]

Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT) are different manifestations of the same immune disease. Heparin binds to platelets in the absence of an antibody and releases small amounts of platelet factor 4 (as occurs in heparin-associated thrombocytopenia). PF4 avidly binds heparin to form a heparin-PF4 (H-PF4) complex, which is antigenic in some people. In these individuals IgG antibodies to the H-PF4 complex are produced within 5 to 15 days after exposure to heparin and continue to circulate in the absence of more heparin for approximately 3 to 6 months.[404] IgG-anti-H-PF4 antibodies plus H-PF4 complexes form *HIT complexes,* which unite IgG Fc terminals to platelet Fc receptors (Fig. 12-11). This binding strongly stimulates platelets to release more PF4.[405] A self-perpetuating, accelerating cascade of platelet activation, release, and aggregation ensues. Since platelet granules contain several procoagulatory proteins (e.g., thrombin, fibronectin, factor V, fibrinogen, and von Willebrand factor), release also activates coagulation proteins to generate thrombin.

The intensity of the immune reaction varies between patients, but also varies by the indications for heparin use. Both heparin and PF4 must be available to form the antigenic H-PF4 complex. Patients who do not have conditions that activate platelets have a low incidence of HIT following administration of heparin, because few PF4 molecules are available to form H-PF4 complexes. In medical patients the incidence of thrombocytopenia after heparin is about 0.5%, the incidence of HITT is approximately 0.25%, and only 3% have IgG anti-H-PF4 antibodies by enzyme immunoassay.[406] Large doses of heparin are given and huge numbers of

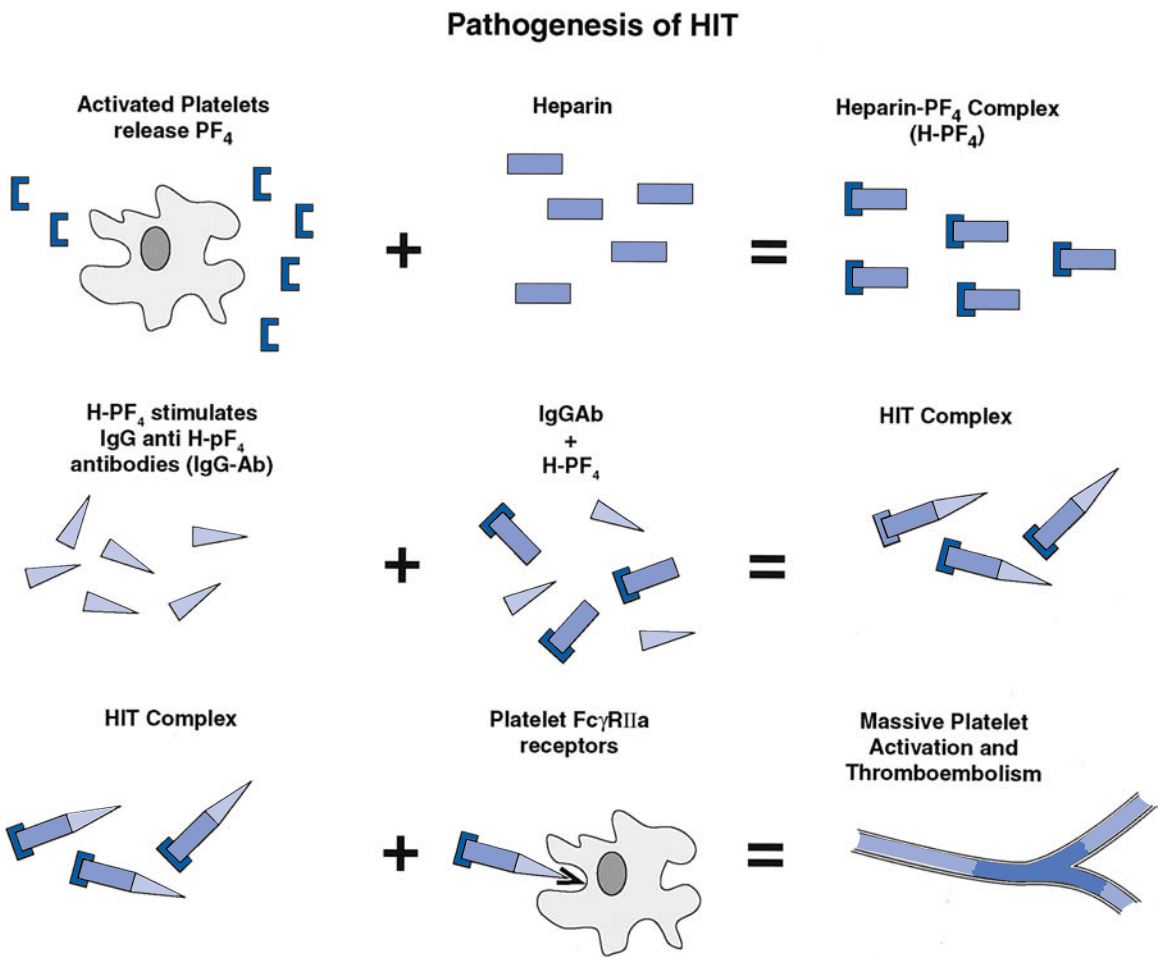

Figure 12-11. The generation of HIT complexes. Read each horizontal group of three left to right beginning at top left. See text for full explanation.

platelets are activated during CPB. Thus after CPB, 50% of patients have IgG anti-H-PF4 antibodies, 2% have immune heparin-induced thrombocytopenia, and approximately 1% develop HITT.[406] A combination of three ingredients is necessary to produce HIT or HITT: heparin, platelet factor 4, and IgG anti-H-PF4 antibodies. Since IgG antibodies are transient, a second heparin exposure 6 months after HIT is not likely to produce HIT or HITT,[404] but will stimulate production of new IgG antibodies to the H-PF4 complex. The danger is a second heparin exposure when IgG anti-H-PF4 antibodies are still circulating.

IgG anti-H-PF4 antibodies are detected in two ways. The serotonin release test detects the release of radioactive serotonin from normal platelets washed by the patient's serum.[407] An enzyme immunoassay measures IgG anti-H-PF4 antibodies directly. Both assays are equally sensitive in patients with clinical HIT, but the enzyme immunoassay is more sensitive in detecting IgG anti-H-PF4 antibodies in patients without other evidence of the disease.[407]

The clinical presentation of HIT may be insidious. If the platelet count was originally normal, the earliest sign is an abrupt decrease of at least 50% in platelet count (to less than 150,000/μL) in a patient who has had exposure to heparin within the past 5 to 15 days.[404] This event is a preoperative stop sign for elective cardiac operations. After CPB, platelet counts below 80,000/μL should trigger an order to stop all heparin, including heparin flushes, and to obtain daily platelet counts. The patient should be thoroughly examined for deep vein thrombosis, extremity ischemia, stroke, myocardial infarction, or any evidence of intravascular thrombosis using ultrasound and appropriate radiographic technology. Any evidence of vascular thrombosis should prompt a plasma sample for IgG anti-H-PF4 antibodies. A positive antibody test confirms the diagnosis of HIT in patients with thrombocytopenia and HITT in those with either venous or arterial thrombosis or both. It is important to stress that HIT or HITT is a clinical diagnosis and that a positive antibody test is not required before stopping heparin.

Once the diagnosis of HIT or HITT is suspected, management must focus on prevention of further intravascular thrombosis. Bleeding is rarely the problem; intravascular

thrombosis is. Neither heparin nor platelet transfusions should be given; platelet transfusions only add more PF4 if heparin and IgG anti-H-PF4 antibodies are still circulating. If heparin is proven absent from the circulation, platelet transfusions may be used very cautiously if the patient has significant nonsurgical bleeding. Surgical measures to reopen thrombosed large arteries are usually futile because the platelet-rich thrombus (white clot) often extends into small arteries and arterioles. An inferior vena cava filter is recommended if pulmonary embolism is likely or has occurred.

Modern management also includes full anticoagulation with recombinant hirudin (Lepirudin), argatroban, or possibly bivalirudin to prevent further extension of thrombosis or development of clinical intravascular thrombosis. This may occur in 40 to 50% of patients with HIT who are treated only with heparin cessation.[408] At present there is little experience with argatroban in cardiac surgical patients with HITT, but the drug is a direct thrombin inhibitor, has attractive pharmacokinetics, and is approved for patients with HITT. Full anticoagulation with hirudin in fresh postoperative cardiac surgical patients is recommended, but the safety zone between bleeding and thrombosis is narrow. The patient must be carefully monitored for pericardial tamponade and signs of hidden bleeding. Hirudin is monitored by activated partial thromboplastin time and the range used is similar to that with intravenous heparin. The effective blood concentration of hirudin for thrombin inhibition is 0.5 to 1.5 μg/mL.[409] To achieve this, 0.2-mg/kg/h infusions are recommended.[409] Dose must be reduced in patients with renal failure because the kidney clears the drug. Argatroban is sometimes a better choice, but it should be remembered that it is difficult to manage in the presence of liver disease since it is metabolized in that organ. In most patients oral anticoagulation with warfarin is started at the same time as intravenous hirudin, but warfarin should not be started prior to hirudin.

Emergency or urgent open heart surgery with CPB using hirudin is possible in patients with circulating IgG anti-HPF4 antibodies. The therapeutic level of drug should be between 3.5 and 4.5 μg/mL during CPB.[409] Greinacher recommends bolus doses of 0.25 mg/kg IV and 0.2 mg/kg in the priming volume followed by an infusion of 0.5 mg/min until 15 minutes before stopping CPB.[409] At that time 5 mg of hirudin is added to the perfusate to prevent clotting within the heart-lung machine.

Patients who require elective cardiac surgery are best deferred until circulating IgG anti-H-PF4 antibodies are absent by enzyme immunoassay. Patients with a history of HIT who require elective cardiac surgery with CPB should have IgG anti-H-PF4 antibodies measured in their serum before surgery is scheduled. If antibodies are absent, elective surgery can be safely carried out using heparin anticoagulation, *if the first re-exposure to heparin is the bolus dose given just before starting CPB.* Since HIT requires the presence of the H-PF4 complex plus IgG anti-H-PF4 antibodies to form the HIT complex, and since it takes about 5 days to produce these antibodies, HIT or HITT will not occur if no further heparin is given after operation.

COAGULATION AND EXTRACORPOREAL PERFUSION THROMBIN GENERATION

Generation of thrombin during cardiopulmonary bypass and other applications of extracorporeal circulatory technology is the cause of the thrombotic and bleeding complications associated with ECP. Theoretically, if thrombin formation could be completely inhibited during ECP, the consumptive coagulopathy, which consumes coagulation proteins and platelets and causes bleeding complications, would not occur.

Thrombin generation and the fibrinolytic response primarily involve the extrinsic and intrinsic coagulation pathways, the contact and fibrinolytic plasma protein systems, and platelets, monocytes, and endothelial cells.

Contact System

The contact system includes four primary plasma proteins—factor XII, prekallikrein, high-molecular-weight kininogen, and C-1 inhibitor[410]—and is activated during CPB and clinical cardiac surgery.[411] This system is involved in complement and neutrophil activation and the inflammatory response to ECP, but is not involved in thrombin formation in vivo. However, when blood contacts a negatively charged surface (protein surfaces contain both positive and negative charges) in ECP, small amounts of factor XII are adsorbed and undergo a conformational change to factor XIIa.[373,412] Factor XIIa in the presence of high-molecular-weight kininogen activates factor XI and initiates the intrinsic coagulation pathway (Fig. 12-12). Thrombin also activates factor XI, and is the predominating agonist in vivo in pathologic states.[413]

Intrinsic Coagulation Pathway

The intrinsic coagulation pathway probably does not generate thrombin in vivo, but does initiate thrombin formation when blood contacts nonendothelial cell surfaces such as perfusion circuits.[414,415] Factor XIa, produced by activation of the contact system and subsequently thrombin generation, activates factor IX, which forms part of the intrinsic tenase complex.[416,417] Factor XI is primarily activated by thrombin (see Fig. 12-12).

Extrinsic (Tissue Factor) Coagulation Pathway

The extrinsic coagulation pathway is the major coagulation pathway in vivo and is a major source of thrombin generation during CPB and clinical cardiac surgery.[418,419] Exposure of blood to tissue factor by direct contact in the wound or by wound blood aspirated into the ECP circuit

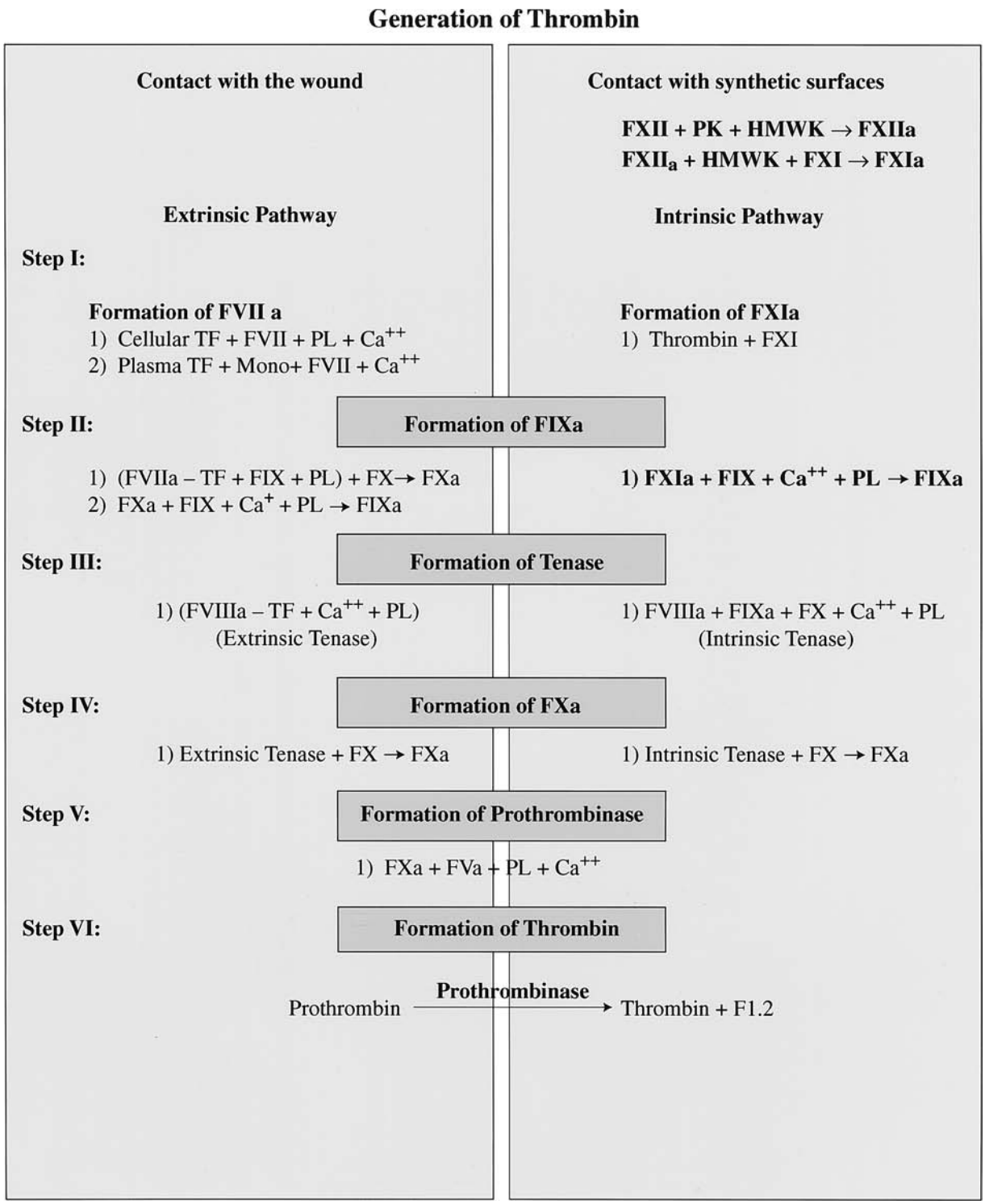

Figure 12-12. Steps in the generation of thrombin in the wound and in the perfusion circuit via the extrinsic, intrinsic, and common coagulation pathways. Ca^{++} = calcium ion; HMWK = high-molecular-weight kininogen; mono = monocyte; PK = prekallikrein; PL = cellular phospholipid surface; TF = tissue factor. Activated coagulation proteins are indicated by the suffix "a."

initiates the extrinsic coagulation pathway.[417] Tissue factor (TF) is a cell-bound glycoprotein that is constitutively expressed on the cellular surfaces of fat, muscle, bone, epicardium, adventitia, injured endothelial cells, and many other cells except pericardium.[419–421] Plasma TF associated with wound monocytes is a second source of TF and may be an important source during CPB and clinical cardiac surgery.[422] Tissue factor is the cofactor for the activation of factor VII to factor VIIa, which is part of extrinsic tenase (see Fig. 12-12).

Tenase Complexes

Intrinsic and extrinsic tenase catalyze the activation of factor X to factor Xa (see Fig. 12-12). Extrinsic tenase is formed by the combination of tissue factor, factor VIIa, calcium, and a phospholipid surface to cleave a small peptide from factor X to form factor Xa.[417] Extrinsic tenase also generates small amounts of factor IXa,[423] which greatly accelerates formation of intrinsic tenase and is the major pathway for the formation of factor Xa. Intrinsic tenase is produced by the combination of factor IXa, factor VIIIa, and calcium on the surface of an activated platelet,[424] and catalyzes production of factor Xa 50 times faster than extrinsic tenase.[417] Factor Xa activates factors V and VII in feedback loops.

Common Coagulation Pathway

Factor Xa is the gateway protein of the common coagulation pathway. Factor Xa slowly cleaves prothrombin to alpha-thrombin, the active enzyme, and a fragment, F1.2, but the reaction is 300,000 times faster if catalyzed by the *prothrombinase complex.*[417] The prothrombinase complex is produced when factor Xa, in the presence of Ca^{2+}, is anchored by factor Va onto a phospholipid surface provided by platelets, monocytes, or endothelial cells.[417] Either factor Xa or thrombin activates factor V to factor Va. The prothrombinase complex cleaves prothrombin to alpha-thrombin and a fragment, F1.2, and is the major pathway producing thrombin.[417] F1.2 is a useful marker of the reaction.

Thrombin

Thrombin is a powerful enzyme that accelerates its own formation by several feedback loops.[425] Thrombin is the major activator of factor XI and the exclusive activator of factor VIII in the intrinsic pathway. Thrombin is a secondary activator of factor VII, but once formed may be the most important activator in the wound. Lastly, thrombin is the primary activator of factor V in the formation of the prothrombinase complex (see Fig. 12-12).

Thrombin has both procoagulant and anticoagulant properties.[425] Thrombin is the enzyme that cleaves fibrinogen to fibrin and in the process creates two fragments, fibrinopeptides A and B. Thrombin activates platelets via the platelet thrombin receptor and thus may be the major agonist for platelets both in the wound and in the perfusion circuit. Thrombin also activates factor XIII to cross-link fibrin to an insoluble form and to attenuate fibrinolysis. Lastly, thrombin activates thrombin-activated fibrinolysis inhibitor, which alters fibrin to reduce lysis.[425]

Thrombin also stimulates the production of anticoagulants. Surface glycosaminoglycans, such as heparan sulfate, inhibit thrombin and coagulation via antithrombin. Thrombin stimulates endothelial cells to produce tissue plasminogen activator (t-PA), which is the major enzyme that cleaves plasminogen to plasmin. Thrombin also stimulates the production of nitric oxide and prostaglandin by endothelial cells. Thrombin in the presence of thrombomodulin activates protein C, which in the presence of protein S destroys activated factor V and VIII.

Thrombin Generation during Extracorporeal Perfusion

All applications of extracorporeal perfusion and exposure of blood to nonendothelial cell surfaces generate thrombin.[365–367] F1.2 is a protein fragment that is formed when prothrombin is cleaved to thrombin; thus F1.2 is a measure of thrombin generation but not of thrombin activity. F1.2 and thrombin-antithrombin complex increase progressively during clinical cardiac surgery with CPB, during applications of circulatory assist devices,[368,379] and during extracorporeal life support (see Fig. 12-10). The amount of thrombin produced seems to vary with the intensity of the stimuli for thrombin production and may vary with age, comorbid disease, and clinical health of the patient. The cytokines interleukin-1-beta (IL-1-beta) and tumor necrosis factor-alpha (TNF-alpha) are procoagulant and inhibit the thrombomodulin/protein C anticoagulant pathway and stimulate production of type I plasminogen activator inhibitor.[426] Complex cardiac surgery that requires several hours of CPB produces more F1.2[366] than short procedures with minimal exposure of circulating blood to the wound.[427] Thrombin generation varies with the amount and type of anticoagulant used; surface area of the blood-biomaterial interface; duration of exposure to the surface; turbulence, stagnation, and cavitation within perfusion circuits; and to a lesser degree temperature and the "thromboresistant" characteristics of biomaterial surfaces.[428] Very high concentrations of heparin, sufficient to increase spontaneous bleeding, reduce F1.2 production, probably by interfering with thrombin-activated feedback loops,[429] since heparin does not directly inhibit thrombin formation.

For many years blood contact with the biomaterials of the perfusion circuit was thought to be the major stimulus to thrombin formation during CPB and open heart surgery. Increasing evidence indicates that the wound is the major source of thrombin generation during CPB and clinical cardiac surgery.[430–431] This understanding has encouraged development of strategies to reduce the amounts of circulating thrombin during clinical cardiac surgery by either discarding wound blood[432] or by exclusively salvaging red cells by centrifugation and washing in a cell saver. The reduced thrombin formation in the perfusion circuit has also supported misguided strategies for reducing the systemic heparin dose during first-time coronary revascularization procedures using heparin-bonded circuits.[427] While there is no good evidence that heparin-bonded circuits reduce thrombin generation,[367] there is strong evidence that discarding wound plasma or limiting exposure of circulating blood to the wound (e.g., less bleeding in the wound) does reduce the circulating thrombin burden.[376,432]

CELLULAR PROCOAGULANTS AND ANTICOAGULANTS

Platelets

Platelets are activated by thrombin, contact with the surface of nonendothelial cells, heparin, and platelet-activating factor produced by a variety of cells during all applications of extracorporeal perfusion and/or recirculation of anticoagulated blood that has been exposed to a wound. Circulating thrombin and platelet contact with surface-adsorbed fibrinogen in the perfusion circuit are probably the earliest and strongest agonists. Circulating thrombin, although rapidly inhibited by antithrombin, is a powerful agonist and binds avidly to two specific thrombin receptors on platelets: PAR-1 and GPIb-alpha.[433] As CPB continues, C5a, C5b-9,[434,435] plasmin,[436] hypothermia,[437] platelet-activating factor (PAF), interleukin-6,[438] cathepsin G, serotonin, epinephrine, eicosanoids, and other agonists also activate platelets and contribute to their loss and dysfunction.

The initial platelet reaction to agonists is shape change. Circulating discoid platelets extend pseudopods, centralize granules, express glycoprotein Ib (GPIb) and GPIIb/IIIa receptors,[439] and secrete soluble and bound P selectin receptors from alpha granules.[440] GPIIb/IIIa ($alpha_{IIb}beta3$) receptors almost instantaneously bind platelets to exposed binding sites on the alpha- and gamma-chains on surface-adsorbed fibrinogen (Fig. 12-13).[441] The number of adherent platelets is proportional to the amount of surface-adsorbed fibrinogen recognized by fibrinogen antibody,[442] but the density of adherent platelets also varies with the chemical and physical composition of the surface biomaterial.[443,444] Rough surfaces accumulate more platelets than smooth surfaces.[445] Fewer platelets adhere to polyurethane, cuprophane, and PMEA (poly-2-methoxyethylacrylate) than to silicone rubber.[374,428] Platelet adhesion and aggregate formation reduce the circulating platelet count, which is already reduced by dilution with pump priming solutions.

Plasma fibrinogen forms bridges between platelets expressing GPIIb/IIIa receptors to produce circulating platelet aggregates. Platelet bound P-selectin binds platelets to monocytes and neutrophils to form aggregates.[446] During ECP some adherent platelets detach, leaving membrane fragments behind,[447] to produce platelet microparticles and partially fragmented platelets.[448,449] Some of these platelet membrane fragments also detach and circulate.[448,449]

A small percentage of activated platelets synthesize and release a variety of chemicals and proteins from granules that include thromboxane A_2,[450] platelet factor 4, beta-thromboglobulin,[451] P-selectin, and serotonin. Platelet lysosomes release neutral proteases and acid hydrolases.[452]

During ECP the circulating platelet pool is reduced by dilution, adhesion, aggregation, destruction, and consumption. The platelet mass consists of a reduced number of morphologically normal platelets, platelets with pseudopod formation, new and larger platelets released from megakaryocytes,[453] partially and completely degranulated platelets, platelet membrane fragments, platelet microparticles, and resealed platelets that have lost some of their membrane receptors.[446,447,452,453] Most of the circulating platelets appear structurally normal,[453] but bleeding times increase and remain prolonged for several hours after protamine.[454] The functional state of the circulating intact platelet during and early after CPB is reduced, but it is not clear whether this functional defect is intrinsic or extrinsic to the platelet. Flow cytometry studies of circulating intact platelets show little change in platelet membrane receptors.[455] In prolonged applications of ECP, platelets are consumed and may or may not be adequately replaced by new platelets from the bone marrow.[456]

Monocytes

During CPB and clinical cardiac surgery the concentration of plasma tissue factor, which normally is 0.26 to 1.1 pM,[422,457] doubles to 2.0 pM.[432] During cardiac surgery wound plasma contains 6 to 11 pM.[432] In the wound with calcium present, monocytes associate with plasma tissue factor to rapidly accelerate the conversion of factor VII to factor VIIa.[458] This association is specific for monocytes—the reaction is essentially nil for platelets, neutrophils, and

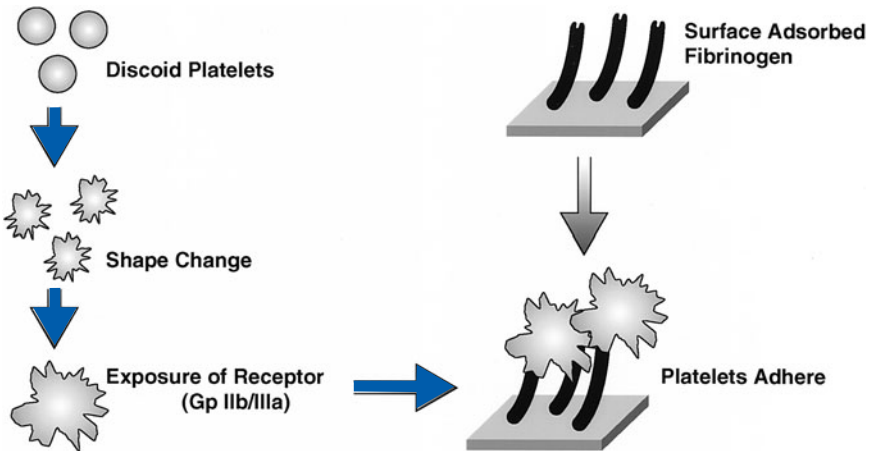

Figure 12-13. Adhesion of activated platelets binding to surface-adsorbed fibrinogen via GPIIb/IIIa ($\alpha_{IIb}\beta3$) receptors. The same receptors bind plasma fibrinogen molecules to form platelet aggregates.

lymphocytes—and does not occur if monocytes, plasma tissue factor, or factor VII is not present. Monocytes also synthesize and express tissue factor, but this process, which peaks 3 to 4 hours after monocytes are activated,[458] is not a major source of tissue factor during CPB and clinical heart surgery but does occur during prolonged perfusions.[459] Plasma microparticles, also present in wound plasma, are procoagulant[460] and monocytes may express the procoagulant CD 11b receptor,[461] but the clinical importance of these pathways in thrombin generation is not clear and probably minor. The major sources of tissue factor in the wound are the combination of monocytes, plasma tissue factor, and cell-bound tissue factor.

Agonists for activating monocytes during CPB and clinical cardiac surgery include C5a,[462] endotoxin, IL-6, IL-1-beta, TNF-alpha, and monocyte chemotactic protein-1 (MCP-1). Monocytes and macrophages produce MCP-1, IL-1-beta, IL-6, and TNF-alpha;[463,464] express tissue factor,[458] Mac-1,[461] L-selectin, and MCP-1;[465] and form aggregates with platelets.[440] For the most part, monocyte reactions are slow and peak concentrations of cytokines occur several hours after CPB ends.[466–468]

Endothelial Cells

Endothelial cells, charged with maintaining the fluidity of circulating blood and the integrity of the vascular system, are activated during CPB and clinical cardiac surgery by thrombin, C5a,[469] IL-1, and TNF-alpha.[470] Endothelial cells produce both procoagulants and anticoagulants. Procoagulant activities of endothelial cells include expression of tissue factor and production of a host of procoagulant proteins, including collagen, elastin, microfibillar protein, laminin, fibronectin, thrombospondin, von Willebrand factor, factor V, platelet-activating factor, and plasminogen activator inhibitor-1, and the vasoconstrictors endothelin-1 and renin. Endothelial cells also bind von Willebrand factor, vibronectin, and factors IXa and Xa. Anticoagulant activities of endothelial cells include the production of t-PA, heparin sulfate, dermatan sulfate, protein S (which accelerates the activation of protein C), tissue factor inhibitor protein, thrombomodulin and protease nexin 1 (which both bind thrombin), prostacyclin,[471] nitric oxide, and adenosine. Prostacyclin concentrations increase rapidly at the beginning of CPB and then begin to decrease.[472] During clinical cardiac surgery endothelin-1 peaks several hours after CPB ends.[473]

Except for expression of tissue factor and expression of CD11b/CD18 (Mac-1), which is weakly procoagulant, endothelial cell receptors do not participate heavily in thrombin generation during ECP.

Neutrophils

During ECP neutrophils express Mac-1 receptors,[474] which bind factor X and fibrinogen and weakly facilitate thrombin formation. Neutrophils secrete elastase, which can destroy protease inhibitors such as antithrombin and coagulation factors such as factor V and may contribute significantly to the equilibrium between the fluid and gel forms of blood.

FIBRINOLYSIS

Circulating thrombin activates endothelial cells to produce t-PA, which binds avidly to fibrin.[475–477] Endothelial cells are the principal source of t-PA.[476] The combination of t-PA, fibrin, and plasminogen cleaves plasminogen to plasmin; plasmin cleaves fibrin.[476] This reaction produces the protein fragment D-dimer, which is a useful marker of fibrinolysis, and a marker of thrombin activity because fibrin is cleaved from fibrinogen by thrombin. Kallikrein produced by the contact system cleaves pro-urokinase to urokinase; however, this enzyme is less important in fibrinolysis than t-PA because urokinase binds poorly to fibrin.[477] F1.2, D-dimer, and fibrinopeptide A (produced by the conversion of fibrinogen to fibrin) increase during extracorporeal perfusion, indicating ongoing thrombin production, fibrin formation, and fibrinolysis.[366,367,478,479] D-dimer and other fibrin degradation products are themselves anticoagulants inhibiting fibrin polymerization.[476]

Fibrinolysis is controlled by native protease inhibitors, $alpha_2$-antiplasmin, $alpha_2$-macroglobulin, and plasminogen activator inhibitor-1.[477] Plasminogen activator inhibitor-1, produced by endothelial cells, directly inhibits t-PA and urokinase, but little is produced during CPB and open cardiac surgery.[480] $Alpha_2$-antiplasmin rapidly inhibits unbound plasmin, preventing the enzyme from circulating, but poorly inhibits plasmin bound to fibrin. $Alpha_2$-Macroglobulin is a slow inhibitor of plasmin.

Plasmin is both a stimulator and inhibitor of platelets, depending on concentration and temperature.[481] High concentrations of plasmin at normothermia and low concentrations during hypothermia cause conformational changes in platelets, centralization of platelet granules, and internalization of platelet GPIb receptors but not GPIIb/IIIa receptors.[482]

CONSUMPTIVE COAGULOPATHY

Simultaneous and ongoing thrombin formation and fibrinolysis is by definition a consumptive coagulopathy[483] and is present in all applications of ECP. In the normal state the fluidity of blood and the integrity of the vascular system are established and maintained by an equilibrium between procoagulants favoring clot and anticoagulants favoring liquidity (Fig. 12-14A). Blood contact with ECP systems and the wound disrupts this equilibrium to produce a massive procoagulant stimulus that overwhelms natural anticoagulants; therefore an exogenous anticoagulant, heparin, is required for nearly all applications of ECP (Fig. 12-14B). Exceptions are only possible in applications that produce a relatively weak procoagulant stimulus and a minimal thrombin burden that can be contained by natural anticoagulants. Surgeons

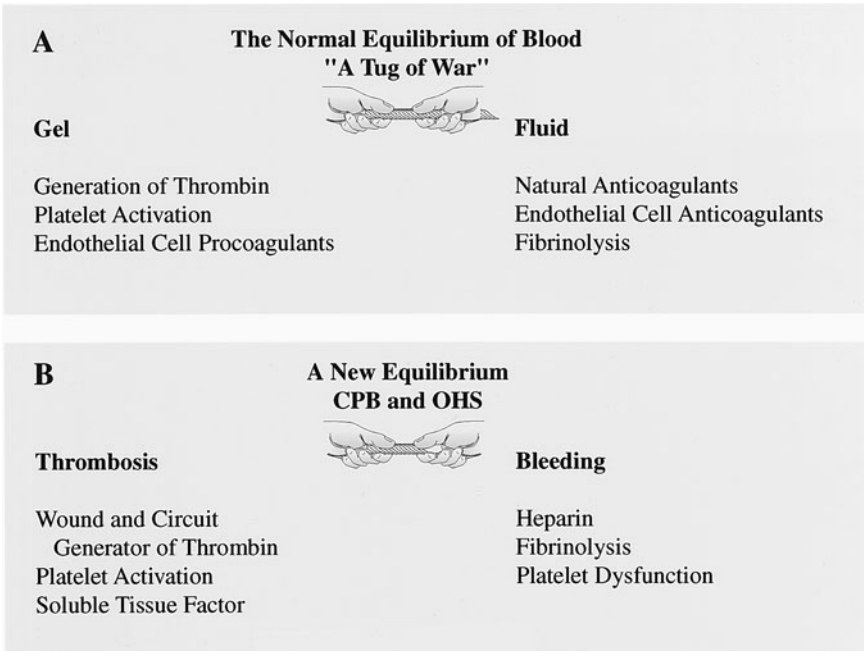

Figure 12-14. (A) The balance between procoagulant and anticoagulant forces that produces an equilibrium that allows blood to circulate. (B). During CPB and OHS (open heart surgery) the normal equilibrium is disturbed by changes in both procoagulants and anticoagulants. Imbalance of procoagulants risks thrombosis; an imbalance of anticoagulants risks bleeding.

must realize that any blood exposure to nonendothelial cell surfaces, including prosthetic heart valves, produces a procoagulant stimulus whether or not clot is produced. Except for the healthy endothelial cell, no nonthrombogenic surface exists.

This concept of an equilibrium between procoagulants and anticoagulants is helpful in managing the thrombotic and bleeding complications associated with all applications of ECP. During ECP procoagulant stimuli, manifested by thrombin formation that is not measurable in real time, must be balanced by either increased anticoagulation or a reduction in the thrombin burden to maintain equilibrium. After ECP, anticoagulants must be inhibited to avoid excessive bleeding. During consumptive coagulopathy, coagulation proteins and platelets are consumed and may become too deficient to generate thrombin and fibrin-platelet clots. In cardiac surgical patients many additional variables affect the coagulation equilibrium and impact the availability of coagulation proteins and functional platelets. These variables include the quantity of blood in contact with the wound, surface area of the perfusion system, duration of perfusion, circulating anticoagulants, and to lesser degrees temperature and the rheology and biomaterials of the perfusion system. Patient factors also affect the coagulation equilibrium; these include age, infection, history or presence of cardiogenic shock, massive blood losses and transfusions, platelet coagulation deficiencies, fibrinolysis, liver disease, cachexia, reoperation, and hypothermia.

MANAGEMENT OF BLEEDING

The cornerstone of bleeding management is meticulous surgical hemostasis during all phases of an operation. The surgical techniques, topical agents, and customary drugs used do not need reiteration for trained surgeons. Most cardiac surgical operations involving CPB are accompanied by net blood losses between 200 and 600 mL. Reoperations, complex procedures, prolonged (>3 hours) cardiopulmonary bypass, and patient factors listed above may be associated with excessive and ongoing blood losses. Most surgeons use an antifibrinolytic, such as aprotinin or epsilon-aminocaproic acid, to reduce fibrinolysis in prolonged or complex operations. Problem patients who bleed excessively after heparin neutralization require an attempt to rebalance pro- and anticoagulants to near normal pre-CPB concentrations.

The most useful tests in the operating room are an activated clotting time or a protamine titration test to assess the presence of heparin, prothrombin time to uncover deficiency in the extrinsic coagulation pathway, and platelet count. If heparin is neutralized, the partial thromboplastin time may be measured to assess possible deficiency of coagulation proteins. Other tests such as measurements of fibrinogen, template bleeding time, and the thromboelastography are controversial and/or difficult to obtain. Platelet counts below 80,000 to 100,000/μL require platelet transfusions in bleeding patients, except those with IgG anti-H-PF4 antibodies, to add functioning platelets to the mass of partially dysfunctional platelets.

Measurements of F1.2 and D-dimer are two tests that can be very helpful and probably should be made available on an emergency basis in hospitals that perform complex procedures and offer mechanical circulatory and respiratory assistance. F1.2 measures thrombin formation by factor Xa, and if absent or low, there may be a deficiency in the concentrations of coagulation proteins; fresh frozen plasma is needed. If F1.2 and D-dimer (a measurement of fibrinolytic activity) are both elevated, thrombin is being formed and an

antifibrinolytic (aprotinin or epsilon-aminocaproic acid) is needed to neutralize plasmin. If both markers or F1.2 remain elevated after the antifibrinolytic drug, this indicates continuing thrombin generation and the cause (e.g., usually infection) should be aggressively treated with antibiotics. Some thrombin is needed to stop bleeding, but excessive thrombin production feeds the consumptive coagulopathy. As with disseminated intravascular coagulopathy,[483] no guaranteed therapeutic recipe is known; success requires patience, persistence, and judicious use of platelets, antifibrinolytics, specific clotting factors, and replacement transfusions to rebalance the coagulation equilibrium at near normal concentrations of the constituents.

THE INFLAMMATORY RESPONSE

The inflammatory response to CPB is initiated by contact between heparinized blood and nonendothelial cell surfaces.[484–486] Blood contact with nonendothelial cell surfaces in the wound and in the perfusion circuit activates plasma zymogens and cellular blood elements that constitute part of the body's defense reaction to all noxious substances including infectious agents, toxins, foreign antigens, allergens, and also injuries. All surgery, like accidental trauma, triggers an acute inflammatory response, but the continuous exposure of heparinized blood to nonendothelial cell surfaces followed by reinfusion of wound blood and recirculation within the body greatly magnifies this response in operations in which CPB is used. Although far from fully described and understood, this primary "blood injury" produces a unique response, which is different in detail from that caused by other threats to homeostasis.

The principal blood elements involved in this acute defense reaction are contact and complement plasma protein systems, neutrophils, monocytes, endothelial cells, and to a lesser extent platelets. Lymphocytes are also altered by CPB,[487,488] but are more involved in the immune response to foreign proteins and acute rejection and do not materially contribute to the acute response to CPB. Likewise, eosinophils and basophil/mast cells are primarily activated by IL-5 and IgE antibodies, respectively, and have prominent roles in allergy, parasitic diseases, and histamine production. When activated during CPB, the principal blood elements release vasoactive and cytotoxic substances, produce cell signaling inflammatory and inhibitory cytokines, express complementary cellular receptors that interact with specific cell signaling substances and other cells, and generate a host of vasoactive and cytotoxic substances that circulate.[489] Normally these reactive blood elements mediate and regulate the defense reaction,[490–492] but during CPB an orderly, targeted response is overwhelmed by the massive activation and circulation of these reactive blood elements.

Admittedly there is considerable overlap between the plasma and blood cellular responses involved in bleeding and thrombosis, ischemia/reperfusion,[493] acute rejection, and acute and chronic inflammation, but these responses are separated in this book in the interest of simplification. This section offers a simplified overview of the acute inflammatory response to cardiopulmonary bypass; the detailed interactions of the body's defense system against hurtful stimuli are under active and intense investigation and are far beyond the author's expertise.

PRIMARY BLOOD CONSTITUENTS

Complement

The complement system constitutes a group of more than 30 plasma proteins that interact to produce powerful vasoactive anaphylatoxins, C3a, C4a, and C5a, and the terminal complement cytotoxic complex, C5b-9.[494] Complement is activated by three pathways, but only the classical and alternative pathways are involved in cardiopulmonary bypass,[495,496] although a role for the mannose-lectin pathway has not been excluded. Direct contact between heparinized blood and the synthetic surfaces of the extracorporeal perfusion circuit activates the contact plasma proteins and the classical complement pathway.[495] Activation of C1, possibly by activated factor XIIa, sequentially activates C2 and C4 to form C4b2a (classical C3 convertase) that cleaves C3 to form C3a and C3b (Fig. 12-15).[494]

Generation of C3b activates the alternative pathway, which involves factors B and D in the formation of C3bBb, which is the alternative pathway C3 convertase that cleaves C3 to form C3a and C3b (see Fig. 12-15). Whereas the classical pathway proceeds in sequential steps, the alternative pathway contains a feedback loop that greatly amplifies cleavage of C3 by membrane-bound C3 convertase to membrane-bound C3b and C3a. During CPB complement is largely activated by the alternative pathway.[496–498]

The complement system is activated at three different times during CPB and cardiac surgery: during blood contact with nonendothelial cell surfaces[495,499] and wound exudate containing tissue factor;[485] after protamine administration and formation of the protamine-heparin complex;[495,500] and after reperfusion of the ischemic, arrested heart.[493] CPB and myocardial reperfusion activate complement by both the classical and alternative pathways; the heparin-protamine complex activates complement by the classical pathway.[495] Other agonists that activate the classical pathway during CPB include endotoxin,[496] apoptotic cells, and C-reactive protein.[494]

The two C3 convertases effectively merge the two complement pathways by producing C3b, which activates C5 to C5a and C5b (see Fig. 12-15). C3a and C5a are potent vasoactive anaphylatoxins. C5a, which avidly binds to neutrophils and therefore is difficult to detect in plasma, is the major agonist. C3b acts as an opsonin, which binds target cell hydroxyl groups and renders them susceptible to phagocytic cells expressing specific receptors for C3b.[494,497] C5b is the first component of the terminal pathway that ultimately leads to formation of the membrane attack complex, C5b-9.

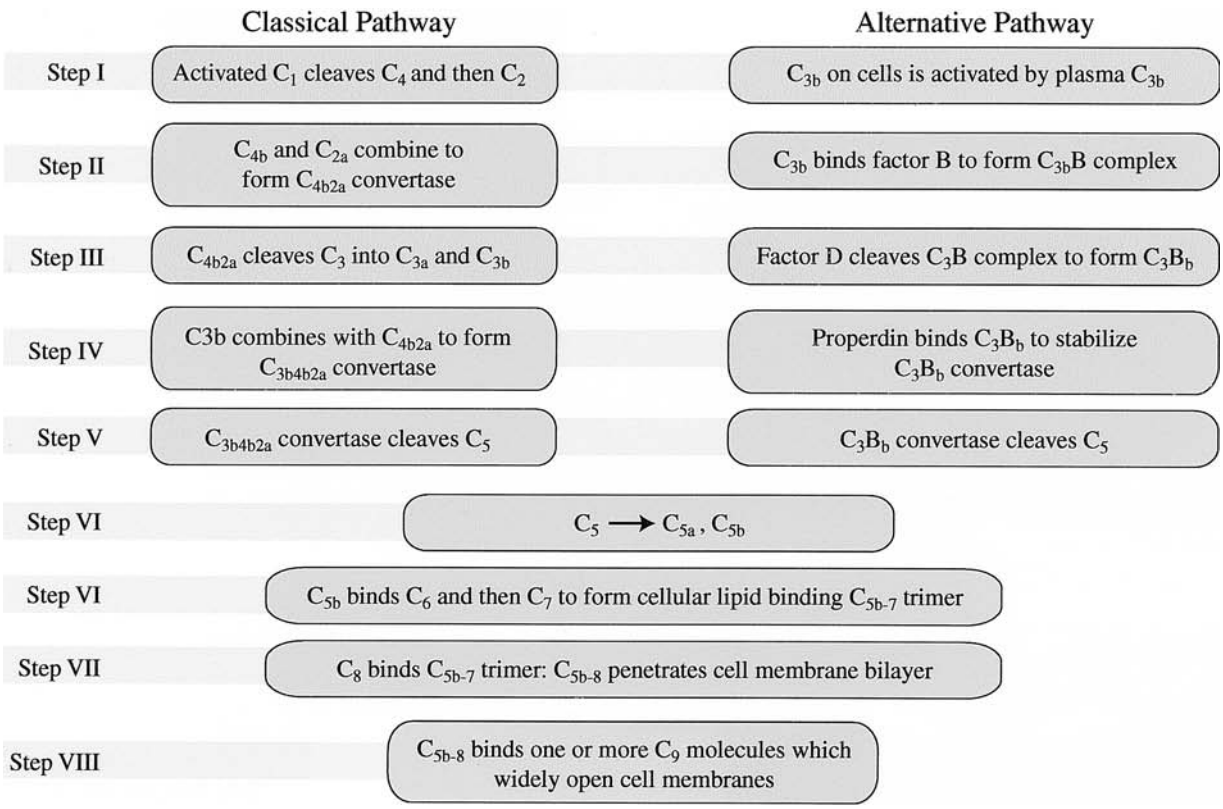

Figure 12-15. Steps in activation of the classical and alternative complement pathways and formation of the membrane attack complex, C5b-9. (*Adapted with permission from Walport*[494] *and Plumb and Sadetz.*[684])

In prokaryotic cells like erythrocytes, C5b-9 creates transmembrane pores, which cause death by intracellular swelling following loss of the intracellular/interstitial osmotic gradient. In eukaryotic cells, deposits of C5b-9 may not be immediately lethal but may eventually cause injury mediated by release of arachidonic acid metabolites (thromboxane A_2 and leukotrienes) and oxygen free radicals by macrophages and neutrophils, respectively.[497]

Together, C5a and C5b-9 play major roles in promoting neutrophil–endothelial cell interactions through upregulation of specific adhesion molecules (see below). Importantly, C5b-9 may also activate platelets and promote platelet-monocyte aggregates.[501] As such, these complement proteins contribute to neutrophil loss from the circulation by adhesion to surface-bound platelets,[501] but more importantly to endothelial cells. The interaction between complement proteins and neutrophils contributes to postoperative organ damage in both adults[502] and in children.[503]

Normally, several regulatory proteins modulate the inflammatory actions of C5a and C5b-9 by inactivating convertases, which cleave C3 and C5,[504] but these inhibitors are usually overwhelmed during CPB. Two proteins, factors H and I, are soluble; three others, complement receptor 1 (CD35), decay accelerating factor, and membrane cofactor protein (CD46), are membrane bound.[494] Factor I cleaves C3 into inactive iC3b, which cannot form C3 convertase, but can be an opsonin.[505] Factor H is the dominant complement regulatory protein and competes with factor B in binding to C3.[494] CD59 and homologous restriction factor are direct inhibitors of the membrane attack complex.[497,506]

Neutrophils

Leukocyte counts decrease in response to hemodilution during CPB and increase moderately after operation.[486,507] Only a few neutrophils attach to synthetic surfaces, to each other, or to platelets and monocytes.[507,508] Nevertheless, neutrophils are strongly activated during CPB (Fig. 12-16).[486,509] The principal agonists are kallikrein[510] and C5a[511,512] produced by the contact and complement systems, respectively.[511,513,514] C5a, generated early during CPB and clinical cardiac surgery, is a particularly potent chemotactic protein that induces neutrophil chemotaxis, degranulation, and superoxide generation.[515] Other agonists involved during CPB include IL-1-beta,[516] TNF-alpha,[492,517] IL-8,[518] C5b-9,[512] factor XIIa,[519] heparin, histamine, hypochlorous acids, and products of arachidonate metabolism (leukotriene B_4),[492] platelet activating factor (PAF), and thromboxane A_2.[515] Lastly, CPB, perhaps mediated by IL-6 and IL-8,[520] partially inhibits neutrophil apoptosis and prolongs the period of neutrophil activity.[521]

Neutrophils are recruited to localized areas of injury or inflammation by chemokines, complement proteins (C5a),

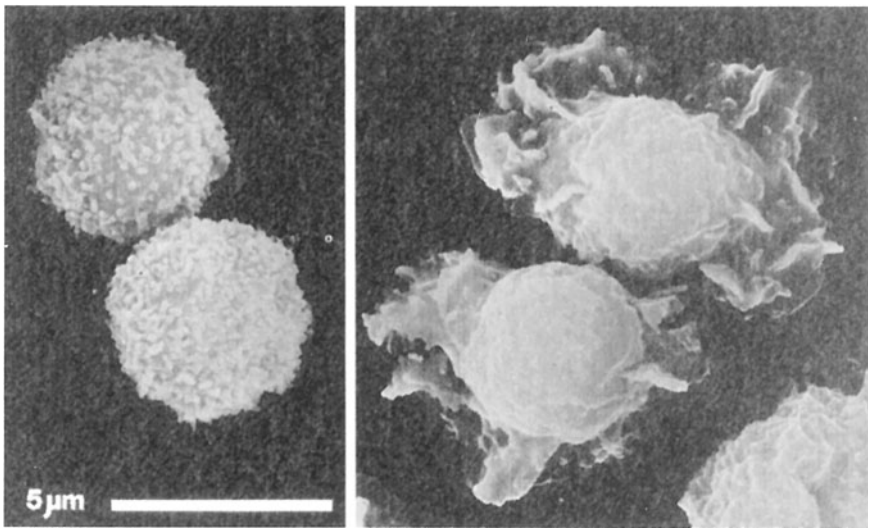

Figure 12-16. Scanning electron micrographs of resting neutrophils (left) and 5 seconds after exposure to a chemoattractant (right). (*Reproduced with permission from Baggiolini M: Chemokines and leukocyte traffic. Nature 1998; 392:565.*)

IL-1-beta, TNF-alpha, and adhesion molecules. Neutrophils respond to the CXC (alpha) family of chemokines that includes IL-8, platelet factor 4 (PF4), neutrophil activating factor-2, and granulocyte chemotactic protein 2.[522–524] During CPB thrombin stimulates endothelial cell production of PAF.[492] Thrombin and PAF cause rapid expression of P-selectin by endothelial cells[490] and circulating IL-1-beta and TNF-alpha stimulate endothelial cells to synthesize and express E-selectin.[490,525] Regional vasoconstriction reduces blood flow rates within local vascular beds to allow neutrophils to marginate near endothelial cell surfaces. L-selectins are constitutively expressed by all types of activated leukocytes and lightly bind to endothelial cell mucin-like glycoproteins before being shed with the onset of transmigration.[490] P-selectin weakly binds to P-selectin glycoprotein-1 on neutrophils;[526] E-selectin binds to a different sialyl Lewis antigen (CD62E). Selectin binding causes the slowly passing neutrophils to roll and eventually stop (Fig. 12-17).[527] Stronger adherence is produced by intracellular adhesion molecule-1 (ICAM-1) expressed on endothelial cells, which binds beta-2 neutrophil integrins, principally CD11b/CD18 (Mac-1) and to some extent CD11a/CD18.[490,528] These adhesion molecules from the immunoglobulin superfamily completely stop neutrophils[529] and the process of transmigration begins in response to chemoattractants and cytotoxins produced in the extravascular space.[530,531] Platelet-endothelial cell adhesion molecule-1 expressed on leukocytes and endothelial cells mediates transmigration of leukocytes.[532] This trafficking is strongly regulated by IL-8 produced by neutrophils, macrophages, and other cells. During CPB neutrophils express the Mac-1 (CD11b/CD18) receptor[533,534] and CD11c/CD18, which binds to fibrinogen and a complement fragment,[528] and VLA-4 (alpha1beta4) receptors that are involved in cellular adhesion.[528] Neutrophil receptor CXCR1 is not affected by CPB, but CXCR2 is downregulated.[535]

Using pseudopods and following the scent of complement proteins (C5a, C3b, and iC3b),[536] IL-8,[492,518,537,538] hypochlorous acids, leukotriene B_4,[539] and locally produced IL-1 and TNF-alpha,[492,537] neutrophils arrive at the scene of inflammation to begin the process of phagocytosis and release of cytotoxins. Organs and tissues experience periods of ischemia followed by reperfusion (lung, heart, and brain) during CPB, and as a result express adhesion receptors[540] and reactive oxidants,[541] and are sources of neutrophil chemoattractants.[520,542]

Neutrophils vary considerably among individuals in expression of adhesive receptors[543] and responsiveness to chemoattractants during CPB. There also is substantial variation in measurements of soluble and cellular adhesion receptors.[534] The presence of diabetes,[544] oxidative stress,[545] and perhaps genetic factors (see below) influences expression of cellular and soluble adhesive receptors and cytokines, which affect neutrophil adhesion and release of granule contents. It is difficult to show a correlation between markers of neutrophil activation and measurements of organ dysfunction.[546]

Neutrophils contain a potent arsenal of proteolytic and cytotoxic substances. Azurophilic granules contain lysozyme, myeloperoxidase, cationic proteins, elastase, collagenases, proteinase 3, acid hydrolases, defensins, and phospholipase.[547] Specific granules contain beta-2 integrins, lactoferrin, lysozyme, type IV collagenase, histaminase, heparanase, complement activator, alkaline phosphatase, and membrane-associated NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) oxidase.[515] Activated neutrophils, in a "respiratory burst," also produce cytotoxic reactive oxygen and nitrogen intermediates including superoxide anion, hydrogen peroxide, hydroxyl radicals, singlet oxygen molecules, N-chloramines, hypochlorous acids, and peroxynitrite.[490,548] Finally, neutrophils produce arachidonate metabolites, prostaglandins, leukotrienes, and platelet-activating factor. During CPB these vasoactive and cytotoxic substances are produced and released into the extracellular environment and circulation.[486,489] Circulation of these substances mediates many of the manifestations of the "whole

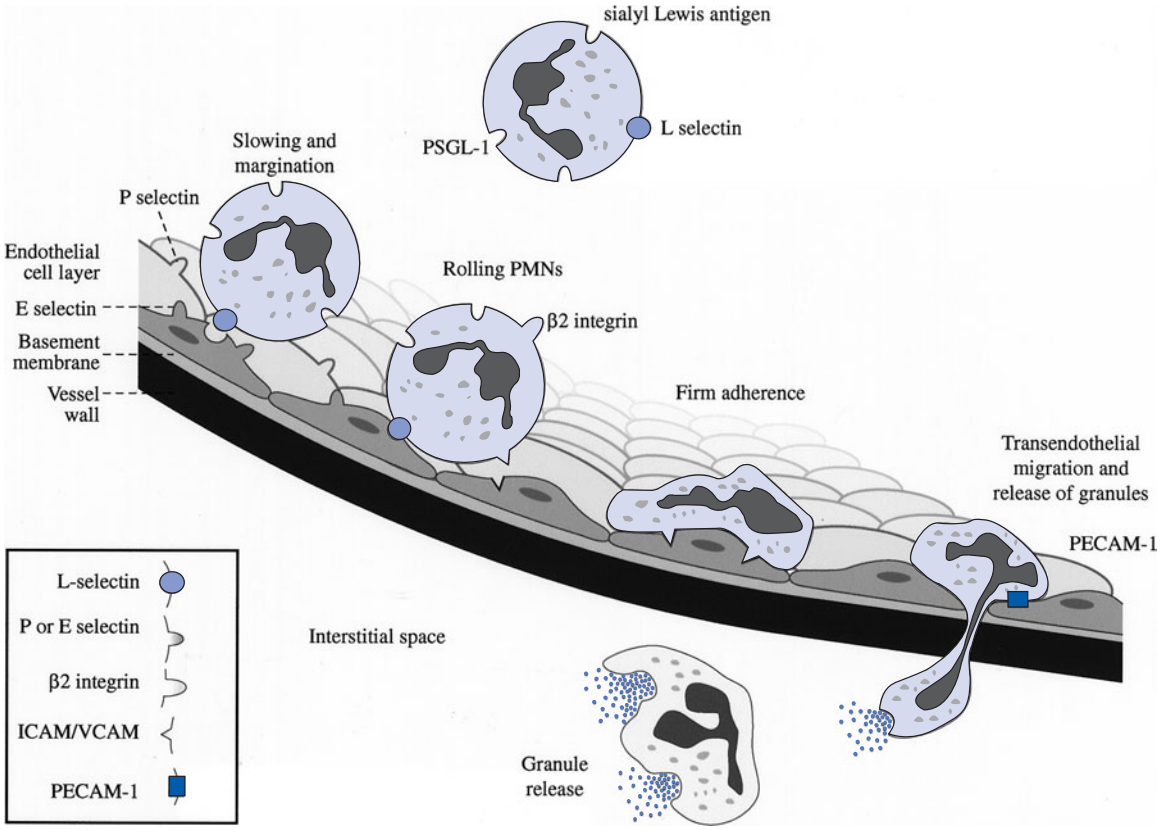

Figure 12-17. Mechanism of arrest and transmigration of neutrophils into the interstitial space. Neutrophils constitutively express L-selectin, which binds to endothelial cell glycoprotein ligands. Simultaneously, early response cytokines stimulate endothelial cells to rapidly express P-selectin and later E-selectin receptors, which weakly bind neutrophil P-selectin glycoprotein-1 (PSGL-1) ligands. Marginated neutrophils, which are slowed by local vasoconstriction and reduced blood flow, lightly adhere to endothelial cells via selectin expression and begin to roll. Neutrophils activated by C5a, kallikrein, and early response cytokines express β-2 CD11b and c receptors, which bind firmly to cytokine-activated endothelial cell integrins, intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Once arrested, L-selectins are shed and platelet-endothelial cell adhesion molecule (PECAM) receptors on endothelial cell surfaces mediate neutrophil transmigration through endothelial cell junctions, led by chemoattractants into the interstitial space. PMN = polymorphonuclear leukocyte; PSGL-1 = P-selectin glycoprotein ligand-1.

body inflammatory response" or "systemic inflammatory response syndrome" associated with CPB and clinical cardiac surgery.[549]

Monocytes

Monocytes and macrophages (tissue monocytes) are relatively large, long-lived cells that are involved in both acute and chronic inflammation. Monocytes respond to chemical signals, are mobile, phagocytize microorganisms and cell fragments, produce and secrete chemical mediators, participate in the immune response, and generate cytotoxins.[550] Monocytes are activated during CPB[551] and have a major role in thrombin formation.[552] Monocytes also produce and release many inflammatory mediators during acute inflammation including proinflammatory cytokines (principally TNF-alpha, IL-1-beta, IL-6, IL-8, and MCP-1), reactive oxygen and nitrogen intermediates, and prostaglandins.[524]

The mechanism by which monocytes are initially activated during CPB is not known, but the most likely candidates are C5a,[550] thrombin,[553] platelet factor 4, and bradykinin,[554] which are four potent agonists rapidly generated from blood contact with nonendothelial cell surfaces. Monocytes possess a huge list of surface receptors,[550] but those apt to be involved in the inflammatory response to CPB are C5a and three other complement proteins (IL-1, CD11b/CD18, and CD 11c/CD18), leukotriene B_4, and the C-C family of chemokine receptors.[550] Monocytes also possess C-reactive protein receptors, which when activated, strongly upgrade proinflammatory cytokine production.[491]

Monocytes are the major source of the early response cytokines IL-1-beta and TNF-alpha,[491,554] which play an important role in directing both neutrophils and monocytes to local sites of inflammation. Monocytes are also the major producer of IL-8,[491] which also is produced by neutrophils[492] and induces neutrophil chemotaxis.[490] Other cytokines

produced by monocytes include IL-1-alpha, IL-6, and IL-10.[491] Monocytes also produce important growth factors, matrix proteins, interferons, and a variety of enzymes, including elastase, collagenases, acid hydrolases, prostaglandins, and lipooxygenase products,[524] and contain myeloperoxidase, which converts hydrogen peroxide into more powerful oxidants.

Endothelial Cells

Endothelial cells are activated during CPB and open heart surgery by a variety of agonists. The principal agonists for endothelial cell activation during CPB are thrombin, C5a,[555] and the cytokines IL-1-beta and TNF-alpha.[537,556] Other agonists, such as endotoxin, histamine, and interferon-gamma (from lymphocytes), are less important during CPB, and endothelial cells are largely unresponsive to chemokines.[525]

IL-1-beta and TNF-alpha induce the early expression of P-selectin and the later synthesis and expression of E-selectin, which are involved in the initial stages of neutrophil and monocyte adhesion.[490] The two cytokines also induce expression of ICAM-1 and vascular cell adhesion molecule-1, which firmly bind neutrophils and monocytes to the endothelium and initiate leukocyte trafficking to the extravascular space (see Fig. 12-17).[492,525,537] Experimentally ICAM-1 is upregulated during CPB in pulmonary vessels[557] and there is evidence that P- and E-selectins are upregulated during CPB and in myocardial ischemia-reperfusion sequences. IL-1-beta and TNF-alpha induce endothelial cell production of the chemotactic proteins IL-8 and MCP-1, and induce production of prostaglandin I_2 (prostacyclin) by the cyclooxygenase pathway[532,558] and nitric oxide by nitric oxide synthase.[532,559] These two vasodilators reduce shear stress and increase vascular permeability and therefore enhance leukocyte adhesion and transmigration. Lastly, IL-1-beta and TNF-alpha stimulate endothelial cell production of proinflammatory cytokines, IL-1, IL-6, IL-8, MCP-1, and PAF.[525]

In addition to nitric oxide and prostacyclin, endothelial cells produce the vasoconstrictor endothelin-1[489,560] and inactivate other vasoactive mediators, including histamine, norepinephrine, and bradykinin.[561] Prostacyclin concentrations increase rapidly at the beginning of CPB and then begin to decrease.[562] Endothelin-1 peaks several hours after CPB ends.[563]

Platelets

Platelets are probably initially activated during CPB by thrombin, which is the most potent platelet agonist, but plasma epinephrine, PAF, vasopressin,[564] cathepsin G[565] from other cells, serotonin, and adenosine diphosphate (ADP) secreted by platelets, and internally generated thromboxane A_2[566] contribute to activation as CPB continues.[489] Platelets possess several protease-activated receptors[564] to most of these agonists and to collagen, which has an important role in adhesion and thrombus formation. Collagen binding causes release of thromboxane A_2 and ADP, which help recruit platelets.[564] Platelets contribute to the inflammatory response by synthesis and release of eicosanoids;[566] serotonin from dense granules; IL-1-beta;[567] CXC chemokines, PF4, neutrophil-activating protein-2, IL-8, and endothelial cell neutrophil attractant-78; and C-C chemokines, macrophage inflammatory protein-1a, MCP-3, and RANTES[568] from alpha granules. Platelets also produce and release acid hydrolases from membrane-bound lysozymes. Platelet-secreted cytokines, neutrophil-activating protein-2, RANTES, PF4, IL-1-beta, IL-8, and endothelial cell neutrophil attractant-78 may be particularly involved in the inflammatory response to CPB because of strong activation of platelets in both the wound and perfusion circuit.

Circulating monocytes and neutrophils constitutively express P-selectin glycoprotein-1, which interacts with aggregated platelets via P-selectin expressed on activated platelets.[526] Platelets aggregrate using platelet GPIIb/IIIa (alpha2beta3) receptors attached to symmetric fibrinogen molecules to form bridges between platelets. During CPB platelets aggregate with each other and also to monocytes and neutrophils.[507,561]

OTHER MEDIATORS OF INFLAMMATION

Anaphylatoxins

The anaphylatoxins C3a, C4a, and C5a are bioactive protein fragments released by cleavage of complement proteins C3, C4, and C5. These fragments have potent proinflammatory and immunoregulatory functions and contract smooth muscle cells, increase vascular permeability, serve as chemoattractants, and in the case of C5a, activate neutrophils and monocytes.[514] Anaphylatoxins contribute to increased pulmonary vascular resistance, edema, and neutrophil sequestration and an increase in extravascular water during CPB. The duration of postoperative ventilation directly correlates with plasma C3a concentrations.[569–570] C3a and C5a are important mediators in ischemia/reperfusion injuries.

Cytokines

Cytokines are small, cell-signaling peptides produced and released into blood or the extravascular environment by both blood and tissue cells. Cytokines stimulate specific receptors on other cells to initiate a response in that cell. All blood leukocytes and endothelium produce cytokines, but many tissue cells including fibroblasts, smooth muscle cells, cardiac myocytes, keratinocytes, chrondrocytes, hepatocytes, microglial cells, astrocytes, endometrial cells, and epithelial cells also produce cytokines.[537,554,571] IL-1-beta and TNF-alpha are early response cytokines that are promptly produced at the site of injury by resident macrophages.[537] These cytokines stimulate surrounding stromal and parenchymal cells to produce more IL-1-beta and TNF-alpha and chemokines, particularly IL-8 and MCP-1, which are powerful chemoattractants for neutrophils and macrophages, respectively. Together with IL-6, the cytokine that regulates

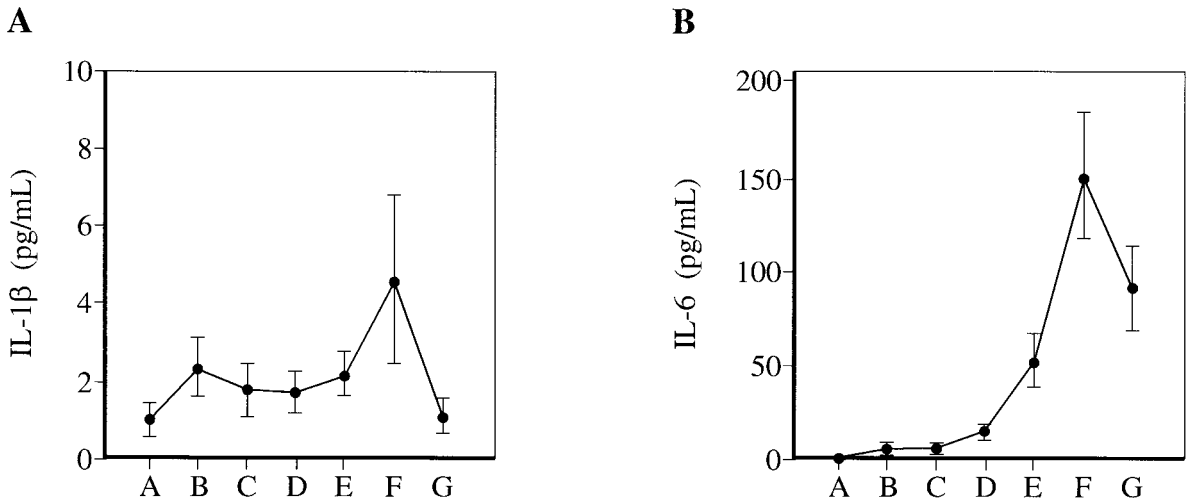

Figure 12-18. Changes in IL-1-β (A) and IL-6 (B) in 30 patients who had elective first-time myocardial revascularization. Letters on the *x* axis represent the following events: A, induction of anesthesia; B, 5 minutes after heparin; C, 10 minutes after starting CPB; D, end of CPB; E, 20 minutes after protamine; F, 3 hours after CPB; G, 24 hours after CPB. (*Redrawn from Steinberg et al.*[466])

production of acute-phase proteins (e.g., C-reactive protein and alpha$_2$-macroglobulin) by the liver,[572] these five cytokines are the major proinflammatory cytokines involved in the acute inflammatory response to CPB.

The major anti-inflammatory cytokine involved during CPB is IL-10.[573] IL-10 inhibits synthesis of proinflammatory cytokines by monocytes and macrophages[574] and induces production of IL-1 receptor antagonist (IL-1ra), which downgrades the response to IL-1.[554,575] IL-13 downregulates production of IL-1, IL-8, and IL-10 and reduces monocyte production of reactive oxidants;[576] its role during CPB is undetermined.

Proinflammatory cytokines increase during and after clinical cardiac surgery using CPB, but peak concentrations usually occur 12 to 24 hours after CPB ends (Fig. 12-18).[570,577–581] Measured amounts differ greatly in timing and within and between studies, probably because of differences in the duration of CPB, perfusion temperatures,[582] perfusion equipment, and aortic cross-clamp times; differences in methods of myocardial protection; possibly variable concentrations of inhibitory cytokines;[583–585] and perhaps exogenous factors such as priming solutions, anesthesia, and intravascular drugs.[570,577–581] Some of the variation in measurements between studies also may be due to patient factors such as age, left ventricular function, and genetic factors.[586] The presence of the APOE4 allele (one of the common human polymorphisms of the gene encoding apolipoprotein E) is associated with increased TNF-alpha and IL-8.[586] Patients who are homozygous for TNF-beta-2 have elevated levels of TNF-alpha and IL-8 during both on- and off-pump cardiac surgery.[587] Carriers of APOE4 have reduced concentrations of IL-1ra, the inhibitory peptide of IL-1.[588] Additional hints of a genetic role in the acute inflammatory response are the association between postoperative serum creatinine and different APO-epsilon alleles[589] and the association between length of stay after coronary artery surgery and 174GG polymorphism of the IL-6 gene.[590]

Reactive Oxidants

Neutrophils, monocytes, and macrophages produce reactive oxidants, which are cytotoxic inside the phagosome, but act as cytotoxic mediators of acute inflammation outside. Four enzymes generate a large menu of reactive oxidants: NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) oxidase, superoxide dismutase, nitric oxide synthase, and myeloperoxidase.[548] The enzyme NADPH oxidase adds a free electron to molecular oxygen to create superoxide (O_2^-) and two hydrogen ions, H^+. Superoxide dismutase catalyzes the conversion of superoxide to hydrogen peroxide, H_2O_2, and molecular oxygen. Nitric oxide synthase produces nitric oxide (NO) from NADPH, arginine, and oxygen, and myeloperoxidase uses H_2O_2 to oxidize halide ions to hypochlorous acids.[591–592] The four products produced by these enzymes, O_2^-, H_2O_2, NO, and hypochlorous acids, generate all reactive oxidants from nonenzymatic reactions with other molecules or ions.[548]

Free radicals have one or more unpaired electrons and are highly reactive in scavenging hydrogen ions from other molecules. $OH^\cdot$ is produced from H_2O_2 by low-valence iron or copper ions, which are reduced to the original low valence after the reaction by various reducing agents, such as ascorbic acid. Secondary free radicals, containing carbon, oxygen, nitrogen, or sulfur, are formed when a free radical reacts with molecules that lack unpaired electrons;[548] this self-perpetuating sequence produces a chain reaction of highly cytotoxic substances.

Endotoxins

Endotoxins, including lipopolysaccharides, are fragments of bacteria that are powerful agonists for complement,[593] neutrophils, monocytes, and other leukocytes. Endotoxins have been detected during CPB[593–596] and after aortic cross-clamping using a very sensitive bioassay.[597,598] Sources include contaminants in sterilized infusion solutions, the bypass circuit, and possibly the gastrointestinal tract due to changes in microvascular intestinal perfusion, which may translocate bacteria.[599] Intestinal microvascular blood flow is sensitive to both flow rate and duration of CPB. In some instances leakage of endotoxin into the systemic circulation occurs if clearance by the hepatic Kupffer cells fails. The quantitative significance of the role of endotoxins in the acute inflammatory response to CPB is unknown.

Metalloproteinases

CPB induces the synthesis and release of matrix metalloproteinases,[600] which are one of the four major classes of mammalian proteinases. These proteolytic enzymes have a major role in degradation of collagens and proteins in the extracellular matrix and vascular basement membrane and in the pathogenesis of atherosclerosis and postinfarction left ventricular remodeling. The significance and possible injury produced by activation of these interstitial degradation enzymes over the long term remain to be determined.

Angry Blood

Blood circulating during clinical cardiac surgery with cardiopulmonary bypass can be a stew of vasoactive and cytotoxic substances, activated blood cells, and microemboli. Shear stress, turbulence, cavitation, and other rheologic forces and C5b-9 cause hemolysis of some red cells. Complement anaphylatoxins,[514] bradykinin formed by activation of the contact proteins,[490,513] and proinflammatory cytokines stimulate endothelial cells to contract, allowing extravasation of intravascular fluid into the extravascular space.[601] Numerous circulating vasoactive substances cause vasoconstriction or vasodilatation of heterogeneous regional vascular networks.[489] As neutrophils and monocytes migrate across the endothelial cell barrier, stromal and parenchymal cells are exposed to a cytotoxic environment mediated by neutral proteases, collagenases and gelatinases, reactive oxidants, lipid peroxides, C5b-9, and other cytotoxins.[486,545,602,603] This injury is magnified by microemboli produced from platelet-leukocyte aggregates, lipids, and other blood elements and emboli from other sources (see section 12C). The manifestations of the inflammatory response include systemic symptoms such as malaise, fever, increased heart rate, mild hypotension,[582] interstitial fluid accumulation,[604] and temporary organ dysfunction, particularly of the brain, heart, lungs, and kidneys.

The magnitude of this defense reaction during and after CPB is influenced by many exogenous factors that include the surface area of the perfusion circuit, the duration of blood contact with extravascular surfaces, the amount of unwashed cardiotomy suction blood returned to the patient, general health and preoperative organ function of the patient, blood loss and replacement, organ ischemia and reperfusion injury, sepsis, different degrees of hypothermia, periods of circulatory arrest, genetic profiles, corticosteroids, and other pharmacologic agents. When well managed, these factors result in a postoperative patient with few, if any, overt manifestations of inflammation.

CONTROL OF THE ACUTE INFLAMMATORY RESPONSE TO CARDIOPULMONARY BYPASS

Off-Pump Cardiac Surgery

Myocardial revascularization without either CPB or cardioplegia reduces the acute inflammatory response but does not prevent it.[605–607] The response to surgical trauma, manipulation of the heart, pericardial suction, heparin, protamine, other drugs, and anesthesia activates the extrinsic clotting system and produces an increase in the markers of acute inflammation, C3a, C5b-9, proinflammatory cytokines (TNF-alpha, IL-6, and IL-8), neutrophil elastase, and reactive oxidants,[545] but the magnitude of the response is significantly less than that observed with CPB.[606–608] Although it has not been shown that the attenuated acute inflammatory response directly reduces organ dysfunction,[605,608] elderly patients and those with reduced renal and pulmonary function often tolerate off-pump surgery with less morbidity and mortality than patients treated with CPB.[608–611]

Perfusion Temperature

Release of mediators of inflammation is temperature sensitive. Normothermic CPB increases the release of cytokines and other cellular and soluble mediators of inflammation,[582] whereas hypothermia reduces production and release of these mediators until rewarming begins.[612] Perfusion at tepid temperatures between 32 and 34°C is a reasonable compromise for many operations requiring 1 to 2 hours of CPB.[580,602]

Perfusion Circuit Coatings

Ionic- or covalent-bonded heparin perfusion circuits are the most widely used surface coatings and are often combined with reduced doses of systemic heparin in first-time myocardial revascularization patients.[613] It is well established that heparin is an agonist for platelets, complement, factor XII, and leukocytes, but there is no reproducible evidence that heparin coating either produces a nonthrombogenic surface or reduces activation of the clotting cascade.[614–615] A review of a large portion of this literature concluded that heparin-bonded circuits reduced concentrations of the terminal complement complex, C5b-9 (Fig. 12-19),[616] but for nearly every study showing a beneficial anti-inflammatory or antithrombotic effect, another study shows no effect.[617] Clinical trials that have combined heparin-coated circuits with

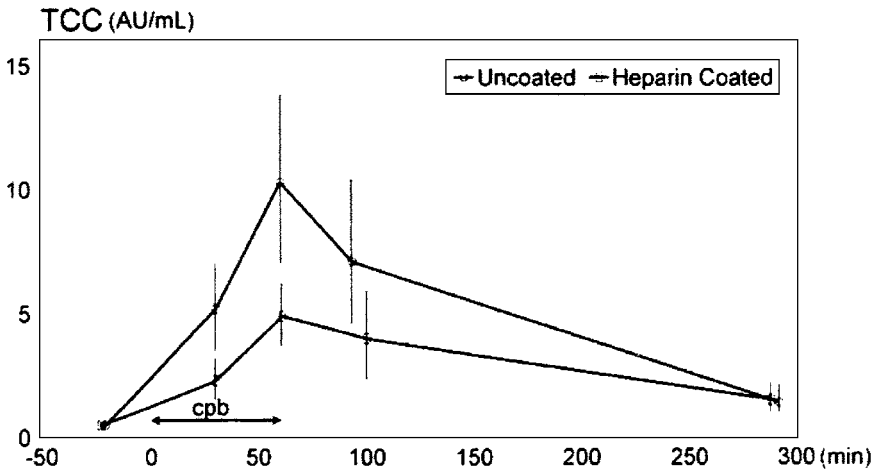

Figure 12-19. Changes in C5b-9 (TCC) terminal complement complex in heparin-coated (n = 15) and uncoated (n = 14) perfusion circuits during myocardial revascularization. The two curves are significantly different by ANOVA ($p = .004$). (*Reproduced with permission from Videm et al.*[173])

reduced systemic heparin and exclusion of field-aspirated blood from the perfusion circuit have demonstrated modest clinical benefits.[618] However, most trials, including a large European trial of 805 patients, have not observed clinical benefits except in certain subsets of patients that are not the same between studies[617,619–624] and which report sporadic differences that barely reach statistical significance.[624,625] Excluding unwashed field blood from the perfusion circuit reduces admixture of high concentrations of thrombin,[552] fibrinolysins,[626] cytokines, activated complement,[422] and leukocytes to the perfusate. Exclusion of these inflammatory mediators may be more important in reducing the amounts of vasoactive and cytotoxic substances circulating within the body than the heparin surface coating.

New surface coatings are being developed or undergoing clinical trials.[627] Surface-modifiying additives are chemicals used in low concentrations to reduce interfacial energy and modify the mosaic of adsorbed surface plasma proteins. One commercially available surface-modifiying additive uses a triblock copolymer containing polar and nonpolar chains of polycaprolactone-polydimethylsiloxane-polycaprolactone.[628] In clinical trials this surface significantly reduced platelet loss and granule release, and reduced markers of thrombin generation.[629–630] PMEA (poly-2-methylethylacrylate) is another manufactured surface coating designed to reduce surface adsorption of plasma proteins. Laboratory studies show reduced surface adsorption of fibrinogen and reduced bradykinin and thrombin generation in pigs.[631] Early clinical studies show significant reductions in C3a, C4D, and neutrophil elastase, but ambivalent effects on IL-6 and platelets.[632–633]

Modified Ultrafiltration

Although effective in pediatric cardiac surgery,[634–635] ultrafiltration to remove intravascular (and extravascular) water and inflammatory substances has produced mixed results in adults.[636] Dialysis during CPB in adults may be beneficial in removing water, potassium, and protein wastes in patients with renal insufficiency.

Leukocyte Filtration

The role of neutrophils in the acute inflammatory response has led to development of leukocyte-depleting filters for the CPB circuit. Multiple groups have investigated these filters in clinical trials, but consistent efficacy in reducing markers of neutrophil activation and improvement in respiratory or renal function are lacking. Most clinical studies fail to document significant leukocyte depletion or clinical benefits.[637–640] Washing cardiotomy suction blood and using leukodepleted allogeneic red cell and platelet transfusions has reduced the interest in leukocyte filtration. Active sequestration of leukocytes and platelets using a separate cell separator during CPB may have beneficial clinical effects,[644,645] but requires a separate inflow cannula and separator system.

Complement Inhibitors

The central role of complement in the acute inflammatory response to CPB provides ample rationale for inhibition. The anaphylatoxins and C5b-9 are direct mediators of the inflammatory response, and C5a is the principal agonist for activating neutrophils and is a potent chemoattractant for neutrophils, monocytes, macrophages, eosinophils, basophils, and microglial cells.[514] C1-inhibitor is a natural inhibitor of complement C1 components C1s and C1r, factor XIIa, kallikrein, and factor XIa.[504] Factor H and C4BP inhibit C3 and C5 convertase subunits, but are poor inhibitors of induced activation of the complement system.[504] None of these inhibitors are attractive candidates for inhibiting complement activation during CPB.

The sequential activation cascade with convergence of the classical and alternative pathways at C3 offers many opportunities for inhibition by recombinant proteins.[641] Using a humanized, recombinant antibody to C5 (h5G1.1-scFv), Fitch and associates demonstrated that generation of C5b-9 was completely blocked in a dose-response manner (Fig. 12-20) and that neutrophil and monocyte CD11b/CD18 expression was attenuated in patients during and for several hours after clinical cardiac surgery using CPB.[642] Large scale clinical trials

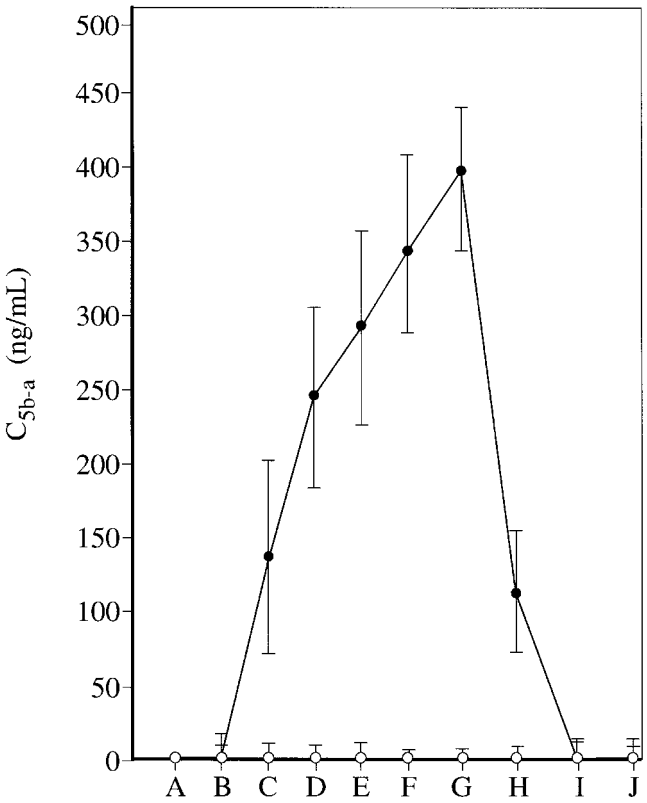

Figure 12-20. Inhibition of C5b-9, complement terminal attack complex, with placebo (solid circles) and 2 μg/kg of h5G1.1-scFv (open circles) during clinical cardiac surgery with CPB. Letters on the *x* axis represent the following events: A, before heparin; B, 5 minutes after drug; C, 5 minutes after cooling to 28°C; D, after beginning rewarming; E, 5 minutes after reaching 32°C; F, 5 minutes after reaching 37°C; G, 5 minutes after CPB; H, 2 hours after CPB; I, 12 hours after CPB; J, 24 hours after CPB. h5G1.1-scFv completely inhibited formation of the C5b-9 terminal attack complex. (*Data redrawn from Fitch et al.*[643])

that have followed but are not yet published have shown modest improvements in morbidity and mortality.

Fung and associates[496] used an anti–factor D monoclonal antibody to inhibit production of complement proteins, Bb, C3a, sC5b-9, and C5a, via the alternate pathway, and to attenuate upregulation of neutrophil and platelet adhesive receptors during CPB in vitro.[496] Undar and coworkers confirmed these results during CPB in baboons and additionally found inhibition of complement C4d, attenuation of IL-6 concentrations, and reduced markers of cardiac injury.[643] Compstatin, a very small (1593-Da) synthetic peptide, binds C3 and therefore inhibits both the classical and alternative pathways.[494] This peptide inhibits generation of C3a and sC5b-9 and neutrophil binding during in vitro CPB.[644] In baboons, after activation of complement by the heparin-protamine complex, compstatin completely inhibits C3 cleavage without causing any change in hemodynamic measurements or side effects.[645]

Other complement recombinant protein inhibitors have been developed and are under active investigation and in clinical trials because of the importance of this plasma protein system in CPB, ischemia/reperfusion, and injuries that summon the acute inflammatory response.[504,646–648] Although any effective and safe inhibitor is welcome, C3 may be a better target for inhibition because both activation pathways are blocked at the point of convergence and because C3 concentrations in plasma are 15 times greater than those of C5.[504,649–651]

Glucocorticoids

Many investigators have used glucocorticoids to suppress the acute inflammatory response to CPB and clinical cardiac surgery, but beneficial effects in adult patients have been inconsistent.[652–654] Steroids reduce release of rapid-response cytokines, TNF-alpha, and IL-1-beta from macrophages,[655] enhance release of IL-10,[656–657] and suppress expression of endothelial cell selectins and neutrophil integrins.[658] Clinically, glucocorticoids decrease endotoxin release,[659] shift the cytokine balance towards the anti-inflammatory side,[659–661] and decrease expression of neutrophil integrins.[652] Clinical results from a few randomized trials are conflicting: one study observed earlier extubation and reduced shivering,[662] but another found increased blood glucose levels and delayed extubation.[663,664] Differences in specific steroids, dosing, and timing may explain some of these discrepancies.

Recent observations regarding the inhibitory effect of glucocorticoids on transcription factor nuclear factor-κB (NF-κB) may provide a rationale for using glucocorticoids to suppress the acute inflammatory response to CPB.[665] This inducible transcription factor controls the expression of genes encoding a wide array of proinflammatory mediators, including cytokines, inducible NO synthase, and adhesion molecules, and is activated by IL-1-beta, TNF-alpha, reactive oxidants, and other noxious stimuli.[654,666–668] Given the multiplicity and redundancy of pathways involved in the inflammatory response to bypass, inhibition of a common "upstream" control point in transcriptional regulation of inflammatory genes is an attractive strategy.

Protease Inhibitors

Aprotinin is a natural serine protease inhibitor in the kinin superfamily that strongly inhibits plasmin and weakly inhibits kallikrein.[669] Plasma concentrations of 4 to 10 KIU (kallikrein inhibitory units) of aprotinin completely inhibit plasmin, but 250 to 400 KIU are required to fully inhibit kallikrein.[669] Clinical doses of aprotinin totally inhibit plasmin, but are not sufficient to completely inhibit kallikrein.[670] The antifibrinolytic and platelet-sparing effects of the drug are well known and significantly reduce blood losses during and after complex cardiac surgery.[671–672] The anti-inflammatory effects of aprotinin are more difficult to quantitate and may reflect multiple mechanisms including partial kallikrein inhibition, direct effects, and inhibition of NF-κB.[673]

In vitro aprotinin inhibits kallikrein formation, and attenuates complement activation and release of platelet beta thromboglobulin and neutrophil elastase.[674] Aprotinin also

reduces neutrophil transmigration and expression of ICAM-1 and vascular cell adhesion molecule-1 by endothelial cells.[675–676] Clinically, aprotinin reduces circulating TNF-alpha, IL-6, IL-8, and neutrophil CD11b expression,[653,677–678] and synergistically increases IL-10 synthesis.[657,678] The drug may also attenuate neutrophil activation and myocardial damage during aortic cross-clamping[679] and reduce overall mortality.[672] Nevertheless, low- or high-dose aprotinin used in large, randomized controlled clinical trials fails to show a reduction in proinflammatory cytokines, activated complement, neutrophil elastase, and myeloperoxidase.[680] Thus the efficacy of aprotinin as an anti-inflammatory agent remains unresolved.

Nafamostat mesilate is a trypsin-like protease inhibitor that inhibits platelet aggregation and release, formation of kallikrein, and factor XIIa and neutrophil elastase release during in vitro extracorporeal recirculation.[681] Early clinical trials show that nafamostat mesilate inhibits fibrinolysis, preserves platelet numbers and function, reduces blood loss, and attenuates the acute inflammatory response by suppressing IL-6, IL-8, and malondialdehyde formation and neutrophil integrin expression.[682–683]

Comment

As described above, CPB and clinical cardiac surgery can produce a broad and acute inflammatory response that varies in degree among patients. The cause is the continuous recirculation of blood that is sequentially in contact with the wound, perfusion circuit, and intravascular compartment, to which is added the washout of reperfused ischemic organs and tissues. The acute inflammatory response together with microembolization is responsible for most of the morbidity of CPB and clinical cardiac surgery. Given the magnitude and diversity of the acute inflammatory response, it appears unlikely that drug cocktails or indirect measures directed against specific mediators of this response will prove more than mildly effective. Efforts to temporarily inhibit the more important mediators, specifically complement[684] and neutrophils, during the perioperative period are more attractive and achievable targets that could produce more immediate clinical benefits. Because our patients are vulnerable to infection and other forms of injury during and immediately after operation, and because the acute inflammatory response is an important first step in healing, the clinician must remember that temporary, reversible inhibitors are probably safer than permanent inhibitors.

Organ Damage

Cardiopulmonary bypass can preempt normal reflex and chemoreceptor control of the circulation, initiate coagulation, activate blood cells, release circulating cell-signaling proteins, generate vasoactive and cytotoxic substances, and produce a variety of microemboli. Venous pressure can be elevated, plasma colloid osmotic pressure is reduced, flow is nonpulsatile, and temperature is manipulated. Tissues and organs may suffer from regional malperfusion that is independent of physiologic controls, and is caused by microemboli, increased interstitial water, and perfusion with a variable amount of cytotoxic substances. Reversible and irreversible cell injury may occur, but damage is diffusely distributed throughout the entire body as individual cells or small groups of cells are affected. Ischemia-reperfusion injury augments damage to the heart and on occasion to other organs. Amazingly, the body is able to withstand and for the most part repair the cellular damage, although some abnormalities may appear later. This section summarizes the reversible and permanent organ damage produced by cardiopulmonary bypass (CPB) and complements the preceding two sections of this chapter.

MECHANISMS

Cardiac output during CPB is carefully monitored and synchronized with temperature and hemoglobin concentration to ensure that the entire body is adequately supplied with oxygen (see earlier section on extracorporeal perfusion systems). Excessive hemodilution reduces oxygen delivery,[685] and hemoglobin concentrations significantly below 8 g/L cause organ dysfunction at temperatures above 30°C.[686] However, regional hypoperfusion is not monitored,[687] is independent of reflex and chemoreceptor controls, and is influenced by the inflammatory response, which produces circulating vasoactive substances.[688–689] Regional perfusion is also influenced by acid-base relationships during cooling and may affect postoperative organ function.[690–691] Alpha-stat management (pH increases during cooling) decreases cerebral perfusion during hypothermia; pH stat (pH 7.40 is maintained by adding CO_2) improves organ perfusion but may increase embolic injury.[692] Temperature differences within the body and within organs produce regional temperature-perfusion mismatch,[693] which can precipitate regional hypoperfusion and acidosis due to inadequate oxygen delivery.

The inflammatory response produces the cytotoxic compounds and activated neutrophils and monocytes that can and do destroy organ and tissue cells (see section 12B). These agents directly access the specialized cells of every organ by passing between endothelial cell junctions to reach the interstitial compartment. Reduced plasma colloid osmotic pressure, elevated venous pressure, and widened endothelial cell junctions[694] increase the volume of the interstitial space during CPB in proportion to the duration of bypass, magnitude of the dissection, transfusions, and other factors. In prolonged complicated perfusions the interstitial

Table 12–5.

Major Sources of Microemboli

Gas	Foreign	Blood
Bubble oxygenators	Atherosclerotic debris	Fibrin
Air entry into the circuit	Fat, fat droplets	Free fat
Residual air in the heart	Fibrin clot	Aggregated chylomicrons
Loose purse-string sutures	Cholesterol crystals	Denatured proteins
Cardiotomy reservoir	Calcium particles	Platelet aggregates
Rapid rewarming	Muscle fragments	Platelet-leukocyte aggregates
Cavitation	Tubing debris, dust	Hemolyzed red cells
	Bone wax, talc	Transfused blood
	Silicone antifoam	
	Glue, Surgicel	
	Cotton sponge fiber	

compartment may increase 18 to 33%,[695] but intracellular water does not increase during CPB.

Microemboli are defined as particles less than 500 microns in diameter. They enter the circulation during CPB from a variety of sources.[696] Table 12-5 summarizes sources of gas, foreign, and blood-generated microemboli, which are more fully discussed in section 12A. Air entry into the perfusion circuit produces the most dangerous gas emboli because nitrogen is poorly soluble in blood and is not a metabolite. Carbon dioxide is rapidly soluble in blood and is sometimes used to flood the surgical field to displace air.[697] Foreign emboli, largely generated in the surgical wound, reach the circulation from the surgical field via the cardiotomy reservoir. The cardiotomy reservoir is the primary source of foreign emboli and the major source of blood-generated emboli, particularly fat emboli.[698] Extensive activation and physical damage to blood elements produce a wide variety of emboli, which tend to increase with the duration of perfusion.[692,699]

STRATEGIES FOR REDUCING MICROEMBOLI

Although discussed in earlier sections, the principal methods for reducing circulating microemboli deserve emphasis and include the following: adequate anticoagulation; membrane oxygenator; washing blood aspirated from the surgical wound;[700] filtering the cardiotomy reservoir; secure purse-string sutures around cannulas; strict control of all air entry sites within the perfusion circuit; removal of residual air from the heart and great vessels; avoidance of atherosclerotic emboli; and selective filtration of cerebral vessels.[701–702]

Many intraoperative strategies are available to reduce cerebral atherosclerotic embolization. These include routine epicardial echocardiography of the ascending aorta to detect both anterior and posterior atherosclerotic plaques and to find sites free of atherosclerosis for placing the aortic cannula.[703] Recently, special catheters with or without baffles or screens have been developed to reduce the number of atherosclerotic emboli that reach the cerebral circulation.[701,704] In patients with moderate or severe ascending aortic atherosclerosis a single application of the aortic clamp, as opposed to partial or multiple applications, is strongly recommended and has been shown to reduce postoperative neuronal and neurocognitive deficits in a large clinical series.[705] Retrograde cardioplegia is preferred over antegrade cardioplegia in these patients to avoid a sandblasting effect of the cardioplegic solution.[706] No aortic clamp may be safe or even possible in some patients with severe atherosclerosis or porcelain aorta. If intracardiac surgery is required in these patients, deep hypothermia may be used with or without graft replacement of the ascending aorta. If only revascularization is needed, pedicled single or sequential arterial grafts,[707] T or Y grafts from a pedicled mammary artery,[708] or vein grafts anastomosed to arch vessels can be used.

In-depth or screen filters (see section 12A) are essential for cardiotomy reservoirs and are usually used in arterial lines. The efficacy of arterial line filters is controversial since

screen filters with a pore size less than 20 microns cannot be used because of flow resistance across the filter. However, air and fat emboli can pass through filters, although 20-micron screen filters more effectively trap microemboli than larger sizes.[709]

CARDIAC INJURY

It is difficult to separate postoperative cardiac dysfunction from injury due to CPB, ischemia/reperfusion, direct surgical trauma, the disease being treated, and maladjustment of preload and afterload to myocardial contractile function. The heart, like all organs and tissues, is subject to microemboli, protease and chemical cytotoxins, activated neutrophils and monocytes, and regional hypoperfusion during CPB before and after cardioplegia or fibrillatory arrest. However, the heart is protected from CPB for at least one-half of the case when the aorta is cross-clamped. Some degree of myocardial "stunning" during the period coronary blood flow is interrupted is inevitable,[710] as is some degree of reperfusion injury after ischemia. Both myocardial edema and distention of the flaccid cardioplegic heart during aortic cross-clamping[711] reduce myocardial contractility. Lastly, if myocardial contractility is weak, excessive preload or high afterload during weaning from CPB increases ventricular end-diastolic volume, myocardial wall stress, and oxygen consumption. Thus postoperative performance of the heart depends on many variables and not just the injuries produced by CPB.

NEUROLOGIC INJURY

Because the brain controls all body activity, even small injuries may produce symptomatic, functional losses that are not detectable or important in other organs. Regional hypoperfusion, edema, microemboli, and circulating cytotoxins may cause subtle losses in cognitive function, behavioral patterns, and physiologic and physical function that can pass unnoticed, be accepted and dismissed, or profoundly compromise the patient's quality of life. Thus the brain is the most sensitive organ exposed to damage by CPB and also the organ that with the heart is most important to protect.

Assessment

Routine assessment of neurologic injury due to CPB is not done for most patients because of the priority of the cardiac lesion and because of costs in time and money. General neurologic examinations by untrained individuals or by members of the surgical team are not adequate to rule out subtle neurologic injuries, and this is the principal reason that the incidence of post-CPB nonstroke neurologic injury varies widely in the surgical literature.[712–714]

For studies designed to assess or reduce neurologic injury caused by CPB, nonroutine preoperative and postoperative tests are required. These special tests include a complete neurologic examination by a trained neurologist. To improve accuracy, a single neurologist should conduct all serial examinations. A standardized protocol of examination should be followed, with uniform reporting of results. The basic, structured examination includes a mental state examination; cranial nerve, motor, sensory, and cerebellar examinations; and examination of gait, station, deep tendon, and primitive reflexes.

The most obvious neuropsychologic abnormalities are coma, delirium, and confusion, but transitory episodes of delirium and confusion are often dismissed as due to anesthesia or medications. More subtle losses are determined by comparison of preoperative and postoperative performances using a standard battery of neuropsychologic tests prepared by a group of neuropsychologists.[715] A 20% decline in two or more of these tests suggests a neuropsychologic deficit that should be followed until resolved or not resolved.[716]

Computed axial tomograms or magnetic resonance imaging (MRI) scans are essential for the definitive diagnosis of stroke, delirium, or coma. Preoperative imaging is usually not necessary when new techniques such as diffusion-weighted MRI imaging, MRI spectroscopy, or MRI angiography are used to assess possible new lesions after operation.[717–719]

Biochemical markers of neurologic injury after cardiac surgery are relatively nonspecific and inconclusive. Neuron-specific enolase (NSE) is an intracellular enzyme found in neurons, normal neuroendocrine cells, platelets, and erythrocytes.[720] S-100 is an acidic calcium-binding protein found in the brain.[721–722] The beta dimer resides in glial and Schwann cells. Both S-100 and NSE increase in spinal fluid with neuronal death[721–722] and may correlate with neurologic injury after CPB.[723] However, plasma levels are contaminated by aspiration of wound blood into the pump and hemolysis, and are often elevated following prolonged CPB in patients without otherwise detectable neurologic injury.[724]

Populations at Risk

Advancing age increases the risk of stroke or cognitive impairment in the general population, and surgery, regardless of type, increases the risk still higher.[725] A European study compared 321 elderly patients without surgery to 1218 patients who had noncardiac surgery and found a 26% incidence of cognitive dysfunction 1 week after operation and a 10% incidence at 3 months.[726] Between 1974 and 1990 the number of patients undergoing cardiac surgery over age 60 and over age 70 increased twofold and sevenfold, respectively.[727] Figure 12-21 illustrates the relationship between age and cognitive dysfunction after coronary artery bypass graft and demonstrates a steep increase after the age of 60. Genetic factors also influence the incidence of cognitive dysfunction following cardiac surgery.[728] The incidence of cognitive dysfunction at 1 week following cardiac surgery is approximately double that of noncardiac surgery.

As the age of cardiac surgical patients increases, the number with multiple risk factors for neurologic injury also

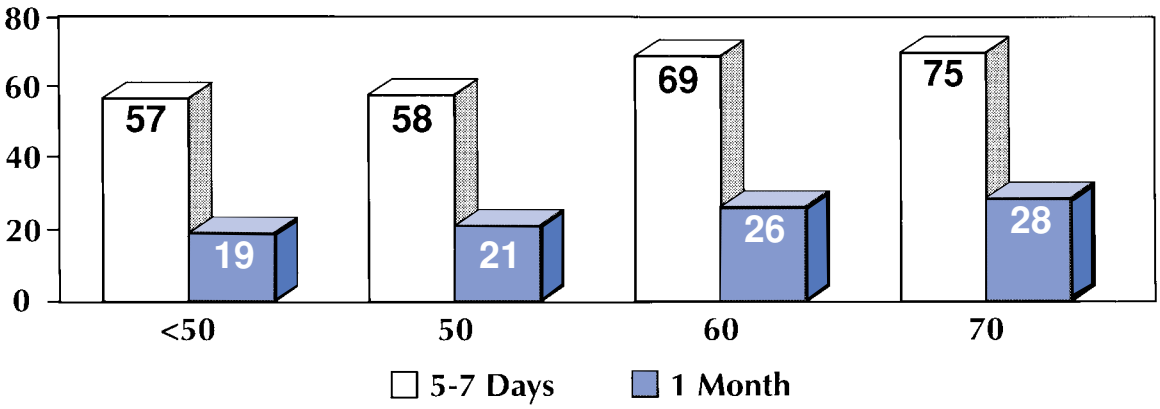

Figure 12-21. Effect of age by decade on neuropsychologic outcome after coronary artery bypass graft surgery. Abnormal neuropsychologic outcomes at 1 week and 1 month postoperatively are more common with advancing age. Percentages of patients with deficits on two or more tests are shown (n = 374). (*Reproduced with permission from Hammon et al.*[131])

increases. Risk factors for adverse cerebral outcomes are listed in Table 12-6.[729] These factors are divided into stroke with a permanent fixed neurologic deficit (type I) and coma or delirium (type II). Hypertension and diabetes occur in approximately 55% and 25% of cardiac surgical patients, respectively.[730] Fifteen percent have carotid stenosis of 50% or greater, and up to 13% have had a transient ischemic attack or prior stroke. The total number of atherosclerotic stenoses in the brachiocephalic vessels adds to the risk of stroke or cognitive dysfunction,[731] as does the severity of atherosclerosis in the ascending aorta as detected by epiaortic ultrasound scanning.[732] Palpable ascending aortic athero-

Table 12–6.

Adjusted Odds Ratios for Type I and Type II Cerebral Outcomes Associated with Selected Risk Factors

Factor	Model for type I cerebral outcome	Model for type II cerebral outcome
Significant factors, $p < .05$		
Proximal aortic atherosclerosis	4.52	
History of neurologic disease	3.19	
Use of intra-aortic balloon pump	2.60	
Diabetes mellitus	2.59	
History of hypertension	2.31	
History of pulmonary disease	2.09	2.37
History of unstable angina	1.83	
Age (per additional decade)	1.75	2.20
Systolic blood pressure >180 mm Hg at admission		3.47
History of excessive alcohol consumption		2.64
History of coronary artery bypass graft		2.18
Dysrhythmia on the day of surgery		1.97
Antihypertensive therapy		1.78
Other factors (p not significant)		
Perioperative hypotension	1.92	1.88
Ventricular venting	1.83	
Congestive heart failure on the day of surgery		2.46
History of peripheral vascular disease		1.64

Source: Adapted with permission from Roach et al.[729]

sclerotic plaques markedly increase the risk of right carotid arterial emboli as detected by Doppler ultrasound.[733] The incidence of severe aortic atherosclerosis is 1% in cardiac surgical patients less than 50 years old and is 10% in those aged 75 to 80.[734]

Mechanisms of Injury

The two major causes of organ dysfunction and injury during CPB are microemboli and hypoperfusion, which are to some extent mutually exclusive. Microemboli are distributed in proportion to blood flow;[735] thus reduced cerebral blood flow reduces microembolic injury but increases the risk of hypoperfusion.[736] During CPB both alpha-stat acid-base management and phenylephrine reduce cerebral injury in adults, probably by causing cerebral vessel vasoconstriction and reducing the number of microemboli.[736–737] Air,[738] atherosclerotic debris,[739] and fat are the major types of microemboli causing brain injury in clinical practice, and all cause neuronal necrosis by blocking small cerebral vessels.[692] Massive air embolism causes a large ischemic injury, but gaseous cerebral microemboli may directly damage endothelium in addition to blocking blood flow.[740] The recent identification of unique small capillary arteriolar dilatations in the brain associated with fat emboli (Fig. 12-22)[741] raises the possibility that these emboli not only block small vessels, but also release cytotoxic free radicals, which may significantly increase the damage to lipid-rich neurons.

Anemia and elevated cerebral temperature increase cerebral blood flow but may cause inadequate oxygen delivery to the brain;[742] however, these conditions are easily avoided during clinical cardiac surgery. Although some investigators speculate that normothermic and/or hyperthermic CPB cause cerebral hypoperfusion,[743] experimental studies indicate that cerebral blood flow increases with temperature.[744] Brain injuries associated with this practice are more likely due to increased cerebral microemboli, which produce larger lesions at higher cerebral temperatures.[735] Reduced brain temperature is protective against neural cell injury and remains an important neuroprotective strategy.

Additional Neuroprotective Strategies

Primary strategies for avoiding air, atherosclerotic particulates, and blood-generated microembolism are presented above and in section 12A. Recommended conditions for protecting the brain during CPB include mild hypothermia (32 to 34°C) and hematocrit above 25%.[744] Temporary increases in cerebral venous pressure caused by superior vena cava obstruction and excessive rewarming above blood temperatures of 37°C should be avoided.[745–746] A randomized study in which patients were mildly rewarmed to 35°C core temperature demonstrated improved neurocognitive outcomes over patients rewarmed to 37°C.[746] Either jugular venous bulb oxygen saturation or near-infrared cerebral oximetry are recommended for monitoring cerebral perfusion in patients who may be at high risk for cerebral injury.[747]

Barbiturates reduce cerebral metabolism by decreasing spontaneous synaptic activity[748] and provide a definite neuroprotective effect during clinical cardiac surgery using CPB.[749] Unfortunately, these agents delay emergence from anesthesia and prolong intensive care unit stays. A recent study of high-risk patients randomized to aprotinin or placebo found a powerful protective effect against stroke for full-dose aprotinin in coronary artery bypass graft patients.[750] A larger randomized multi-institutional study is planned. N-methyl-D-aspartate antagonists, which are effective in animals, provide mild protection compared to control

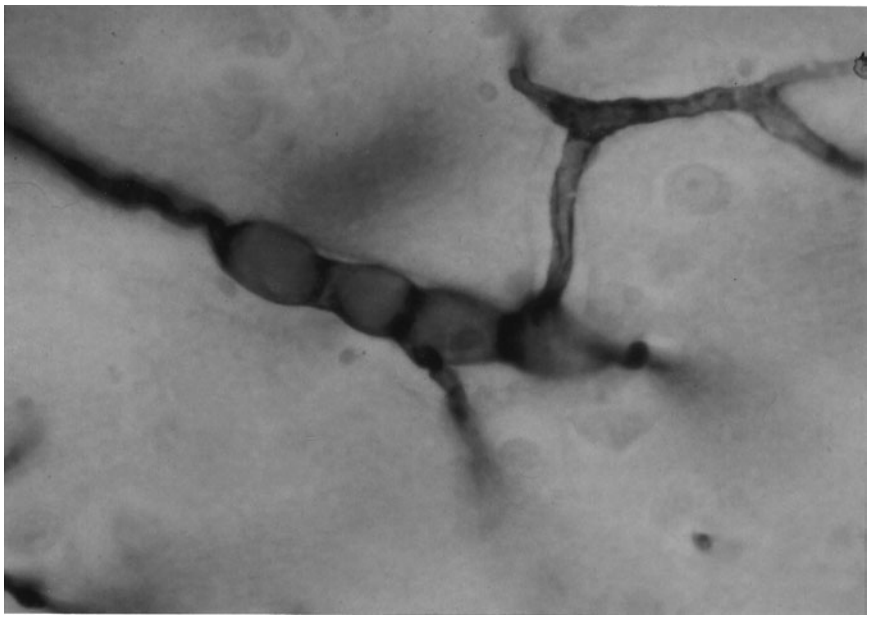

Figure 12-22. Small capillary and arterial dilatations in cerebral vessels in a patient who expired 48 hours after coronary artery bypass graft surgery using cardiopulmonary bypass. Alkaline phosphatase-stained celloidin section, 100 μm thick 100×.

patients, but have a high incidence of neurologic side effects.[751] A small study demonstrated a neuroprotective effect of lidocaine.[752] Currently no pharmacologic agent is recommended for protection of the central nervous system during CPB.

Off-pump myocardial revascularization theoretically avoids many of the causes of cerebral injury due to CPB, but as noted above, many causes of neuronal injury are independent of CPB and related to atherosclerosis and air entry sites into the circulation. Nonrandomized measurements of carotid emboli by Doppler ultrasound indicate fewer emboli and slightly improved neurocognitive outcomes in high-risk patients who have off-pump surgery.[753] A randomized trial of off-pump versus on-pump patients failed to show a significant difference in neurologic outcome between methods.[754]

Prognosis

Neuropsychologic deficits that are present after 3 months are almost always permanent.[755] Assessments after that time are confounded by development of new deficits, particularly in aged patients.[756]

LUNG INJURY

Patient factors and the separate effects of operation and CPB combine to compromise lung function early after operation. Chronic smoking and emphysema are the most common patient factors, but muscular weakness, chronic bronchitis, occult pneumonia, preoperative pulmonary edema, and unrelated respiratory disease are other contributors to postoperative pulmonary dysfunction. Incisional pain, lack of movement, shallow respiratory sighs, increased work of breathing, reduced pulmonary compliance, weak cough, increased pulmonary arterial-venous shunting, and interstitial edema, to some degree are consequences of anesthesia and any operation. CPB significantly adds to this injury.

During CPB the lungs are supplied by the bronchial arteries and pulmonary arterial blood flow may be absent or minimal. Whether or not alveolar cells suffer ischemic/reperfusion injury is unclear, but the lungs are subject to many insults that combine to increase pulmonary capillary permeability and interstitial lung water. Hemodilution, reduced plasma oncotic pressure, and temporary elevation of left atrial or pulmonary venous pressure during CPB or during weaning from CPB increase extravascular lung water.[757,758] Microemboli[759] and circulating cellular, vasoactive, and cytotoxic mediators of the inflammatory response[760–764] reach the lung via bronchial arteries during CPB and with resumption of the pulmonary circulation during weaning. These agents increase pulmonary capillary permeability, perivascular edema, and bronchial secretions, and perhaps cause observed changes in alveolar surfactant.[765] The combination of increased interstitial lung water and bronchial secretions, altered surfactant, patient factors, and the consequences of operation reduces pulmonary compliance and functional residual capacity and increases the work of breathing.[766] All of these changes combine to enhance regional atelectasis, increase susceptibility to infection, and increase the physiologic arterial-venous shunt, which reduces systemic arterial Pa_{O_2}.

Postoperative respiratory care is based upon restoring normal pulmonary capillary permeability and interstitial lung volume; preventing atelectasis; reinflating atelectatic segments; maintaining normal arterial blood gases; and preventing infection and facilitating removal of bronchial mucus. Improved postoperative respiratory care, an understanding of the mechanisms of lung injury during CPB, and efforts to prevent or control the causes of injury[767,768] have markedly reduced the incidence of pulmonary complications in recent years[769] (see Chapter 16 for a more detailed discussion of postoperative care).

Acute respiratory distress syndrome is a rare complication of lung injury during cardiopulmonary bypass and is usually caused by intrabronchial bleeding from traumatic injury by the endotracheal tube or pulmonary artery catheter,[766] or to extravasation of blood into alveoli from acute increases in pulmonary venous pressure or severe pulmonary capillary toxic injury.

RENAL INJURY

As with other organs, the preoperative health of the kidneys is a major factor in the ability of that organ to withstand the microembolic, cellular,[770] and regional malperfusion injuries caused by CPB. Risk factors for postoperative renal dysfunction include age over 70 years, diabetes mellitus, previous cardiac surgery, congestive heart failure, and a complex, prolonged operation.[771] The incidence of acute renal failure requiring dialysis after CPB is remarkably low, averaging 1%; however, the incidence increases to 5% with complex operations.[772]

Some degree of renal injury is inevitable during CPB[773] and postperfusion proteinuria occurs in all patients.[774] Increased expression of neutrophil CD11b receptors and elevated neutrophil count are significantly related to postoperative acute renal failure, defined as a 150% increase in plasma creatinine over baseline.[775] Renal blood and plasma flow, creatinine clearance, free water clearance, and urine volume decrease without hemodilution.[776] Hemodilution attenuates most of these functional changes and also reduces the risk of hemoglobin precipitation in renal tubules if plasma-binding proteins become saturated with free hemoglobin during extracorporeal perfusion. Hemoglobin is toxic to renal tubules and precipitation can block both blood and urine flow to the tubules.[777] Hemodilution dilutes plasma hemoglobin; improves flow to the outer renal cortex; improves total renal blood flow; increases creatinine, electrolyte, and water clearance; and increases glomerular filtration and urine volume.[775]

Perioperative periods of low cardiac output and/or hypotension added to the microembolic, cellular, and cytotoxic injuries of CPB, and to any preoperative renal disease are the major causes of postoperative renal failure.[770,777] Low cardiac output reduces renal perfusion pressure and causes angiotensin II production and renin release, which further decrease renal blood flow. Kidneys, already compromised by preoperative disease and the CPB injury, are particularly sensitive to ischemic injury secondary to low cardiac output and hypotension. Thus perioperative management includes efforts to maximize cardiac output using dopamine or dobutamine if necessary,[778] avoiding renal arterial vasoconstrictive drugs, providing adequate crystalloid infusions to maintain urine volume, and alkalinizing urine to minimize precipitation of tubular hemoglobin if excessive hemolysis has occurred. Preliminary studies with a natriuretic peptide found in human urine, urodilantin, indicate the possibility of attenuating postoperative oliguria.[779]

If perioperative low cardiac output and hypotension do not occur,[780] the normal kidney has sufficient functional reserve to provide adequate renal function during and after operation. The appearance of oliguric renal failure is ominous and usually requires dialysis, which is generally permanent if required for more than 2 weeks.[780] Oliguric renal failure markedly increases morbidity and mortality by approximately eightfold.[781]

INJURY TO THE LIVER AND GASTROINTESTINAL ORGANS

Although subjected to microemboli, cytotoxins, and regional malperfusion during CPB, the enormous functional reserve and reparative processes of the normal liver nearly always overcome the injury without consequences. Often liver enzymes are mildly elevated,[782] and 10 to 20% of patients are mildly jaundiced.[783] Extensive red cell hemolysis increases the likelihood of mild jaundice. Persistent and rising bilirubin two or more days after CPB may precede development of liver failure and is associated with increased morbidity and mortality.[784] Catastrophic liver failure, however, occurs in patients with overwhelming sepsis, oliguric renal failure, anesthetic or drug toxicity, or after a prolonged period of low cardiac output or an episode of hemorrhagic shock and multiple blood transfusions and is uniformly fatal.[785] The liver usually is involved in patients who develop multiorgan failure and is often presaged by sudden hypoglycemia.

PANCREATIC INJURY

Less than 1% of patients develop clinical pancreatitis after CPB, but approximately 30% develop a transitory, asymptomatic increase in plasma amylase and/or lipase.[786–788] Autopsy studies of the pancreas soon after CPB indicate occasional evidence of histologic pancreatitis.[789] A history of recurrent pancreatitis, perioperative circulatory shock or hypotension, excessively prolonged CPB, and continuous high doses of inotropic agents are risk factors for developing postoperative pancreatitis.[790] Experimentally and clinically, high doses of calcium increase intracellular trypsinogen activation and histologic evidence of pancreatitis.[791–793] Fulminant pancreatitis is very rare, but is often fatal.[794]

STOMACH AND GUT INJURY

CPB at adequate flow rates does not decrease splanchnic blood flow.[795] Risk factors for gastrointestinal complications include advanced age, emergency surgery, prolonged CPB, postoperative low cardiac output or shock, prolonged vasopressor therapy, and elevated preoperative systemic venous pressure.[796]

CPB decreases gastric pH, which declines further after operation.[797] Prior to the advent of histamine blockers and regular use of antacids, duodenal and/or gastric erosion, ulcer, and bleeding were frequent complications following clinical cardiac surgery[798] and were associated with mortality that approached 33 to 50%.[799] These complications are now uncommon.

Several days to 1 week after operation very elderly patients rarely may develop mesenteric vasculitis or severe mesenteric vasoconstriction that proceeds to small bowel ischemia and/or infarction in response to vasopressors. New-onset abdominal pain with a silent, rigid abdomen and abrupt rise in white blood cell count may be the only signs of this catastrophic complication, which is frequently fatal. If suspected before infarction, infusion of papaverine or alternative vasodilators directly into the mesenteric arteries may prevent or limit subsequent infarction.[800] The role of CPB in the etiology of this complication is not known.

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12A: Perfusion Systems

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CHAPTER 13

Transfusion Therapy and Blood Conservation

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With the development of cardiac surgery in the 1950s to correct congenital heart defects came the need for large-volume blood transfusions. In the 1960s and 1970s, the introduction of valve prostheses and direct grafting of coronary arteries made the correction of acquired heart disease a possibility. These landmarks, along with the liberal use of homologous blood transfusion therapy, led to rapid growth of the field. Commensurate with the growth of cardiac surgery as a field was an increasing incidence of transfusion-transmitted hepatitis in the 1970s, ultimately alerting the public and treating physicians to the concept of blood conservation. The emergence of infection by human immunodeficiency virus (HIV) greater heightened the interest in this area, leading to the current practices of blood conservation therapy in cardiac surgery.

Historically, open-heart surgery has been associated with a high usage of blood transfusion. Some reports suggest that up to 70% of this patient population requires blood transfusions, resulting in an average of two to four donor exposures per patient.[1,2] It has been reported that 10% of all red blood cell units transfused in the United States are administered during coronary bypass surgery.[3] Almost all patients received blood transfusion in the early days of cardiac surgery. However, with an increased awareness of blood-borne infectious diseases, lack of donors, great cost to both the patient and the institution, allergic reaction, blood-type mismatch, and the needs of special populations such as Jehovah's Witnesses, a greater effort has been made to perform open-heart procedures without blood transfusions even in high-risk patients. Advances in perioperative medications that minimize blood loss; greater tolerance of lower hematocrits, especially on bypass; and improvements in surgical techniques resulting in shorter operative times have allowed for these extensive procedures to be performed without significant blood loss.

The high transfusion rates associated with cardiac surgery have been well characterized and are likely due to the coagulopathy, platelet dysfunction, and red cell hemolysis that occur as a result of the cardiopulmonary bypass circuit.[4–6] The introduction of hemodilution using crystalloid pump-priming solution rather than whole blood dramatically reduced the transfusion requirements seen during coronary artery bypass grafting (CABG) procedures.[7] While this technique has reduced the amount of blood transfused during cardiopulmonary bypass (CPB), the resulting hemodilution contributes to the risk of low intraoperative and postoperative hematocrit, especially in patients who weigh less than 70 kg, thereby posing a new risk for transfusion.

Efforts at reducing the use of homologous blood in cardiac surgery began almost 40 years ago. The efforts to decrease allogeneic blood exposures have been a topic of constant review and attention because of the desires of both patients and their physicians to conserve blood during the perioperative period. These joint efforts have affected virtually every aspect of the manner in which heart surgery and CPB are performed. Our experience combined with the experiences of others has led to the development of an integrated, comprehensive blood conservation program that makes the goal of bloodless heart surgery possible.

PAST EXPERIENCE: A REVIEW OF THE LITERATURE

Since the earlier days of cardiac surgery, there have been several reports of minimizing the use of blood and blood products both intraoperatively and postoperatively. While most of these studies have focused on the use of one particular modality or pharmacologic agent, these techniques were applied in the context of an entire set of blood conservation measures. Collectively the results of these reports provide an important body of information that can be used as an aid to evaluating the relative effectiveness of various combinations of the presently available blood conservation techniques. Table 13-1

Table 13–1.

Literature Review of Blood Conservation Techniques in Patients Undergoing Combined Procedures

Year	Reference	Patients (no.)	Preop. donation	Intraop. donation	Trigger CPB	Trigger postop.	Med. shed	Drugs	Transfused (%)	Units/patient
1967	Beall[61]	1818	No	1180	NS	NS	No	No	8.6	NS
1975	Cohn[62]	400	No	500–1000	15	NS	No	No	96.5	3.9
1976	Cove[63]	44	Yes	No	NS	NS	No	No	75	2.0
1977	Kaplan[64]	60	No	750	NS	NS	No	No	100	5.5
1977	Lilleaasen[65]	30	No	855	NS	NS	No	No	100	3.85
1978	Schaff[66]	63	NS	NS	NS	35	Yes	No	NS	2.4
1979	Thurer[67]	54	No	NS	NS	30	Yes	No	59	1.6
1979	Lambert[68]	774	NS	NS	NS	NS	No	Ami	67	5.5
1983	Johnson[69]	168	NS	No	NS	NS	Yes	No	NS	1.0
1987	Love[70]	58	Yes	No	NS	NS	Yes	No	36	1.1
1988	Giordano[71]	65	No	500	NS	25	No	No	NS	6.32
1988	Giordano[72]	50	No	No	NS	NS	NS	No	NS	13.7
1989	Page[73]	50	No	Yes	17	30	Yes	No	88	3.15
1989	Lepore[74]	67	No	NS	NS	NS	Yes	No	74.6	2.7
1989	DelRossi[33]	170	NS	No	NS	30	No	Ami	NS	2.8
1989	Britton[75]	104	Yes	1000	NS	NS	No	No	34	0.7
1990	Horrow[34]	18	No	No	NS	NS	Yes	Trax	NS	0.6
1991	Horrow[76]	77	NS	NS	NS	24	Yes	Trax	32	NS
1991	Carey[77]	222	Yes	No	21	24	Yes	No	53	2.2
1992	Scott[78]	60	Yes	575	18	24	Yes	No	58	4.0

1992	Ikeda[79]	3022	No	Yes	21	NS	Yes	No	72	9
1992	Dzik[80]	79	Yes	NS	NS	NS	NS	NS	32	NS
1993	Helm[81]	35	No	1562	15	22	Yes	No	17	1.0
1994	Rosengart[82]	15	No	1180	15	NS	Yes	Ap	0	0
1994	Wong[83]	20	No	1200	18	24	No	No	30	0.45
1994	Murkin[84]	29	No	No	NS	20	No	Ap	58.6	4.1
1994	Axford[85]	16	No	No	NS	25	Yes	No	62	8.6
1995	Shinfield[86]	20	No	No	NS	NS	NS	Ap	50	1.1
1995	Spiess[87]	591	NS	NS	NS	NS	No	No	78.5	6
1995	Parolari[88]	1310	Yes	Yes	NS	24	No	Ap	21.1	0.84
1995	Sandrelli[29]	348	Yes	Yes	18	24	Yes	Ap	12.6	0.34
1998	Shapira[89]	114	No	No	20	25	No	Ami	35	0.7
2001	Tempe[90]	60	No	Yes	NS	24	No	Ap	60	0.75
2001	Van der Linden[91]	636	No	Yes	20	21	No	Ap	18	0.51
2004	Moskowitz[92]	307	Yes	Yes	20	24	Yes	Ap	11	0.5

NS = not stated.

summarizes the findings of 35 studies of patients undergoing non-CABG or combined procedures requiring CPB.

Table 13-2 similarly summarizes the findings of 41 studies of patients undergoing CABG only. These studies provide information about the techniques applied, as well as outcome measures of patients receiving homologous transfusions. Although preoperative autologous donation was applied only sporadically (12 of 73 studies), nonblood prime was applied almost universally (65 of 73 studies). The majority of studies achieving very low transfusion rates used low to low-moderate transfusion triggers both during and following CPB. Conversely, the studies reporting high rates of transfusion either used higher transfusion triggers or the triggers were not stated, indicating that the investigators likely did not recognize or place enough emphasis on this essential blood conservation measure. Finally, the studies that achieved overall transfusion rates of less than 30% used the cornerstones of blood conservation, namely, pre- or intraoperative autologous blood donation, nonblood priming, return of residual circuit blood to the patient, low or moderately low intra- and postoperative transfusion triggers, and reinfusion of shed mediastinal blood. Several of these studies bear special attention.

The first program to report less than 10% transfusion rates in non–Jehovah's Witness CABG patients was that of Cosgrove and colleagues at the Cleveland Clinic in 1978.[8] This report of 50 patients undergoing elective CABG demonstrated transfusion rates of only 6%, with a mean of 0.06 unit per patient receiving blood. Included in Cosgrove's study were the six principal techniques of blood conservation stated earlier, many of which are still used today in blood conservation programs throughout the world, namely

1. Intraoperative autologous donation
2. Nonblood prime
3. Return of all residual CPB circuit blood
4. Intraoperative salvage
5. Use of the lowest safe level of anemia during CPB as well as in the postoperative period
6. Reinfusion of shed mediastinal blood

Later studies took advantage of pharmacologic developments such as serine protease inhibitors, antifibrinolytics, and erythropoietin. By the early 1990s, these pharmacologic adjuncts to blood conservation had become readily available and could be categorized as agents useful in perioperative stimulation of bone marrow for red blood cell production (e.g., erythropoietin) and agents useful in reducing postoperative bleeding (e.g., serine protease inhibitors and antifibrinolytics).

In 1990, Ovrum and colleagues confirmed the effectiveness of the simple "core" approach to blood conservation.[9] In 121 consecutive elective CABG patients, the authors achieved a transfusion rate of 4.1% and 0.06 unit per patient. In 1991, Ovrum applied these same principles to 500 elective CABG patients and obtained similar low rates of transfusion (2.4% of patients).[10] The authors found this six-step blood conservation program to be simple, safe, and cost-effective.

By the 1990s, there also were some technical advances in CPB designed to minimize the need for transfusions as well as for hemodilution. With better oxygenators came a reduction in the volume of the CPB circuit, accompanied by a reduction in the amount of hemodilution that occurred.[11] Circuit volume could be further reduced by replacing as much of the crystalloid circuit prime as possible with autologous blood drained from the arterial cannula into the circuit immediately prior to CPB, called *retrograde autologous priming* (RAP), as well as displacing the venous side of the crystalloid prime when first initiating CPB.[12] These relatively simple maneuvers can reduce the crystalloid prime to a volume of roughly 200 mL. In addition, technical advances such as leukocyte filters and heparin-bonded circuits reduced the inflammatory response of the body to the blood interface with the CPB circuit, which ultimately can lead to less homologous blood requirement.[13,14]

The addition of newer pharmacologic and technologic advances to the proven "core" conservation measures as established by Cosgrove and Ovrum had the potential to markedly reduce and even eliminate the need for transfusion even in the face of the more difficult patient characteristics increasingly being encountered. This then became the goal of blood conservation programs.

PREOPERATIVE MANAGEMENT

Identification of Patients at Risk

The coagulopathy associated with CPB is related primarily to the interaction of blood components with the artificial surfaces of the CPB circuit, which results in derangements in platelet function, abnormal functioning of the coagulation cascades, and excessive fibrinolysis. The administration of high-dose heparin to prevent coagulation within the CPB circuit and hypothermia achieved during bypass further contribute to hemostatic derangements. Finally, while the use of asanguineous crystalloid prime rather than the whole-blood pump prime used historically has reduced the amount of blood transfused during CPB dramatically, the resulting hemodilution contributes to the risk of low intraoperative and postoperative hematocrit, which can be independent risk factors for transfusion in the postoperative period. Other risk factors can be assessed in the preoperative state that can identify those patients who may be at high risk of bleeding or who have a low red cell mass, both of which may require autologous blood transfusions.

One of the most important predictors of postoperative bleeding in the surgical patient is a personal or family history of any excessive bleeding or documented bleeding disorders. Many disorders can be confirmed with simple laboratory tests demonstrating some level of coagulation derangement. However, in the cardiothoracic patient population, medications and acquired medical diseases and their associated hemostatic defects are likely to be the most common risk for bleeding. Some of the most commonly seen problems are summarized in Tables 13-3 and 13-4. Notably, the use of

Table 13–2.

Literature Review of Blood Conservation Techniques in Patients Undergoing CABG

Year	Reference	Patients (no.)	Preop. donation	Intraop. donation	Trigger CPB	Trigger postop.	Med. shed	Drugs	Transfused (%)	Units/patient
1974	Zubiate[93]	477	Yes	1800	15	22	No	No	29	1.1
1978	Yeh[94]	240	NS	NS	NS	33	No	No	77.8	1.45
1979	Schaff[95]	135	No	NS	NS	NS	Yes	No	100	2.4
1979	Cosgrove[8]	50	No	675	15	NS	Yes	No	6	0.06
1980	Bayer[96]	1246	NS	NS	NS	NS	NS	No	NS	2.6
1984	Weisel[97]	13	No	NS	21	21	No	No	50	1.4
1985	Cosgrove[26]	441	No	NS	15	22	Yes	No	10	0.3
1986	Belcher[98]	90	No	550	NS	25	No	No	10	0.18
1987	Breyer[99]	43	No	No	18	25	Yes	No	42	2.23
1988	Hartz[100]	21	NS	NS	NS	NS	NS	NS	30	NS
1989	Dietrich[101]	25	No	739	15	30	Yes	No	68	1.6
1989	Tyson[102]	52	No	Yes	NS	25	Yes	No	74.5	4.5
1989	Owings[103]	107	Yes	250–500	NS	NS	Yes	No	27	0.8
1990	LoCicero[104]	100	No	No	NS	NS	Yes	No	31	0.7
1990	Jones[105]	50	NS	1000	21	23	Yes	No	34	0.67
1991	Jones[106]	100	No	1000	15	21	Yes	No	18	0.31
1991	Ovrum[10]	121	No	815	15	25	Yes	No	4.1	0.06
1991	Ovrum[9]	500	No	799	15	25	Yes	No	2.4	NS
1992	Davies[107]	32	No	857	20	24	No	No	NS	1.6

(*Continued*)

Table 13–2.

Literature Review of Blood Conservation Techniques in Patients Undergoing CABG (Continued)

Year	Reference	Patients (no.)	Preop. donation	Intraop. donation	Trigger CPB	Trigger postop.	Med. shed	Drugs	Transfused (%)	Units/patient
1992	Watanabe[108]	26	Yes	NS	18	21	NS	Epo	0	0
1992	Johnson[109]	18	Yes	750	NS	25	Yes	No	0	0
1993	Kulier[110]	12	Yes	No	NS	NS	NS	Epo	0.08	0.33
1993	Karski[111]	75	NS	NS	18	20	Yes	Trax	28	NS
1993	Sutton[112]	60	No	No	NS	NS	No	No	NS	1.7
1993	Ward[113]	17	No	No	24	24	Yes	No	89	NS
1993	Tobe[114]	24	No	750	NS	NS	Yes	No	71	4.1
1993	Schoenberger[115]	50	No	799	18	25	Yes	No	35	0.8
1994	Paone[116]	314	No	No	18	20	No	No	31.5	2.34
1994	Lemmer[117]	151	No	No	18	21	Yes	Trax	40	2.2
1994	Petry[118]	45	No	1000	20	30	No	No	66	1.3
1994	Arom[119]	100	NS	NS	NS	NS	No	Ami	NS	1.4
1995	Helm[58]	45	No	1607	15	22	Yes	No	28	1.2
1996	Helm[120]	100	No	1450	15	22	Yes	Ap/epo	0	0
1997	Rosengart[121]	30	No	1300	15	22	Yes	Ap/epo	0	0
1999	Rousou[122]	175	NS	No	20	20	No	Ami	4	NS
2001	Karkouti[123]	1007	No	Yes	18	20	Yes	TA	29.4	0.5
2004	Takai[124]	228	NS	NS	NS	NS	No	No	NS	0.88
2004	Lilly[125]	244	No	NS	NS	NS	No	No	NS	1.0

NS = not stated.

Table 13–3.

Medications Associated with an Increased Risk of Bleeding

Drug	Effect on hemostasis
Aspirin	Irreversible platelet inhibition by blocking platelet cyclooxygenase
Heparin	Inhibition of factors II and X, both direct and indirect thrombocytopenia
	Mostly antibody-mediated (HIT)
Coumadin	Multiple factor deficiency by blocking gamma-carboxylation
	Vitamin K–dependent factors
Antibiotics	Multiple factor deficiency owing to vitamin K malabsorption
Multiple drugs	Thrombocytopenia owing to bone marrow inhibition of platelet production

aspirin alone or included in other medications intended for pain relief or treatment of other ailments is very common. The prevalence among patients undergoing unplanned surgery may be as high as 50%, and this may be even higher among patients with previously diagnosed coronary artery disease.[15,16] The currently published data would suggest that this does not represent a significant bleeding risk, and there is little evidence to suggest that bleeding times correlate with operative blood loss in these patients.[17,18]

Herbal Extracts for Cardiovascular Health

The use of herbal extracts and complementary medicine has become popular in the prevention of arterial thrombotic disease. In 1997, an estimated $21 billion was spent in the United States on complementary and alternative therapies.[19,20] Herbs such as thyme and rosemary have been shown to have a direct inhibitory effect on platelets.[21]

Despite the increased potassium contained in fruits and nuts, menu planning for patients on warfarin can

Table 13–4.

Acquired Diseases Associated with an Increased Risk of Bleeding

Condition	Effect on hemostasis
ESRD/uremia	Irreversible platelet dysfunction by platelet inhibitory metabolites
Liver disease	Multiple factor deficiency owing to defective synthesis
	Thrombocytopenia owing to hypersplenism
Malabsorption	Multiple factor deficiency from vitamin K deficiency
SLE	Thrombocytopenia and thrombocytopathy owing to platelet autoantibodies
	Factor deficiency owing to prothrombin deficiency occasionally associated with lupus-type inhibitor
Amyloid	Capillary fragility owing to vascular amyloid infiltration
	Factor X deficiency owing to absorption by amyloid
Malignancy	Thrombocytopenia and anemia owing to chemotherapy
	Thrombocytopenia owing to marrow infiltration of tumor
	Factor deficiency owing to DIC (advanced stages of cancer) as well as some chemotherapeutic agents

include a healthy diet of these foods without compromising the stability of their oral anticoagulation therapy because most fruits are not important sources of vitamin K, with the exception of some berries, green fruits, and prunes.[22] In a case report regarding fish oil supplementation, it was demonstrated that additional anticoagulation could have resulted from an interaction with warfarin therapy. This case reveals that a significant rise in the international normalization ratio (INR) occurred after the dose of concomitant fish oil was doubled. Fish oil, an omega-3 polyunsaturated fatty acid, consists of eicosapentaenoic acid and docosahexaenoic acid. This fatty acid may affect platelet aggregation and/or vitamin K–dependent coagulation factors. Omega-3 fatty acids may lower thromboxane A_2 supplies within the platelet, as well as decrease factor VII levels.[23]

The popularity of herbal additives can be evidenced by the over $700 million spent annually and the continued expected spending on such products.[24] Despite the potential benefits of many herbs with regard to improved well-being, many adverse risks exist. Primarily there is an increased cardiovascular risk among the more commonly used supplements, as seen in Table 13-5.[25]

Health care workers can play a crucial role in identifying possible drug interactions by asking patients taking warfarin about herbal and other alternative medicine product use. Furthermore, the clinical importance of herb-drug interactions depends on many factors associated with the particular herb, drug, and patient. Herbs should be labeled appropriately to alert consumers to potential interactions when used concomitantly with drugs and to recommend a consultation with their general practitioners.

Autologous Blood Donation

One of the primary concerns in blood conservation is the patient's size and preoperative red blood cell volume. Two early reports by Cosgrove and Utley demonstrated these factors in addition to preoperative anemia as independent risk factors for blood transfusion.[26,27] As will be discussed later in this chapter, there are several relatively simple manipulations to the CPB circuit that can be made to reduce the amount of hemodilution that the patient experiences while on bypass to reduce the overall risk of transfusions.

Table 13–5.

Herbs with Adverse Effects

Herb	Adverse effect
Garlic	Increased bleeding
Ginger	Platelet dysfunction Hypertension
Gingko	Increased bleeding Platelet dysfunction
Ginseng	Hypertension
Licorice	Hypertension

Preoperative autologous donation (PAD) is a recognized strategy to reduce the risk of homologous blood transfusion in the perioperative period. Although this technique has been in practice since the 1960s, its use in cardiac surgery did not achieve widespread acceptance until the 1980s, with the advent of HIV, as an effort to reduce homologous blood exposures. Unfortunately, in cardiac surgery, the acuteness of the operations and dealing with an older and sicker patient population often preclude PAD because there must be enough preoperative time for autologous collection as well as for red blood cell mass regeneration prior to arriving in the operating room. However, for that select, elective cardiac surgical patient for whom PAD is possible, it is a good option to reduce homologous blood exposures.

Several preoperative characteristics can identify the cardiac patient who is eligible for PAD. The first criterion is that the patient be able to wait the required time for donation and red blood cell regeneration. This length of time typically varies depending on the type of surgical procedure planned (larger operative procedures likely requiring a larger amount of blood) and patient characteristics (e.g., body size, blood volume, and hematocrit). In general, this time is a minimum of 2 weeks per unit of blood donated to allow for red blood cell regeneration. The second criterion is that the patient be healthy enough to undergo donation. This criterion would preclude patients with severe left main stem stenosis, critical aortic stenosis, congestive heart failure, and idiopathic hypertrophic subaortic stenosis, as well as patients with severe coronary artery disease and ongoing ischemia, given that many of these patients would have been screening failures for the first criterion. The third criterion is that the patient not have active endocarditis. The time between donation and receiving the PAD unit is ample time for bacteria to replicate in the donated unit with resulting bacteremia, which is potentially life-threatening. The fourth criterion is that the patient has an adequate hematocrit and red blood cell mass. A preoperative hematocrit of less than 33% regardless of red blood cell mass is a contraindication to PAD according to the American Association of Blood Banks (AABB) guidelines. A patient with a hematocrit of greater than 33% may be eligible provided that other criteria are met.

Several options exist for patients who historically were not eligible for PAD. Recombinant erythropoietin can be used to accelerate red blood cell production in anemic patients; this strategy is used commonly in Jehovah's Witness patients to increase their red blood cell mass prior to surgery.[21] However, this can be quite costly; as a result, it is usually reserved for patients who are unable to tolerate homologous blood transfusions whether for religious reasons or because they have a rare blood type. An alternative strategy is to stimulate the body to increase the release of endogenous erythropoietin by allowing patients with hematocrits below the traditional cutoff to undergo PAD. The

resulting anemia experienced by the patient in the postdonation period is a strong stimulant for endogenous erythropoietin production, ultimately leading to an increase in red blood cell mass.[28]

Red blood cell mass is related to patient body size.[29] A traditional cutoff of 110 lb had been used for PAD. However, the AABB does make specific allowances for PAD in smaller patients. The current recommendation is that no more than 15% of the patient's effective blood volume should be removed at any given time, which takes into account smaller patient body size. PAD should be pursued aggressively for these small patients with low red blood cell mass and hematocrit because they are at highest risk of receiving a blood transfusion at some time during their hospital stay. The mean rate of red blood cell generation of the studies that provided adequate data is 0.46 unit per week, or slightly less than 1 unit every 2 weeks.[30] In conjunction with PAD, oral iron therapy should be initiated at the time of first donation to ensure adequate iron stores for red blood cell regeneration.

Owing to the relatively acute illness of the population, rarely is there sufficient time for PAD in the cardiothoracic surgical patient. In addition, PAD has been supplanted largely by intraoperative blood salvage techniques for reasons of cost-effectiveness (i.e., blood withdrawal, preparation, storage, and potential erythropoietin therapy add to costs) and because of advances in intraoperative blood salvage techniques such as intraoperative autologous donation (IAD; discussed later in this chapter), retrograde autologous prime of the CPB circuit, use of cell salvage, and regular use of cardiotomy suction.

PHARMACOLOGIC STRATEGIES FOR BLOOD CONSERVATION

A number of drugs have been used to decrease blood loss and the use of blood transfusion associated with cardiac surgery (Table 13-6). Interest has been renewed recently in antifibrinolytics, a relatively old class of drug. Currently, three such medications are used clinically; two are synthetic antifibrinolytics (i.e., epsilon-aminocaproic acid and tranexamic acid), and one is naturally occurring (i.e., aprotinin derived from bovine lung). Linked with the resurgence of interest in these drugs is interest in diminishing homologous blood transfusions related to cardiac surgery.

Epsilon-Aminocaproic Acid

Epsilon-aminocaproic acid (EACA) is a synthetic antifibrinolytic agent first described in 1959 that derives its effect by forming reversible complexes with either plasminogen or plasmin, saturating the lysine-binding sites and thus displacing plasminogen and therefore plasmin from the surface of fibrin. This blockage of plasminogen binding to fibrin blocks plasminogen activation and therefore fibrinolysis. The overall effect is to block the dissolution of the fibrin clot.

Several studies have demonstrated the efficacy of EACA in reducing bleeding following open-heart surgery. Although EACA was first used in situations in which excessive bleeding was encountered, Lambert and colleagues used EACA in 1979 to successfully treat patients with coagulation disorders, who comprise 20% of total primary coronary bypass patients.[32] DelRossi used EACA in 1989 as a prophylactic tool to reduce blood loss in 350 patients undergoing CPB, having an impact on both blood loss and transfusion of autologous blood and blood products.[33]

Tranexamic Acid

The mechanism of action of tranexamic acid (TA) is similar to that of EACA. The significant difference between EACA and TA is that TA is roughly 10 times more potent than EACA. As with EACA, postoperative bleeding and homologous blood requirements were similarly decreased with the use of TA, as shown by Horrow in 1990 in 38 patients undergoing CPB.[34]

Table 13–6.

Antifibrinolytics Used in Cardiac Surgery and Their Mechanism of Action

Antifibrinolytic	Mechanism of action
Epsilon-aminocaproic acid (Amicar)	Forms a complex with plasminogen through lysine-binding sites, thus blocking their adhesion to fibrin
Tranexamic acid (Cyklokapron)	Forms a complex with plasminogen through lysine-binding sites, thus blocking their adhesion to fibrin
Aprotinin (Trasylol)	Serine protease inhibitor with an antifibrinolytic effect carried by the inhibition of plasmin and kallikrein
	Protection of platelet GP Ib, reducing thrombin-mediated consumption of the platelets

Aprotinin

Aprotinin is a low-molecular-weight serine-protease inhibitor with a lysine residue occupying its active center. It is a naturally occurring polypeptide isolated from bovine lung. Reversible enzyme-inhibitor complexes with various proteases are formed that display activity against trypsin, plasmin, streptokinase-plasma complex, tissue kallikrein, and plasma kallikrein. Because aprotinin is a nonspecific serine antiprotease, it intervenes in the coagulation cascade in multiple loci, working to decrease bleeding in CPB patients by its antiplasmin and antikallikrein effects.

Aprotinin was first used in cardiac surgery by Tice and colleagues, who described the administration of 10,000 to 20,000 kallikrein inhibitory units (KIU), resulting in rapid establishment of hemostasis in five patients who had undergone CPB; they also demonstrated increased bleeding and increased fibrinolytic activity.[35] The currently accepted regimen of high-dose aprotinin (5 to 6 million unit average total dose) is reflective of the experiences of the Hammersmith group, which serendipitously saw a reduction in bleeding in patients receiving aprotinin to reduce kallikrein-mediated lung inflammation during CPB.[36] Since this report, multiple reports have emerged citing the efficacy of aprotinin as compared with other antifibrinolytics and controls in reducing bleeding complications, homologous blood transfusions, and inflammation primarily in the reoperative setting.[37–39] Despite these advantages, Mangano and colleagues reported that aprotinin use was associated with an increased risk of renal failure, myocardial infarction, and stroke.[40] In this nonrandomized observational trial of 4374 patients undergoing revascularization, the group concluded that aprotinin use was not prudent in comparison with less expensive alternatives such as aminocaproic acid and TA. Limitations to this study include nonblinded randomization and a significantly higher operative risk in the aprotinin study group that required complicated propensity adjustment to statistically match groups. Randomized, blinded studies need to be performed before definitive recommendations can be made.

Recombinant Activated Factor VII

The use of recombinant factor VII has been shown to induce hemostasis in patients with severe hemophilia A or B with factor specific inhibitors.[41] Recombinant activated factor VII complexes with all available tissue factor to activate factor X directly and induce thrombin generation. This leads to the formation of a tight and stable fibrin plug that is resistant to early fibrinolysis.[42]

Off-label use in cardiac surgery has been indicated when all efforts at conventional hemostasis have been exhausted. These include non–red blood cell product support (e.g., fresh-frozen plasma, platelets, and cryoprecipitate), topical agents, desmopressin, and antifibrinolytics. When hemostasis is still not satisfactory, we have given a recombinant factor VIIa (rFVIIa) dose of between 75 and 100 μg/kg. Efficacy is variable with rFVIIa use, ranging from no difference from standard therapy to causing mortal thrombosis.

Heymann and colleagues reported in a retrospective analysis that rFVIIa was safe with regard to risk of thrombosis, but blood loss and transfusion rates were similar. High mortality rates were seen in both groups in house and at 6 months (approximately 30% and 50%, respectively).[43] Conversely, Raivio reported in a retrospective series that rFVIIa was significantly more effective in restoring hemostasis; however, severe postoperative thromboembolic complications occurred in 25% of the patients.[44] The rFVIIa doses in these two studies ranged from 60 to 80 μg/kg and from 24 to 192 μg/kg, respectively.

Diprose and colleagues compared rFVIIa to placebo in a randomized, double-blind study following complex noncoronary artery cardiac surgery. The group found in this 20-patient study that homologous transfusions were significantly fewer in the study group cohort. There were no differences in regard to adverse events, but this pilot study had limitations that include being underpowered and prone to type I error.[45] Despite the effectiveness that has been demonstrated in single-patient case reports and small-scale studies, we recommend caution when using this product until more prospective, randomized studies are available to determine safety and effectiveness.

TOPICAL HEMOSTATIC AGENTS

The limited efficacy of topical agents such as oxidized cellulose and microfibrillar collagen has led to the development of new products with novel applicator systems that are direct activators of the clotting cascade. Additionally, pericardial lavage with aprotinin or EACA has been shown to be ineffective at reducing transfusion requirements and may enhance mediastinal adhesion formation.[46–48] As a result of the limitations of more traditional agents, the new-generation topical agents have gained appeal owing to their inherent effectiveness as well as their ease of use.

Bioglue (Cryolife, Inc., Kennesaw, GA) is a biologic glue approved initially for use in the repair of aortic dissection. This product is composed of purified bovine serum, albumin, and glutaraldehyde. The action is almost instantaneous because glutaraldehyde exposure leads to the tenuous binding of lysine molecules, proteins, and tissue surfaces. Raanani described the use of Bioglue as an aid in aortic reconstructive surgery, avoiding the use of stiff Teflon felt strips.[49]

Tisseel VH (Baxter Healthcare Corp., Glendale, CA) is a topical protein solution sealer that is sprayed onto hemorrhagic surfaces. This fibrin sealant contains fibrinogen, thrombin, calcium chloride, and aprotinin. When the protein and thrombin solutions are mixed and sprayed topically, a viscous solution that sets rapidly into an elastic coagulum is produced. A study by Rousou demonstrated that fibrin sealant was safe with regard to viral transmission and

Table 13–7.

Antiplatelet Agents

Drug	Binding	Mechanism	Half-life
Clopidogrel (Plavix)	Irreversible	ADP-mediated platelet aggregation	8 h
Abciximab (ReoPro)	Noncompetitive	GP IIb/IIIa inhibition	30 min
Tirofiban (Aggrastat)	Reversible	GP IIb/IIIa inhibition	2.2 h
Eptifibatide (Integrillin)	Reversible	GP IIb/IIIa inhibition	2.5 h

highly effective in controlling localized bleeding in cardiac operations.[50]

The gelatin-based hemostatic sealant FloSeal (Fusion Medical Technologies, Inc., Mountain View, CA) activates the clotting cascade and simultaneously forms a nondisplacing hemostatic plug. A FloSeal kit contains a bovine-derived gelatin matrix, a bovine-derived thrombin component, and a syringe applicator. The gelatinous matrix is biocompatible and reabsorbed in 6 to 8 weeks. In a series of patients undergoing open-heart procedures, the Fusion Matrix Group studied FloSeal versus Gelfoam-Thrombin in procedures in which standard surgical means were ineffective at controlling bleeding.[51] FloSeal stopped bleeding in a significantly higher number of patients than did standard therapy with no differences in adverse events; however, there was no mention of each product's effect on transfusion rates.

PLATELET INHIBITORS AND THEIR EFFECT ON BLOOD USAGE

Platelet inhibition with the relatively new drug class glycoprotein (GP) IIb/IIIa receptor antagonists has greatly reduced the need for emergent CABG in patients undergoing angioplasty or coronary stenting procedures. However, these agents pose a new challenge for the cardiac surgical team for patients referred for surgery in terms of bleeding risk.

The final common pathway of platelet aggregation leading to coronary artery occlusion is the cross-linking of receptor GP IIb/IIIa on adjacent platelets by adhesive plasma proteins (fibrinogen). As a result, receptor blockade of GP IIb/IIIa results in blocking platelet aggregation and subsequent thrombus formation. A population of patients with ischemic heart disease who may be expected to require CABG despite maximal therapy with GP IIb/IIIa inhibitors still remains. Currently, there are no controlled studies of the effect of GP IIb/IIIa inhibitors on patients undergoing CABG. However, the use of these inhibitors may enhance the risk of bleeding compared with elective procedures in patients not receiving these agents. The currently used agents are summarized in Table 13-7. Current guidelines for patients requiring CABG include

1. Stop the GP IIb/IIIa inhibitor.
2. Delay surgery for up to 12 hours if abciximab, tirofiban, or eptifibatide is used, and delay up to 7 days if clopidogrel is used.
3. Maintain standard heparin dosing despite elevated bleeding times.
4. Use ultrafiltration via the zero-balance technique while on CPB.
5. Transfuse platelets as needed as opposed to prophylactically, preferably once off CPB and after protamine administration.[52]

Heparin-Induced Thrombocytopenia and Cardiac Surgery

Heparin-induced thrombocytopenia and thrombosis (HITT) is a serious complication of heparin therapy. This immunologic response develops in approximately 1 to 3% of patients treated with unfractionated heparin (UFH) for 5 to 10 days.[53,54] HITT is a severe prothrombotic condition, with affected individuals having a 20 to 50% risk of developing new thromboembolic events. The mortality rate is approximately 20%; in addition, approximately 10% of patients require amputations or suffer other major morbidity.[55,56] Although there is no best way to anticoagulate these patients, when surgical delay is unavoidable, few options exist. Most reports, however, are limited single case reports with significant morbidity and mortality.

Currently, direct thrombin inhibitors (DTIs) are recommended for HITT (Table 13-8). Limitations of these agents include the lack of a reversal agent and route of clearance.[57]

These agents have several advantages over UFH. Since they do not rely on antithrombin III levels and do not bind to plasma proteins, the anticoagulant effect is more predictable. Also, DTIs inhibit fibrin-bound thrombin as well as fluid-phase thrombin, leading to a greater antithrombotic effect.

Specific recommendations on how to treat patients with HITT cannot be given at this time. Diagnosis of HITT

Table 13–8.

Direct Thrombin Inhibitors for HITT

Drug	Monitored	Excretion	Half-life
Lepirudin (Refludan)	APTT 1.5–2.5 times baseline	Kidney	40–60 min
Argatroban	APTT 1.5–3 times baseline	Liver	45 min
Bivalirudin (Angiomax)	APTT or ACT 1.5–3 times baseline	Kidney	25 min

is difficult because assays vary in both specificity and sensitivity. Second, and key to this dilemma, are the lack of randomized trials. Most data available for treating these patients are derived from single case reports and small retrospective trials. Dosing of the available anticoagulation agents is not fully understood, and there is no reversal agent. Since drug elimination varies for these agents, renal or liver function needs to be fully assessed. Table 13-9 lists information regarding detection and choices of agents when presented with patients with HITT.

Table 13–9.

Cardiac Surgery in Patients with Previous HITT

Clinical pathlogy	Immunologic disorder when IgG antibodies attach to platelet factor IV sites. This leads to activation of both platelets and coagulation system.
Incidence	Up to 50% of post–cardiac surgery patients develop HITT. antibodies. Of these, 7 to 40% lead to in vitro platelet activation. Development of HITT only occurs in 1 to 3% of postoperative cardiac patients despite the high seroconversion rate. However, HITT-related mortality has been reported as high as 28%.
Differntial diagnosis	Unexpected platelet count drop of 50% or greater. Increased risk of venous thrombosis preoperatively and arterial thrombosis postoperatively. Most thrombotic episodes are not seen until at least 5 days because HITT antibodies usually do not develop until higher bypass heparin doses are given.
Laboratory testing	Enzyme immune assays for detecting platelet factor IV–reactive HITT antibodies and platelet activation assays that use washed platelets. Washed assays, however, have greater specificity but take longer to perform
Anticoagulation monitoring during cardiac surgery	When heparin is used, a standard celite activated clotting time (ACT) test can be performed. When using thrombin inhibitors, an alternative but complicated ecarin clotting time (ECT) can be performed. The ECT correlates better than the ACT to drug level, but the ACT has been used successfully
Anticoagulation reversal	When using heparin, standard protamine reversal is sufficient. Direct thrombin inhibitors have no reversal agents at this time. Drug elimination is enzymatically with bivalirudin, renally with other agents such as hirudin, and via the hepatobiliary system for Argatroban. A hemoconcentrator can be used toward termination of bypass or postoperatively.
Anticoagulation better cardiac surgery	Monitor platelet count drops for HITT detection. Nonheparin agents should be used for all patients with HITT history or when antibodies are present. These alternatives include aspirin, wafarin (only if thrombocytopenia is resolved), and direct thrombin inhibitors. Valve prophylaxis can be resumed similar to warfarin therapy.

INTRAOPERATIVE AND POSTOPERATIVE MANAGEMENT

Intraoperative Period

Intraoperative autologous donation (IAD) of whole blood has many advantages over PAD. IAD does not require a delay in surgery; it can be performed efficiently and with minimal additional cost. In addition, the blood product obtained by IAD is whole blood, which is transfused within 2 to 3 hours of collection and therefore contains active platelets and factors. The resulting advantages are the avoidance of coagulopathy frequently seen after CPB and the addition of red blood cell mass capable of oxygen transport. The storage process limits the amount of blood loss during surgery via lap pads and discard suction and spares the damaging effects of the heart-lung machine, which include contact activation of platelets and complement as well as red blood cell hemolysis. Because IAD serves to decrease red blood cell requirements in a volume-dependent manner, the maximum amount of blood should be removed from each individual patient in order to optimize blood conservation efforts. The amount of blood that an individual patient is capable of donating via IAD depends strictly on the patient's own physiologic parameters, estimated blood volume (based on height-weight normogram), pre-IAD hematocrit, and pre-CPB hematocrit.[58]

Minimal hemodilution by red blood cell priming of the CPB circuit is a useful technique in avoiding transfusions. Techniques include low-prime circuitry and retrograde autologous prime (RAP).[59] Up to 90% of the crystalloid prime of the CPB circuit can be displaced with autologous blood using RAP. This technique involves partial priming of the bypass circuit with the patient's own blood from the arterial cannula just prior to instituting CPB. In addition, the venous loop also can be primed in a similar manner when first instituting CPB, displacing the crystalloid prime in the venous loop. The result is the replacement of virtually all the crystalloid prime with autologous blood, thereby reducing the amount of hemodilution the patient experiences on CPB.

TRANSFUSION TRIGGERS

The literature indicates that the anesthetized patient on full CPB at moderate hypothermia can safely tolerate a hematocrit as low as 15%, with the exception of patients at risk for decreased cerebral oxygen delivery, namely, those with a history of cerebrovascular accident (CVA), diabetes, or cerebrovascular disease.[60] These latter patients can tolerate a hematocrit as low as 18% when using moderate hypothermia.[61] Once the patient is warm and being weaned from CPB, these percentage points are raised by 2% each (17% and 20%, respectively) because the relative protective effects of the hypothermia are no longer present. In our institution, once the patient is off CPB, our practice has been to retransfuse all or as much as possible remaining blood in the CPB circuit to the patient and then give all available cell salvage blood, including any blood remaining in the CPB circuit that was not initially given back to the patient, then any IAD blood, and then finally PAD blood if available. Then and only then, if the hematocrit remains unsatisfactorily low, does the patient receive homologous blood.

Once the patient leaves the operating room, we use a transfusion trigger corresponding to a hematocrit of 22% in asymptomatic patients. In patients older than 80 years of age, a trigger of 24% is used. These numbers are meant to serve as guidelines; if a patient is at all symptomatic (i.e., tachycardic, hypotensive, ischemic, or showing any evidence of end-organ hypoperfusion), he or she will receive homologous blood transfusion therapy. To apply minimum transfusion standards safely and appropriately, the cardiac surgeon or anesthesiologist must have an understanding of the lowest safe level of anemia under the variety of conditions encountered by the cardiac surgical patient. This understanding then can be combined with an assessment of the patient's clinical status to determine the true need for red blood cell transfusion.

COST OF BLOOD CONSERVATION

In today's economic environment, it is important to discuss patient treatment modalities in terms of cost. There is no question that some aspects of the blood conservation approach are more costly than others (Table 13-10). However, when taken in the context of the cost of blood products, their use, the potential reduction in the risk of reexplorations, and the reduction or elimination of the risks of homologous blood exposures, these costs may seem a little more reasonable.

CONCLUSION

Historically, cardiac surgery has been associated with a high incidence of blood transfusion, with up to 70% of these patients receiving homologous blood transfusions at some point during their hospital stay. However, with improving technology, awareness of blood conservation techniques, and better pharmacologic agents, a multidisciplinary approach to blood conservation can make "bloodless heart surgery" entirely possible. For the purely elective patient, these techniques are initiated preoperatively with PAD, whereas other patients are eligible for one or all of the remainder of the in-hospital techniques described. Using a team approach that both optimizes and integrates the use of each of these measures, the use of homologous blood can be markedly reduced in a majority of cardiac surgical patients.

Table 13–10.

Relative Costs of Blood Conservation Agents Used in a Single Institution

Agents	Approximate cost
EACA (Amicar)	$30 per case
Tranexemic acid	$25 per case
Aprotinin (Trasylol)	$1200 per case
Erythropoietin (Procrit)	$130 per 20,000-unit dose
Homologous banked PRBCs	$210 per unit
PAD	$340 per unit
Platelets (pheresed only)	$600 per 6 units
FFP	$55 per unit
Cryoprecipitate	$53 per 10 units
Blood irradiation	$16 per bag
Blood CMV testing	$25 per bag

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CHAPTER 14

Deep Hypothermic Circulatory Arrest

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Hypothermia is the most efficient measure to prevent or reduce ischemic damage to the central nervous system when blood circulation is reduced. The central nervous system has a high metabolic rate and limited energy stores, which make it extremely vulnerable to ischemia. Because the central nervous system is the most sensitive organ to ischemia, attention has been centered mainly on neurologic outcome when perfusion was reduced, with the indirect assumption that if the brain or the spinal cord could tolerate undamaged the reduced perfusion, the other organs would too. With the introduction of regional cerebral perfusion, many surgeons have shifted their practice from a deep to a moderate systemic hypothermia during repair of the aortic arch. Consideration (that will not be discussed here) then should be given to specific protection of the abdominal viscera when a long period of reduced perfusion is anticipated.

CEREBRAL METABOLIC RATE

Reduction of Metabolism

The brain uses up to 20% of total-body oxygen consumption, with 40% of its energy used in the preservation of cellular integrity and 60% in the transmission of nerve impulses.[1] Hypothermia reduces the metabolic rate of the central nervous system and lengthens the period of ischemia tolerated. The central nervous system almost exclusively extracts its energy through aerobic glycolysis. The uptake of oxygen or glucose consequently is a reliable parameter of the cerebral metabolic rate. Using oxygen and glucose consumption, animal studies showed a drop in the brain metabolic rate of 50% at 28°C, 19% at 18°C, and 11% at 8°C.[2,3] Comparable results using less precise methods of measurement were obtained in humans[4] (Table 14-1). The reduction in metabolic rate in relation to temperature espouses an exponential curve, with a greater drop at high temperatures (about 6% for 1°C around 37°C) than at low temperatures (about 1% at 15°C).[2,4,5] A luxurious perfusion of the brain is rapidly set when the metabolic rate is reduced and perfusion flow rate maintained. The arteriovenous difference of oxygen, glucose, and brain-produced metabolites decreases. The luxurious perfusion is, however, of limited help in view of an ischemic period because additional energetic reserve cannot be stored in neurons. The obvious clinical implication of these findings is that although reduced, the metabolism of the brain is not suppressed by hypothermia and actually remains relatively high at 18°C, a common target temperature in surgical practice. Assuming an ischemic tolerance of 5 minutes at normothermia, the calculated safe period of circulatory arrest for the central nervous system would not exceed 25 minutes at 18°C and 38 minutes at 13°C[4] (see Table 14-1).

Cellular activity, be it mechanical, biochemical, or electrical, is an important determinant of energetic requirement superimposed on basal metabolism.[6] Obtaining a complete suppression of cerebral electrical activity consequently should be an important goal in the strategy of brain protection when a significant period of cerebral ischemia is anticipated. In the clinical setting, electrocerebral silence (as assessed by electroencephalography) is obtained at a mean nasopharyngeal temperature of 17.5°C.[7] Wide variations in the temperature inducing silence, however, exist between individuals and methods of cooling. The variations are also amplified by the fact that the brain temperature is not measured directly. The correlation between nasopharyngeal and jugular bulb venous temperature shows minimal difference during cooling (nasopharyngeal temperature therefore is a reliable surrogate for brain temperature) but a significant underestimation of the brain temperature during rewarming.[8] In one large study, the minimal nasopharyngeal temperature to obtain electrocerebral silence in all patients was 12.5°C; at the classic 18°C, 40% of patients still exhibited electrical activity.[7]

Table 14–1.

Effect of Temperature on Cerebral Metabolic Rate

Temperature (°C)	CMR (% baseline)	Duration of Safe CA (min)	$CMRO_2$ (mL/100 g/min)	pMPFR (mL/kg/min)
37	100	5	1.48	100
32	70 (66–74)	7.5 (6.5–8)	0.82	56
30	56 (52–60)	9 (8–10)	0.65	44
28	48 (44–52)	10.5 (9.5–11.5)	0.51	34
25	37 (33–42)	14 (12–15)	0.36	24
20	24 (21–29)	21 (17–24)	0.20	14
18	17 (20–25)	25 (21–30)	0.16	11
15	14 (11–18)	31 (25–38)	0.11	8

CMR: cerebral metabolic rate; CA: circulatory arrest; $CMRO_2$: cerebral metabolism rate for oxygen; pMPFR: predicted minimal perfusion flow rate.
Data derived from McCullough JN, Zhang N, Reich DL, et al: Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg 1999; 67:1895; and Kern FH, Ungerleider RV, Reves JG, et al: Effect of altering pump flow rate on cerebral blood flow and metabolism in infants and children. Ann Thorac Surg 1993; 56:1366.

Anesthetists often administer cortisone at the beginning of anesthesia to reduce the production of proinflammatory cytokines and barbiturates a few minutes before circulatory arrest to shut down any residual electrical activity.[9] The action of these agents is difficult to establish and remains controversial. Barbiturates, for instance, can have a two-edged–sword effect because they cause cerebral vasoconstriction—with halving of cerebral blood flow[10]—and showed a detrimental effect on preservation of the energy molecules of the brain.[11] Their early administration could result in inappropriate cooling of the brain and disturbed energy states. If ever, they should be administered only when the target temperature is achieved, just before arrest.[12] The evidence supporting the use of high-dose cortisone to reduce postischemic neurologic damage (such as that observed in spinal cord injury[13]) is lacking totally in deep hypothermic circulatory arrest. In view of its immunosuppressive effect,[14] the use of high-dose methylprednisolone cannot be recommended at this time.

Duration of Circulatory Arrest

The duration of safe circulatory arrest at a given temperature should not be seen as a clear cutoff point but as a broad zone during which successive biochemical alterations occur, followed by ultrastructural and finally by structural changes (Fig. 14-1). The potential for recovery exists during the initial phase of biochemical alteration but decreases as ischemia persists and becomes more dependent on reperfusion conditions. The cerebral metabolic rate of oxygen and glucose often has been used as a surrogate for adequate energetic metabolism of the brain and consequently adequate maintenance of cellular homeostasis.[5,15] The recovery of oxygen consumption is already impaired after 15 minutes of ischemia at 18°C,[3] and cerebral-produced lactate (a marker of anaerobic metabolism) is detectable in the effluent blood after 20 minutes of ischemia.[16] Definitive damage to the brain, however, is unlikely if perfusion is reinstituted adequately after this time period.

Monitoring the evolution of intracellular high-energy molecules and pH points out more precisely the moment when the exhaustion of energetic substrates may trigger the cascade of deleterious biochemical reactions. Nuclear magnetic resonance can provide continuous measurements of the relative concentration of phosphocreatine and adenosine triphosphate, the principal energetic molecules of the brain, as well as that of inorganic phosphate (the split product of these molecules) and intracellular pH. The electromagnetic signal of phosphocreatine decreases rapidly, followed by that of adenosine triphosphate, after institution of circulatory arrest.[6] These signals become hardly detectable after 32 to 36 minutes of ischemia at 15°C in animals.[17–19] Parallel to their disappearance, the signals of inorganic phosphate and pH rise progressively within the cells.

DIRECT AND DELAYED ISCHEMIC INJURY

Direct Injuries

Cessation of blood delivery to neurons leads to an immediate reduction in the production of energetic molecules and a

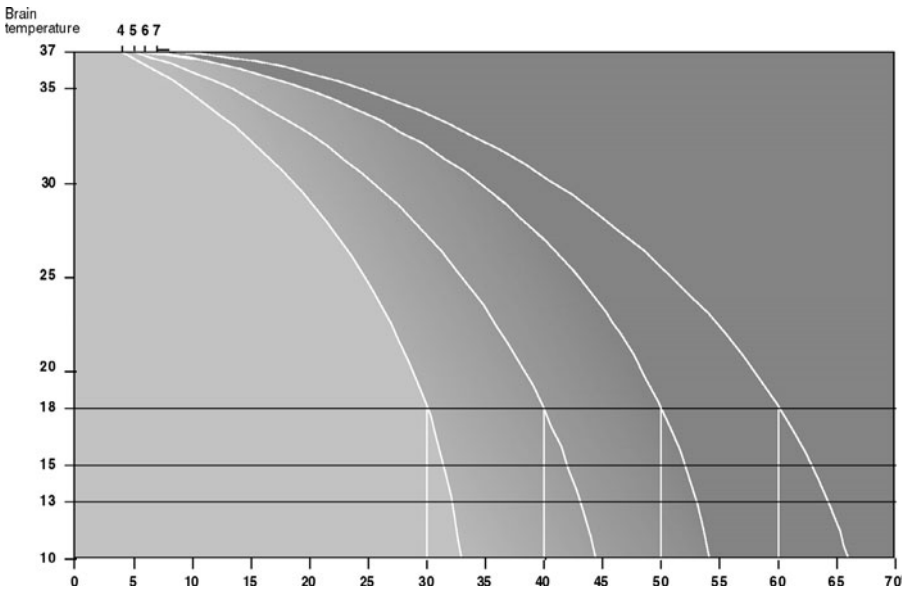

Figure 14-1. Consequences of circulatory arrest in relation to temperature and duration of cerebral ischemia. The dark shading depicts the periods of safe circulatory arrest. The light shading depicts the periods of excessive and damaging circulatory arrest. The transitional area depicts the periods where the risk and extent of brain damage depend on the conduct of surgery and pharmacologic intervention. A dominance of the dark shading is compatible with reversible deficits, whereas a dominance of the light shading is associated with irreversible injuries.

state of progressive energy failure. Cellular injury occurs because of a rapidly occurring intracellular acidosis and a more progressive dissipation of ionic gradient across membranes. The dissipation of ionic gradient initiates a cascade of destructive events that rapidly escape regulatory control.[6] At this stage, accumulation of calcium within cells (which interferes with many fundamental biochemical reactions) and attraction of osmotically obligated water are striking.[20] Mitochondrial swelling with dilatation of the intercristal spaces is the first ultrastructural sign of ischemic injury that progresses eventually to membrane rupture. With low adenosine triphosphate concentration, the massive release of calcium into the cytoplasm initiates necrotic cellular death. If the concentration of adenosine triphosphate is sufficient, the release of mitochondrial proteins, such as cytochrome *c* and apoptosis-inducing factors, induces cellular apoptosis.[21] Other ultrastructural signs of neuronal injury are clumping of chromatin and nuclear rupture, rupture of the endoplasmic reticulum, and detachment of ribosomes with the consequent loss of the ability to synthesize RNA and proteins.

The endothelial cells are also extremely sensitive to ischemia. The continuous activation and production of vasoactive factors, among which nitric oxide plays a central role, are impaired after endothelial ischemia. The endothelial dysfunction results in an increase in cerebral vascular resistance.[18,22] This is exemplified clinically by the loss of diastolic perfusion of the brain in Doppler analysis of the middle cerebral artery after circulatory arrest.[23] Nitric oxide is a potent short-acting vasodilator that regulates online the local vascular tone. The molecule further inhibits the aggregation of platelets and adherence of polymorphonuclear cells (PMNs) to the endothelium, two critical steps in the initiation of reperfusion injury.[24,25] The stimulation of nitric oxide production after circulatory arrest improves cerebral perfusion and accelerates recovery of high-energy phosphate and cerebral metabolism.[18,22]

Delayed Injuries

Delayed injuries occur on and after restitution of perfusion. Reperfusion injuries operate at a cellular and at a vascular level. At the cellular level, the restitution of oxygen provokes the formation of highly reactive free radicals, which are able to disintegrate the membrane structure. At the vascular level, the recirculation of blood in ischemic territories induces a tight aggregation and adhesion of platelets and PMNs to the endothelium. These cellular complexes release potent inflammatory mediators and vasoconstrictor agents. Blood elements slug in small capillaries and can shut down the microcirculation and reestablish ischemia. Although a strong theoretical background supports the mechanisms of reperfusion injuries, their real contribution after deep hypothermic circulatory arrest remains uncertain.[20] At the vascular level, the risk of blood slugging seems greatly attenuated by the hemodilution induced by cardiopulmonary bypass.

Electrical hyperactivity of the brain after ischemia can produce extensive damage because the condition recreates a cellular energetic mismatch and induces the release of toxic neurotransmitters. *Excitotoxicity* is a term applied to the death of cells caused by overstimulation of excitatory amino acids and is believed to be a fundamental process involved in postischemic neuronal cell damage. Compromised synaptic reuptake of excitatory amino acids and membrane depolarization associated with ischemia cause a lethal flood of calcium and sodium into the neuron.[26] The mammalian brain paradoxically is extraordinary vulnerable to its own neurotransmitters when they are released in the extracellular space.[27] Glutamate is the principal excitatory neurotransmitter of the

brain and is found in extremely high concentration within neurons and astrocytes. The death of one cell liberates the neurotransmitter from its extracellular space and puts in danger all the surrounding neurons, especially in the context of reduced defense capacity. A series of events starting with the overexcitation of a neuron and ending in its death propagates rapidly and expands exponentially the brain damage. It is unknown if premature resumption of brain activity (before replenishment of energy stores) can trigger the cascade of harmful events. It is evident, however, that hyperactivity of the brain during the rewarming period and thereafter results in the extracellular release of glutamate.[27] Administration of glutamate antagonists after ischemic injury to the brain has shown a protective effect in animals and humans, already in the absence of cerebral hyperactivity.[28,29] These antagonists could prove valuable in circumscribing brain damage once significant neuronal injury has occurred, especially in case of electrical hyperactivity.

Protracted cellular dysfunction and apoptosis lead to a delayed (after a few days) neuronal death. The prolonged inability of the neuron to restore calcium homeostasis and ensure the turnover of cytostructure proteins is responsible for a progressive loss of cellular function and eventual death.[6,30–32] Apoptosis (programmed cellular death) is an active, energy-dependent process characterized by the silent breakdown and phagocytosis of a cell. A profound or long-lasting ischemia results in cellular necrosis, whereas a less severe ischemia results in apoptosis. The importance of apoptotic cell clearance is not well established but certainly underestimated because of the swiftness of the process and the fact that it leaves no inflammatory traces. Apoptosis often has been documented in zones of borderline ischemia—in zones with moderate energy depletion—such as the penumbra surrounding a focal ischemia.[30,33] In a piglet model of deep hypothermic circulatory arrest (DHCA), the apoptotic process was found to start a few hours after reperfusion and to extend over several days. As expected, caspase 3 and 8, the final pathway of the apoptotic process, and cytosolic cytochrome *c* were significantly elevated in the damaged neurons.[32]

CEREBRAL BLOOD FLOW

Low-Flow and Intermittent Perfusion

Low-flow and intermittent perfusion of the brain are able to maintain, respectively restore, intracellular stores of high-energy substrates, prevent anaerobic glycolysis and intracellular acidosis, and consequently prolong cerebral tolerance to ischemia. Continuous monitoring of high-energy molecules established that the minimal perfusion flow able to maintain metabolic homeostasis in animals at 15°C was 10 mL/kg per minute (a flow corresponding to 8% of full flow).[19] The minimal flow rate in humans, extrapolated from the slope of metabolic rate reduction, is 11 mL/kg per minute at 18°C[34,35] (see Table 14-1). In clinical practice, however, wide ranges of minimal flow rates (ranging from 5 to 30 mL/kg per minute at 18°C) have been determined at a given temperature.[34] The wide variation probably is a consequence of hematologic (e.g., hematocrit, management of carbon dioxide) and hemodynamic (e.g., pulsatility and evolution of the "noncerebral" systemic resistance) factors. These facts argue for the use of a significant residual flow (a flow 50% greater than the predicted minimal perfusion flow rate of Table 14-1 for temperatures above 25°C and 100% greater for temperatures under 25°C) when a low-flow perfusion strategy is adopted. Lower flow rates should not be used without close monitoring of the jugular venous saturation or cerebral oxygenated state.[36] A continuous drop in venous saturation and a reduction in cerebral oxyhemoglobin detected by near-infrared spectroscopy are absolute signs of insufficient brain perfusion.[37]

Intermittent perfusion of the brain also results in the absence of lactate production and rapid resumption of normal cerebral metabolism and perfusion after circulatory arrest.[38,39] Oxygen saturation in the saggital sinus fell tremendously (to 16%) after 60 minutes of noninterrupted circulatory arrest, whereas it remained around 55% with intermittent perfusion.[39] This higher oxygen saturation, in combination with the higher blood pH and lower lactate production, acknowledges the nutritive role of intermittent perfusion at low temperatures. Metabolic homeostasis was maintained throughout when intermittent perfusion was established after a relatively short period of ischemia (after every 20 minutes at 18°C). Extending the ischemic period to 30 minutes resulted in a moderate production of lactate and subsequent impaired oxygen extraction in the brain.[3,38] Concerns that repetitive episodes of reperfusion may result in neuronal damage (as has been documented at normothermia[40,41]) have not been validated in the model of deep hypothermic circulatory arrest. One at least may speculate that reperfusion injuries do not happen if recirculation is established before the occurrence of anaerobic glycolysis.

Pulsatile Flow

Pulsatile perfusion provides hemodynamic advantages over nonpulsatile perfusion that become significant with borderline pressure and perfusion flow.[42,43] Once the perfusion pressure falls under the closing pressure of the precapillary arterioles, the vascular bed shuts down and is no longer perfused. The peak pressure in pulsatile perfusion is able to maintain the microcirculation open with a lower mean perfusion pressure and, consequently, a lower flow rate. The phenomenon is amplified after circulatory arrest.[42] A high perfusion pressure (higher than the pressure needed to maintain a capillary bed open) is necessary to reopen closed vascular beds. The postischemic dysfunction of the endothelial cells (with the loss of the vasodilatation dominance[44]) further increases the critical reopening pressure of the capillaries. The peak pressure in a pulsatile perfusion overcomes this critical pressure more quickly. This results in a swifter and more homogeneous restitution of brain perfusion. Cerebral vascular resistance was reduced and recovery of cerebral

metabolic rate improved with pulsatile perfusion after circulatory arrest.[42,43]

MANAGEMENT OF TEMPERATURE

pH Strategy

Two strategies for blood gas management are possible during hypothermia. Alpha-stat management (the mechanism prevailing in reptiles) aims at maintaining normal pH and blood gases (a pH of 7.40 and a $PaCO_2$ of 40 mm Hg) in the rewarmed (to 37°C) blood. In vivo, the hypothermic blood is alkalic and hypocapnic. pH-stat management (the mechanism prevailing in hibernating animals) aims at maintaining normal values in vivo in the hypothermic blood. When rewarmed to 37°C, the blood becomes acidotic and hypercapnic.

Alpha-stat management preserves autoregulation of brain perfusion and optimizes cellular enzyme activity. Because of the blood alkalosis, the curve of oxyhemoglobin dissociation is shifted toward the right, corresponding to an increased affinity of oxygen for hemoglobin. With the further shift of oxyhemoglobin to the right owing to hypothermia, the availability of oxygen carried by the hemoglobin molecule becomes tremendously reduced. At deep temperature, oxygen diluted in blood represents the major source of oxygen to tissues.

The pH-stat strategy, because of the high level of carbon dioxide, results in a powerful and sustained dilatation of the cerebral vessels. Autoregulation of brain perfusion is lost, and cerebral blood flow is increased greatly. The time for temperature equilibration between blood and brain is shortened, resulting in a quick and homogeneous cooling of the brain. Hypercapnia shifts the oxyhemoglobin dissociation curve to the left and results in an increased availability of oxygen to tissues.

A comparison between the two strategies has been performed mainly in neonates and small animals. In piglets, a pH-stat strategy resulted in improved recovery of cerebral metabolism and better histologic and behavioral scores.[45] In neonates, the same strategy provided superior psychometric scores at midterm evaluation.[46] The superiority of the pH-stat strategy has not been confirmed in adults, however. Prospective studies found no differences[47] or even worse neuropsychological outcomes.[48–51] Because it maintains a physiologic coupling between cerebral blood flow and metabolism, the alpha-stat strategy appears advantageous in adults where the risk of under- or overperfusion within the brain is substantial.[51] Cerebral edema, which can be a consequence of cerebral overperfusion, is less likely to occur. Finally, the preservation of cerebral autoregulation may attenuate the inhomogeneous distribution of blood that is prone to occur in patients with an underlying vasculopathy such as atherosclerosis, hypertension, and diabetes.

Cooling and Rewarming

The time required to obtain equilibration of temperature between blood and tissues depends on the temperature gradient on the one hand and the blood flow in the tissue and a tissue-specific coefficient of temperature exchange on the other. Cooling or rewarming over a short period of time results in wide variations in temperature between organs, as well as within an organ itself. A slow rate of cooling or rewarming and a high blood flow are the two factors ensuring homogeneous changes in body temperature. Occlusive vascular disease and altered vascular reactivity may reduce cerebral perfusion significantly and delay temperature equilibration. Enhancement of cerebral cooling can be achieved by local cooling. Ice packed around the head efficiently reduces the temperature of the brain cortex and subcortical area by heat conduction across the skull.[52]

Oxygen availability is reduced during hypothermia because of the shift to the right of the oxyhemoglobin curve. The parallel decrease in metabolic rate is likely to preserve an appropriate balance between availability of and requirement for oxygen. During rapid cooling, however, the affinity of oxygen for hemoglobin rises sharply, whereas the tissue temperature is not equilibrated with that of blood. This effect, combined with the dilution of blood by the priming volume of cardiopulmonary bypass, may create a temporary state of insufficient oxygen availability.[53] Studies in animals confirmed that expedited cooling associated with excessive hemodilution resulted in an uncompensated consumption of energetic molecules and in the development of cellular acidosis before institution of circulatory arrest. In one study it was demonstrated that an increased concentration of hemoglobin was able to compensate for the decreased oxygen availability related to hypothermia.[54] Intracellular acidosis was not present with a hematocrit of 30%, was mild with a hematocrit of 20%, and was severe with a hematocrit of 10%.[55,56] Using intravital microscopy, these investigators further established that the cerebral capillary flow was maintained despite the increased blood viscosity (that is associated with high hematocrit values).[56,57] These findings support the consensus that cooling should be slowly performed and with an adequate hematocrit.[53,54]

Rewarming represents a critical time period—perhaps the most decisive one—during which any additional harm to cerebral cells might induce permanent injury or precipitate their death. It seems logical to strive to obtain rapidly a stable energetic and biochemical homeostasis to prevent the occurrence of delayed injuries. Once initiated, the pathologic processes are difficult to restrain. Moreover, the final impact of a specific therapeutic action is often uncertain owing to the complexity of interrelated biochemical derangements.

Providing a favorable hematologic environment, ensuring optimal hemodynamic conditions, and avoiding cerebral hyperactivity should set the best conditions for optimal recovery of the energy-depleted brain.[58] It seems, therefore, capital to restart perfusion slowly after circulatory arrest. An initial period of "cold blood low-pressure reperfusion" washes out accumulated metabolites, buffers free radicals, and provides substrates for regeneration of high-energy molecules before the resumption of cerebral electrical activity.[59] A sufficient hematocrit during this reperfusion period

is attractive theoretically because of its buffer, redox, and free-radical scavenging capacity.[53,60] Glycemia should be monitored closely, and hyperglycemia should be treated aggressively. Hyperglycemia, stimulated by the release of endogenous catecholamines, increases intracellular acidosis and can prevent or delay the restitution of metabolic homeostasis.[60] During rewarming, cerebral vascular resistance and energetic metabolism are impaired in proportion to the severity of ischemia.[61,62] Cerebral perfusion is reduced, glucose is derived in part from the less efficient anaerobic pathway, and oxygen coupling with the oxidative phosphorylation is disturbed.[30] This vulnerable period can last for 6 to 8 hours after initiation of reperfusion.[62,63] During this time, an abnormally high extraction of oxygen and glucose is necessary to sustain the cerebral metabolic rate.[62] Jugular venous oxygen saturation is often below 40% during this recovering period.[62] Cerebral autoregulation may become unable to compensate for another reduction in oxygen delivery, which could occur with postoperative events such as acute hypotension, hypoxemia, and anemia.

The temperature of the perfusate during the rewarming phase should be managed carefully. Hyperthermia exacerbates cerebral activity and disturbs cellular metabolism after circulatory arrest.[64] It should be stressed that nasopharyngeal temperature underestimates by 2 to 3°C the brain temperature during rewarming.[8] The perfusate temperature should not be allowed to exceed 37°C, keeping in mind that a relative hypothermia actually might be beneficial for optimal brain recovery.[65] Electrical hyperactivity of the brain can trigger overwhelmingly destructive reactions.[27] The disorder is not uncommon after prolonged circulatory arrest and actually is considered a sign of ischemic injury.[66–68] Detection of increased cerebral activity should prompt immediate therapeutic action, which includes deep anesthesia, appropriate sedation, and reduction of temperature. Monitoring the electrical activity of the brain during the rewarming phase (and thereafter if circulatory arrest has exceeded the safe ischemic period or if signs of abnormal electrical activity are present) could help to limit the extent of secondary damage to the brain.

NEUROLOGIC INJURY AFTER DHCA IN CLINICAL PRACTICE

Neurologic deficit after DHCA encompasses a wide range of disorders ranging from deep coma to subtle, hardly perceptible alterations in cognitive functions or behavioral changes. In the immediate postoperative period, the return of sophisticated neurologic functions often is obscured by the administration of sedative and analgesic agents. Neurologic injury presents at that time mostly as a focal or diffuse deficit. A focal deficit is due to interruption of blood in a terminal vascular territory, usually secondary to embolism of material or gas bubbles. Less frequently, a prolonged subliminal perfusion of the brain can result in a localized necrosis in the transition area between two vascular territories (the so-called watershed lesion). The clinical expression typically is a motor-sensory deficit, aphasia, or cortical blindness. Computed tomographic scanning and magnetic resonance imaging usually are able to detect a sharply demarcated area of necrosis in the brain (Fig. 14-2). The prevalence of a focal deficit in clinical series ranges from 5 to 10% after aortic surgery with the use of deep hypothermic circulatory arrest. Age, atherosclerosis, and manipulation of aorta are more potent risk factors than the duration of circulatory arrest.[52] Retrograde perfusion of the aorta during cardiopulmonary bypass (with the arterial cannula inserted into the femoral or iliac artery) also has been associated with an increased risk of focal deficit. The retrograde flow of blood in the aorta can dislodge floating atheromatous plaques and thrombi loosely attached to the walls of thoracic aortic aneurysms.[69–71]

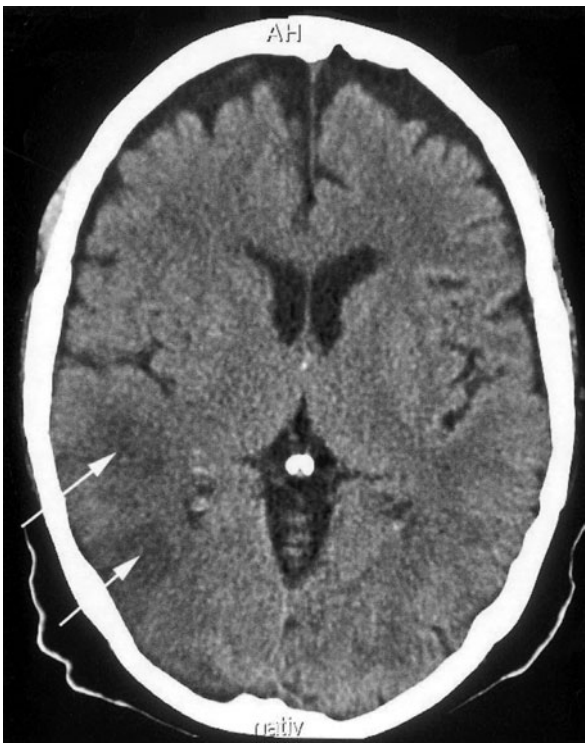

Figure 14-2. Computed tomography performed 2 days after surgery showing multiple focal ischemic lesions of the brain. Areas of demarcated necrosis can be seen (*arrows*) in the temporo-occipital junction of the right hemispheres. The damage was attributed to a retrograde perfusion of the aorta leading to dislodgment and embolization to the brain of mural thrombi.

Diffuse neurologic deficits are due to a global cerebral ischemia that has produced various levels of cellular dysfunction. In the mild forms, the cerebral cells are viable but temporarily unable to function properly. Cerebral areas with reduced perfusion (owing to atherosclerosis) or with increased metabolic activity (such as the hippocampus, which is responsible for the acquisition and treatment of new information) are most vulnerable and affected first by ischemia. The spectrum of neuropsychological disorders ranges from benign and reversible conditions such as transient confusion, stupor, delirium, and agitation to more

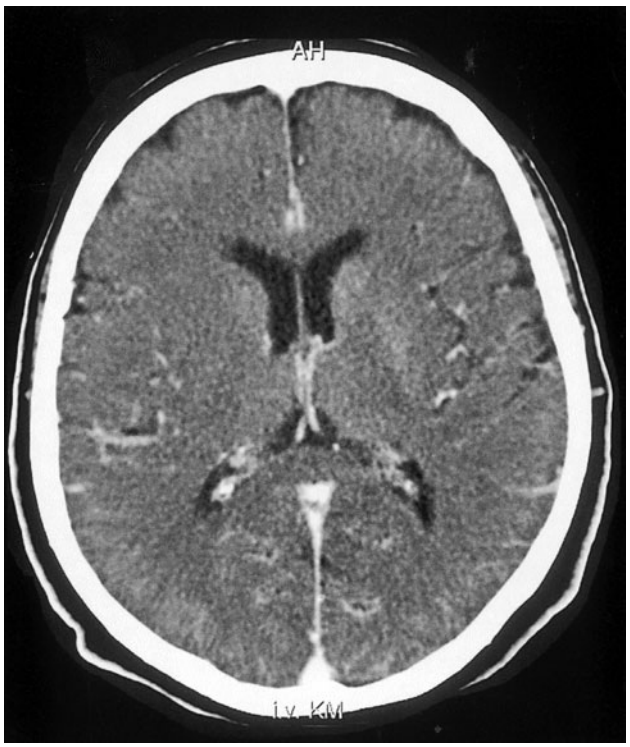

Figure 14-3. Computed tomography with contrast enhancement showing signs of diffuse anoxic lesions of the brain. Of note is the blurred delineation of the cerebral cortex and basal ganglia on the right side.

serious and debilitating ones such as seizures, parkinsonism, and coma. Imaging studies usually are normal, although in the most severe forms, scattered areas of necrosis may appear progressively (Fig. 14-3). The wide range (from 3 to 30%) of prevalence of diffuse deficit after circulatory arrest quoted in the literature reflects the subtle and often unrecognized nature of most deficits. Scrupulous postoperative evaluation of neurologic function discloses a frequency of between 10% and 20%.[67,68,72,73] Age, improper conduct of cardiopulmonary bypass, and prolonged duration of circulatory arrest are recognized risk factors for diffuse deficit. Disorders that impair vascular reactivity and cerebral autoregulation, such as diabetes and hypertension, have been associated sporadically with an increased incidence of diffuse deficit.[74]

For a long time, only relatively coarse and persistent neurologic deficits were accounted for in clinical series. The harm of circulatory arrest was underestimated, and more worrying, the duration of safe circulatory arrest was inferred erroneously. With refinement in neurologic evaluation, including behavioral and cognitive testing, it appears that subtle deficits occur in a much larger proportion of patients after shorter ischemic times. Transient neurologic dysfunction, a condition once not considered a deficit, and postoperative electroencephalographic hyperactivity appear now as definitive markers of long-lasting cerebral injury.[68,72,73,75] One-quarter of patients with transient deficits perform poorly on postoperative neuropsychological testing, and the deficit, affecting mainly memory and fine motor function, persists in many of them after hospital discharge. The risk of transient neurologic deficit starts when deep hypothermic circulatory arrest exceeds 25 minutes.[72,73] The risk initially is linearly related to the duration of circulatory arrest and rises more steeply after 50 minutes of ischemia.[52] Transient neurologic dysfunction may represent the subtlest clinical derangement of the brain that appears first during circulatory arrest.

Based on these findings and accumulated experience, it appears that the great majority of patients can support unharmed a circulatory arrest of 30 minutes at 18°C, provided that electrocerebral silence has been obtained. No deficit or only a transient neurologic dysfunction is expected when the ischemic period extends to 40 minutes, provided that rewarming is performed correctly and hemodynamic stability is maintained postoperatively. With an arrest time of more than 40 minutes, neurologic deficit is prone to occur, particularly in high-risk patients, such as those presenting with diabetes, hypertension, or old age. Further cooling of the brain to 13 to 15°C reduces the risk and makes a deficit again unlikely if the arrest time does not exceed 40 minutes or makes it no more severe than a transient dysfunction if it lasts 50 minutes. In these cases, careful rewarming with close monitoring of cerebral activity, deep anesthesia, and hemodynamic stability are decisive for a favorable outcome.

MEASURES TO PREVENT ISCHEMIC NEUROLOGIC DAMAGE

Reduction of cerebral metabolism and swift surgery are the two fundamental measures able to prevent or reduce brain damage during circulatory arrest. Selective perfusion of the brain has emerged as an important adjunctive protective measure (see Figs. 14-3 and 14-4). The efficacy and safety of selective perfusion has allowed progressive modulation of the level of systemic cooling. When the anticipated ischemic period does not exceed 20 minutes (e.g., as illustrated in Fig. 14-3 for a hemiarch replacement), systemic cooling could be set at 25°C. The duration of cardiopulmonary bypass to equilibrate temperature during cooling and rewarming is greatly reduced. Homeostasis of the blood, in turn, is less disturbed, particularly regarding platelets function and coagulation. When the anticipated ischemic time exceeds 40 minutes (e.g., as illustrated in Fig. 14-4 for a complete resection of the aortic arch), deep systemic hypothermia to 18°C or lower remains the safest measure to protect not only the brain but also the spinal cord and abdominal organs.

Antegrade Cerebral Perfusion

Antegrade perfusion of the brain through cannulas inserted in the innominate artery (or more distally in the right common carotid artery) and left common carotid artery provides the most physiologic and efficient perfusion of the brain.[76] Perfusate temperature is usually set at 18°C and flow

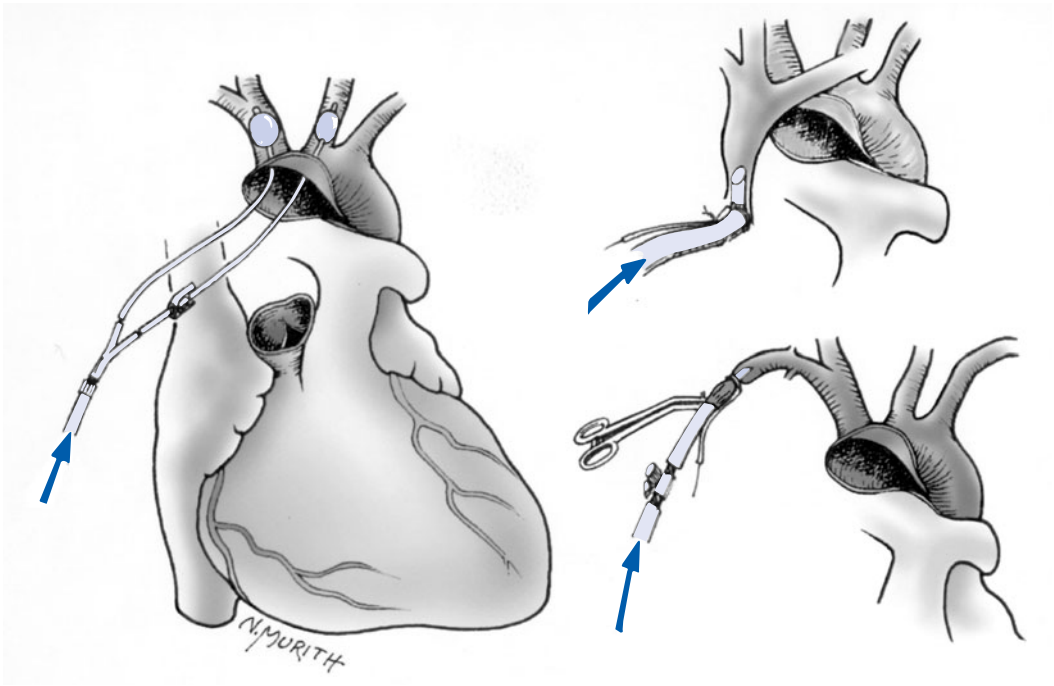

Figure 14-4. Perfusion techniques to reduce ischemic injury to the brain. Bilateral antegrade cerebral perfusion obtained by selective cannulation of the innominate and left common carotid arteries. (*Inset, top right*) Retrograde cerebral perfusion via the superior vena cava. (*Inset, bottom right*) Regional cerebral perfusion (unilateral antegrade perfusion) via cannulation of the right subclavian artery.

between 10 and 20 mL/kg per minute or adjusted to maintain a pressure of between 40 and 50 mm Hg in the right radial artery. Clinical results, especially regarding swift recovery of cerebral function, have been outstanding with this method of perfusion.[76–81] The need to cannulate relatively small and often diseased arch arteries and the presence of additional cannulas in the operating field constitute the main drawbacks of the technique. Cannulation of the common carotid arteries can result in dissection of the arterial wall and embolism of atheromatous plaque material or air. Furthermore, the flow in the artery depends on a proper position of the tip of the cannula within the vessel. For these reasons, many surgeons rely on a unilateral perfusion of the brain, with sole cannulation and perfusion of the right subclavian artery.[81,82] The right vertebral and right common carotid artery territories are perfused in an antegrade fashion. The blood reaches the left cerebral hemisphere through the circle of Willis and, to a lesser extent, through cervicofascial connections. It is therefore important that the takeoffs of the left common carotid and left subclavian arteries be occluded to avoid a steal of blood down these arteries. Occlusion (usually with an inflatable balloon) of the descending aorta is also a useful maneuver to improve overall body perfusion. Effective somatic perfusion (including the abdominal organs, spinal cord, and lower limb musculature) has been documented with this maneuver.[83] The presence of an aberrant right subclavian artery (also called *arteria lusoria*) obviously is a contraindication to the use of this perfusion method. The aberrant origin of the artery usually is identified readily by computed tomographic scanning or magnetic resonance imaging. The burst of blood from the descending aorta during opening of the aortic arch should alert the surgeon to this anatomic variation and prompt a direct cannulation of the ostium of the right and left common carotid arteries.

Sequential perfusion of the cerebral arteries provides additional safety to unilateral cerebral perfusion and avoids cannulation of small or diseased arch arteries.[37,84] The right subclavian artery remains perfused during the whole procedure. A vascular graft is sewn immediately on a common patch of aortic wall including all the arch vessels,[85] or the second branch of a multiple-arm prosthesis is anastomosed to the left common carotid artery. Perfusion then is instituted through this additional graft and enhances, after a short period of time, cerebral perfusion.

Retrograde Cerebral Perfusion

The value of retrograde cerebral perfusion in protecting the human brain still has not been elucidated clearly. No animal model truly replicates the complex anatomy and physiology of the human brain, and none allows a fine neuropsychological evaluation. Conflicting results and conclusions in clinical and experimental studies therefore have been reported. Accepted facts include a deep and homogeneous cooling of the brain hemispheres (the cooling scalp effect) and the

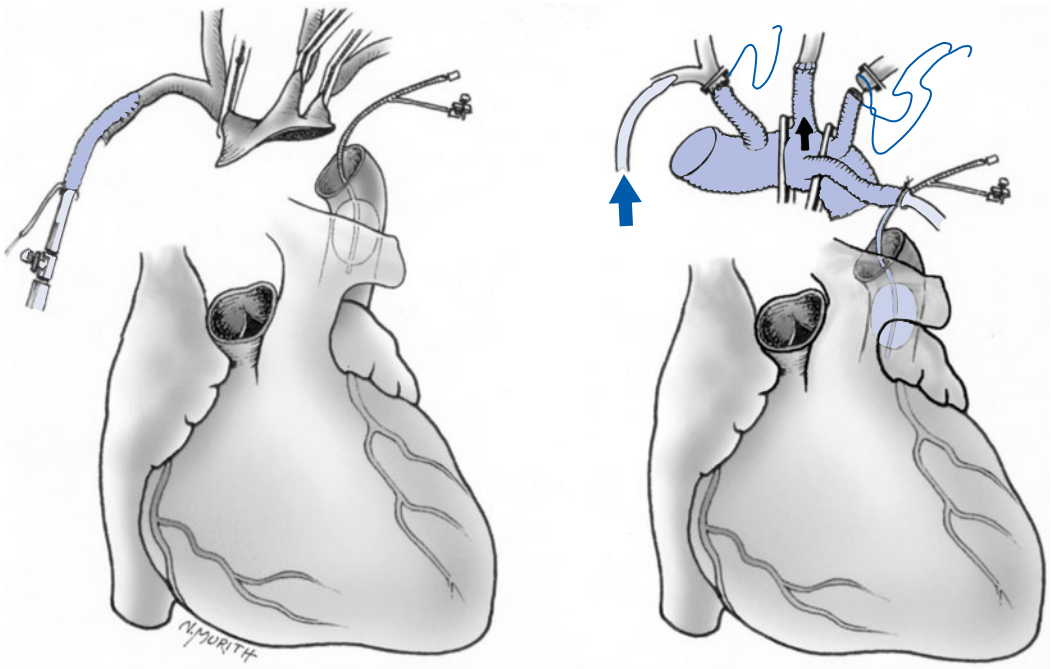

Figure 14-5. Perfusion techniques to reduce ischemic injury to the brain. Sequential bilateral antegrade perfusion of the brain. The branch of a multiple-arm graft is connected initially to the left common carotid artery, allowing rapid establishment of bilateral perfusion of the brain. The other anastomoses are performed thereafter. Perfusion of the right subclavian artery through a graft allows monitoring of the perfusion pressure via the right radial artery.

expulsion of solid particles or gaseous bubbles from the arch arteries. Controversies surround the possible nutritive value of retrograde perfusion.[86] The nutritive value has been demonstrated in rabbits but not in dogs, pigs, or baboons.[87–89] In humans, signs of cerebral perfusion and oxygen uptake have been documented,[90] but the amount of perfusate providing cerebral nutrition is low, corresponding to about 5% of total retrograde flow.[73,88,91] The blood delivered in the superior vena cava flows preferentially in the low-pressure inferior vena cava via the azygos system, the perivertebral venous plexus, and the thoracic wall veins.[92] Even within the brain, the distribution of retrograde flow is inhomogeneous, with a preferential distribution in the saggital sinus and hemispheric veins.[93] The large steal of blood to the inferior venous territory is corroborated by the clinical finding of an extremely small proportion of perfused blood flowing out of the arch arteries. Occlusion of the inferior vena cava to decrease the pressure gradient between the two venous territories effectively reduces the amount of stolen blood but increases the sequestration of fluid in the interstitial tissue.[94] Interstitial edema is another potential problem of retrograde perfusion that can lead to cerebral edema and hypertension, particularly when the perfusion pressure is set above 25 mm Hg.[95] Finally, the finding that the human jugular system may contain competent valves[96] casts definitive doubt regarding the reliability of retrograde cerebral perfusion.

Clinical series, however, have reported encouraging results. A reduction in both mortality and neurologic damage has been documented regularly with the adjunctive use of retrograde cerebral perfusion to classic hypothermia.[80,97–100] Some studies confirmed the limited capacity of retrograde perfusion to sustain cerebral metabolism and stressed the fact that the occurrence of neurologic damage was only delayed.[88,95] Indeed, the risk rises sharply after 60 minutes of deep hypothermic circulatory arrest, perhaps at the extinction of intracellular energy substrates. If most surgeons acknowledge the capacity of retrograde cerebral perfusion to prolong the period of safe circulatory arrest, they consider the method a valuable but not an alternative adjunct to conventional methods when long periods of circulatory arrest are contemplated.[80,97–100]

Integrated Perfusion

Probably the safest approach to a patient requiring a long period of circulatory arrest resides in the integration of complementary methods of perfusion and monitoring.[52,71,85,86] Retrograde perfusion of the aorta through the femoral artery should be avoided in case of thoracic aortic aneurysm in order to reduce the risk of particulate dislodgment with embolization in the brain and myocardium.[69,70] Antegrade perfusion of the aorta is performed with cannulation of the ascending aorta or right subclavian artery. The body is cooled to 18°C. Electroencephalogram and venous jugular saturation are monitored to ensure adequate reduction of cerebral metabolism. Circulatory arrest is established

only after electrocerebral silence has been obtained and jugular venous saturation is greater than 95%. During the 10 to 20 minutes preceding circulatory arrest, the temperature of the perfusate can be lowered to 13°C to further reduce brain temperature and metabolism. The arch arteries are connected to a graft (either with the use of a patch of aortic wall or separately), and antegrade perfusion of the brain is resumed before more extensive resection and repair of the aorta are performed.[71,85] When the risk of particle embolization to the brain is substantial (e.g., in old age or with severe atherosclerosis of the aorta and arch aneurysm with thrombotic material), a short period of retrograde cerebral perfusion can be performed to wash out the arch arteries before antegrade perfusion is reestablished definitively.[52]

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CHAPTER 15

Myocardial Protection

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The term *myocardial protection* refers to strategies and methodologies used either to attenuate or to prevent postischemic myocardial dysfunction that occurs during and after heart surgery. Postischemic myocardial dysfunction is attributable, in part, to a phenomenon known as *ischemia-reperfusion-induced injury.* Clinically, it manifests by low cardiac output and hypotension and may be subdivided into two subgroups: reversible injury and irreversible injury. The two typically are differentiated by the presence of electrocardiographic abnormalities, elevations in the levels of specific plasma enzymes or proteins such as creatine kinase and troponin I or T, and/or the presence of regional or global echocardiographic wall motion abnormalities. With respect to coronary artery bypass grafting (CABG) alone, 10% of patients may experience myocardial infarction (MI), severe ventricular dysfunction, heart failure, and/or death despite advances in surgical technique. The impact from these complications both on families and on society is enormous. From an economic standpoint, the initial hospital cost of CABG is approximately $10 billion annually; it is likely, then, that complications after CABG consume an additional $2 billion in U.S. health care resources each year.[1] The purpose of this chapter is to review the history of myocardial protection, to update the reader regarding the current protective techniques, to examine the mechanisms underlying ischemia-reperfusion injury, and to discuss several new strategies currently under investigation.

HISTORY

Over the past 50 years, many therapeutic strategies have been developed to protect the heart during surgery (Table 15-1). This concept of shielding the heart from perioperative insult originated in 1950 with the review article by Bigelow and colleagues in which hypothermia was reported "as a form of anesthetic" that could be used to expand the scope of surgery.[2] It was proposed that hypothermia could be used as "a technique that might permit surgeons to operate on the bloodless heart without recourse to extracorporeal pumps and perhaps allotransplantation of organs."[2] Five years later, Melrose and colleagues reported another way to stop and restart the heart reliably by injecting potassium citrate into the root of the aorta at both normal and reduced body temperatures.[3] Soon thereafter, the clinical application of potassium citrate arrest was adopted by many centers. Interest in using the Melrose technique waned, however, with subsequent reports that potassium citrate arrest was associated with myocardial injury and necrosis. Within a short time, many cardiac surgeons shifted from using potassium-induced arrest to normothermic cardiac ischemia (i.e., normothermic heart surgery performed with the aorta occluded while the patient was on cardiopulmonary bypass), intermittent aortic occlusion, or coronary artery perfusion. Experimental and clinical evidence showed, however, that normothermic cardiac ischemia was associated with metabolic acidosis, hypotension, and low cardiac output.[4–6]

As a consequence, there was a renewed interest in discovering ways to arrest the heart. Bretschneider published the principle of arresting the heart with a low-sodium, calcium-free solution.[7] It was Hearse and colleagues, however, who studied the various components of cardioplegic solutions, which led to the development and use of St. Thomas solution.[8] The components of this crystalloid solution were based on Ringer's solution with its normal concentrations of sodium and calcium with the addition of potassium chloride (16 mmol/L) and magnesium chloride (16 mmol/L) to arrest the heart instantly. The latter component was shown by Hearse to provide an additional cardioprotective benefit. In 1975, Braimbridge and colleagues introduced this crystalloid solution into clinical practice at St. Thomas Hospital.[9]

Gay and Ebert showed experimentally that lower concentrations of potassium chloride could achieve the same degree of chemical arrest and myocardial protection

Table 15–1.

Therapeutic Innovations for Myocardial Protection

Reference	Year	Innovation
Bigelow WG[2]	1950	Studied the application of hypothermia to cardiac surgery in canines
Swan H	1953	Showed that hypothermic arrest (26°C) in humans provided a bloodless field for operating
Melrose DG, Bentall HH[3]	1955	Introduced the concept of reversible chemical cardiac arrest in canines
Lillehei CW	1956	Detailed a method for delivering hypothermic crystalloid cardioplegia by cannulating coronary arteries
Lam CR	1957	One of the earliest known uses of the term "cardioplegia"
Gerbode F, Melrose DG	1958	Used potassium citrate to induce cardiac arrest in humans
McFarland JA	1960	Challenged the safety of the Melrose technique; changed from potassium arrest to intermittent aortic occlusion or coronary artery perfusion for myocardial protection
Bretschneider HJ[7]	1964	Developed a sodium-poor, calcium-free, procaine-containing solution to arrest the heart
Sondergaard KT	1964	Adopted Bretschneider's cardioplegic solution and was one of the first to routinely use it for myocardial protection in clincial practice
Gay WA, Ebert PA[10]	1973	Credited with revival of potassium-induced cardioplegia; demonstrated that potassium solution could arrest a canine heart for 60 minutes without cellular damage
Roe BB[11]	1973	Demonstrated that "the modalities of cardioplegia, hypothermia, and capillary washout" provided effective myocardial protection
Tyers WA[4]	1974	Demonstrated that an infusion of cold blood to keep the myocardial tissue below 4°C provided 90 minutes of ischemia in animals
Hearse DJ[8]	1975	Emphasized preischemic infusions to negate ischemic injuries in rats; this formula became known as St. Thomas solution no. 1
Braimbridge MV[9]	1975	One of the first to use St. Thomas solution no. 1 clinically
Effler DB	1976	Recommended simple aortic clamping at operating room tempreatures
Buckberg GD[13]	1979	Introduced the use of blood as the vehicle for infusing potassium into coronary arteries
Akins CW[84]	1984	Utilized technique of hypothermic fibrillatory arrest for coronary revascularization without cardioplegia
Murray CE[99]	1986	Noted that brief periods of ischemia and reperfusion enable the heart to withstand longer periods of ischemia
Lichtenstein SV, Salerno TA[90,91]	1991	Reported clincally beneficial results using continuous, warm blood cardioplegia

afforded by the Melrose solution without the associated myocardial necrosis reported earlier.[10] Shortly thereafter, Roe and colleagues reported an operative mortality of 5.4% for patients who underwent cardiac surgery with potassium-induced arrest as the primary form of myocardial protection.[11] In 1977, Tyers and colleagues reported that potassium cardioplegia provided satisfactory protection in over 100 consecutive cardiac patients.[12]

By the 1980s, normothermic aortic occlusion had been replaced for the most part by cardioplegia to protect the heart during cardiac surgery. The major controversy at the time (and one that persists today) was not whether cardioplegic solutions should be used, but what were the ideal components of those solutions. The chief variants consisted of (1) the Bretschneider solution, consisting primarily of sodium, magnesium, and procaine, (2) the St. Thomas solution, consisting of potassium, magnesium, and procaine added to Ringer's solution, and (3) potassium-enriched solutions containing no magnesium or procaine (Table 15-2). Coincident with this controversy, another variant of cardioplegia was introduced, that of using potassium-enriched blood cardioplegia.[13,14] The theory was that blood would be a superior delivery vehicle based on its oxygenating and buffering capacity. Ironically, Melrose and colleagues initially used blood as the vehicle to deliver high concentrations of potassium citrate more than 20 years earlier.

While hypothermia and potassium infusions remain the cornerstone of myocardial protection during on-pump heart surgery, many other cardioprotective techniques and methodologies are available.[3,15] Although many of these techniques have been reported to confer superior protection and improve patient outcomes, the ideal cardioprotective technique, solution, and method of administration have yet to be found. Fortunately, the majority of cardioprotective strategies now available do allow patients to undergo conventional and complex heart operations with an operative mortality rate ranging from less than 2 to 4%.

ISCHEMIA-REPERFUSION INJURY

While the etiology of postischemic myocardial dysfunction after cardiac surgery is multifactorial, three basic types of injury occur during heart surgery: myocardial stunning, apoptosis, and MI. Myocardial stunning is an injury that may last for only a few hours or persist for several days despite the restoration of normal blood flow. Cells that have been reversibly injured (stunned) exhibit no sign of ultrastructural damage. Apoptosis is "suicidal" programmed cell death, characterized by retention of an intact cell membrane, cell shrinkage, chromatin condensation, and phagocytosis without inflammation.[16–19]

There is increasing evidence that apoptotic death of cardiomyocytes caused by ischemia-reperfusion contributes significantly to the development of infarction as well as the loss of cells surrounding the infarct area. A large fraction of dying cells may exhibit features of both apoptosis and necrosis, i.e., both nuclear condensation and plasma membrane damage. Ultimately, however, after more prolonged ischemia, the heart begins to sustain irreversible injury in the form of infarction, necrosis, and a spectrum of reperfusion-associated pathologies manifested as membrane destruction, cell swelling, DNA degradation, cytolysis, and the induction of an inflammatory response collectively called *reperfusion injury.*[20]

While the consequences of inadequate myocardial protection usually are apparent in the immediate postoperative period, the full impact may not be fully appreciated for months. Klatte and colleagues reported that patients with increased peak creatine kinase–myocardial band (CK-MB) enzyme ratios after CABG exhibited a greater 6-month mortality.[21] Specifically, the 6-month mortality rates for patients with peak CK-MB ratios of less than 5, 5 to less than 10, 10 to less than 20, and 20 and greater upper limits of normal were 3.4, 5.8, 7.8, and 20.2%, respectively. Conversely, the cumulative 6-month survival was inversely related to the peak CK-MB ratio. These observations support the concept that myocardial injury occurring as a result of inadequate myocardial protection intraoperatively is associated with subsequent death.

In order to appreciate the strategies that have evolved to protect the myocardium during heart surgery, it is important to understand the mechanisms implicated in the etiology of the various types of myocardial ischemia-reperfusion injury. Significant evidence now exists that the primary mediators of reversible and irreversible myocardial ischemia-reperfusion injury include intracellular Ca^{2+} overload during ischemia and reperfusion and oxidative stress induced by reactive oxygen species (ROS) generated at the onset of reperfusion[22–24] (Fig. 15-1). The molecule nitric oxide (NO) also can interact with ROS to generate various reactive nitrogen species that appear capable of both contributing to and reducing injury.[25,26] In addition, metabolic alterations occurring during ischemia can contribute directly and indirectly to Ca^{2+} overload and ROS formation. For example, decreased cytosolic phosphorylation potential, i.e., $[ATP]/-([ADP] \times [P_i])$, results in less free energy from ATP hydrolysis than is necessary to drive the energy-dependent pumps (sarcoplasmic reticulum Ca^{2+}-ATPase, the sarcolemmal Ca^{2+}-ATPase) that maintain intracellular calcium homeostasis.[27]

Restoration of intracellular pH at the onset of reperfusion via Na^{+}-H^{+} exchange contributes to intracellular Ca^{2+} overload via reversed Na^{+}-Ca^{2+} exchange.[28,29]

The metabolic changes that occur during ischemia also reduce the endogenous antioxidant defense systems of cardiac myocytes. The first line of defense against mitochondrial ROS formation and its deleterious effects is the GSH (reduced glutathione)/GSSG (oxidized glutathione) system, which is directly linked to the NADPH:$NADP^{+}$ ratio via the enzyme glutathione reductase. The depletion of glutathione levels increases ROS formation, oxidative stress, and $[Ca^{2+}]_i$.[30–33] Since NADPH is not formed during ischemia, the normal metabolic mechanism for regenerating the reduced glutathione does

Table 15–2.

Components of Various Cardioplegic Solutions

Solution	Usual components*							Other components
	Sodium	Potassium	Magnesium	Calcium	Bicarbonate	pH	Osmolarity (mOsm/L)	
Bretschneider's no. 3	12.0	10.0	2.0	–	–	5.5–7.0	320	Procaine; mannitol
Lactated Ringer's	130.0	24.0	–	1.5	–	7.14	–	Lactate; chlorine
Tyer's	138.0	25.0	1.5	0.5	20.0	7.8	275	Acetate; gluconate; chloride
St. Thomas no. 2	110.0	16.0	16.0	1.2	10.0	7.8	324	Lidocaine
Roe's	27.0	20.0	1.5	–	–	7.6	347	Glucose; tris buffer
Gay/Ebert	38.5	40.0	–	–	10.0	7.8	365	Glucose
Birmingham	100.0	30.0	–	0.7	28.0	7.5	300–385	Glucose; chloride; albumin; mannitol
Craver's	154.0	25.0	–	–	11.0	–	391	Dextrose
Lolley's	–	20.0	–	–	4.4	7.78	350	Dextrose; mannitol; insulin

**Values are expressed in millimoles per liter unless otherwise noted.*

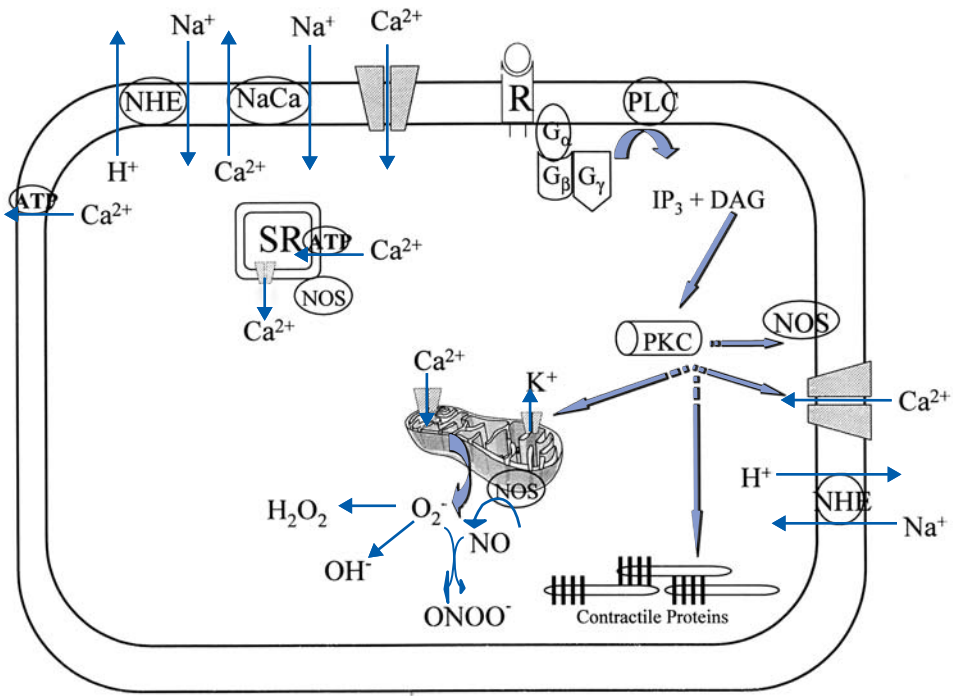

Figure 15-1. Intracellular mechanisms regulate cardiomyocyte Ca^{2+} homeostasis and reactive oxygen species formation, the two primary mediators of myocyte ischemia-reperfusion injury. During ischemia, intracellular Ca^{2+} increases via the inability of energy-dependent Ca^{2+} pumps in the sarcolemma and sarcoplasmic reticulum (SR) to maintain normal low resting cytosolic Ca^{2+} concentrations. Activation of various G protein–coupled receptors (R, alpha- and beta-adrenergic, angiotensin, endothelin, etc.) initiates signaling mechanisms [stimulatory G proteins (G_s) and phospholipase C (PLC)] and also increases Ca^{2+}. The generation of inositol triphosphate (IP_3) from this latter pathway increases Ca^{2+} release from intracellular stores, including SR. diacylglycerol (DAG) formation via the PLC pathway leads to the activation of Ca^{2+}-dependent and -independent isoforms of protein kinase C (PKC). PKC phosphorylation of various proteins and enzymes further modulates Ca^{2+} concentration, metabolism, and contractile protein Ca^{2+} sensitivity. The sodium-hydrogen exchanger (NHE) exchanges intracellular H^+ for extracellular Na^+, and the resulting increase in intracellular Na^+ may result in reverse Na^+ -Ca^{2+} exchange via the sodium-calcium exchanger (Na-Ca). During reperfusion, the generation of reactive oxygen species [superoxide anion (O_2^-), hydroxyl anion (OH^-), and hydrogen peroxide (H_2O_2)] oxidizes various proteins (Ca^{2+} pumps, SR Ca^{2+} release channels, contractile proteins, etc.) that contribute to both reversible and irreversible injury. Superoxide may combine with nitric oxide (NO) generated from sarcolemmal NOS and possibly mitochondrial NOS to form peroxynitrite ($ONOO^-$) and other reactive nitrogen species to modulate ischemia-reperfusion injury. Early reperfusion is also associated with increased NHE activity, further exacerbating Ca^{2+} overload via reverse Na^+ -Ca^{2+} exchange. Preischemic activation of some myocyte inhibitory G protein (G_i)–-coupled receptors, such as adenosine A_1 and opioid receptors, reduces these deleterious effects of ischemia-reperfusion. It also has been proposed that PKC may phosphorylate an ATP-dependent K^+ channel in the mitochondrial membrane and/or membrane-bound nitric oxide synthase (NOS) that protects the myocyte against ischemia-reperfusion injury.

not function. Thus, the formation of ROS during reperfusion occurs at a time when the myocyte's endogenous defense mechanisms are depressed. The NADPH:$NADP^+$ ratio is a primary determinant of the redox state of the cell, and there is evidence that redox state plays a key role in determining the bioactivity and redox state of NO.[26,34,35] In addition, there are several reports that in the absence of normal levels of its cofactors, nitric oxide synthase (NOS) itself can generate superoxide anion.[36,37] Although systolic calcium $[Ca^{2+}]_i$ may return to normal levels early in reperfused stunned myocardium, the transient increases in intracellular $[Ca^{2+}]_i$ can activate Ca^{2+} -dependent protein kinase (PKC), proteases such as calpain, and endonucleases.[38–40] Calpain activation and its subsequent action on contractile proteins have been implicated in the reduction of myofilament Ca^{2+} sensitivity observed in stunned myocardium.[41,42]

Similarly, there is significant evidence that ROS are involved in mediating myocardial stunning. Various spin-trap agents and chemical probes have demonstrated the rapid release of ROS into the vascular space during reperfusion after brief ischemia in vivo.[43–46] It is also now recognized that mitochondria are a primary source of intracellular ROS

in cardiac myocytes.[47,48] Scavengers of ROS and antioxidants attenuate myocardial stunning in vitro and in vivo, and these interventions are effective when administered prior to or at the onset of reperfusion.[22,49,50] It has been shown that ROS can attack thiol residues of numerous proteins such as the SR Ca^{2+}-ATPase, the ryanodine receptor, and contractile proteins.[51–53] This may explain why myofibrils isolated from in vivo reperfused stunned but not ischemic myocardium exhibit reduced Ca^{2+} sensitivity.[54]

More prolonged ischemia, which produces irreversible injury, is associated with more severe intracellular Ca^{2+} overload and further depletion of endogenous antioxidants, conditions that both contribute to and are exacerbated during reperfusion by the production of ROS. The production of ROS during reperfusion appears to contribute to Ca^{2+} overload because exposure of normal myocytes to exogenous ROS is associated with increased L-type Ca^{2+} channel current and increased $[Ca^{2+}]_i$.[33,55,56] Conversely, increases in $[Ca^{2+}]_i$ during ischemia-reperfusion may adversely affect mitochondrial function, leading to further ROS production.[57,58] Mitochondria can buffer small increases in intracellular Ca^{2+} via the Ca uniporter, a process that is energetically favorable owing to the $[Ca^{2+}]$ gradient and the mitochondrial membrane potential. During reperfusion, the increase in cytosolic Ca^{2+} enhances mitochondrial Ca^{2+} uptake. Since excess cytosolic Ca^{2+} has been associated with the loss of myocyte viability, mitochondrial Ca^{2+} buffering is initially cardioprotective.[59] However, continued mitochondrial Ca^{2+} buffering in the face of decreased antioxidant reserves and excess ROS formation sets up a cycle that ultimately may lead to the total collapse of mitochondrial membrane potential and cell death.[58] The synergistic interactions between Ca^{2+} overload and ROS formation during conditions of decreased antioxidant reserves also may provide an explanation of why ROS scavengers are not very effective at reducing irreversible injury when administered at reperfusion.[60,61]

Historically, myocardial ischemia-reperfusion injury has been characterized as either reversible or irreversible (based on staining techniques, enzyme release, and histology). There is now increasing evidence that this injury represents a transition from reversible to irreversible injury and that it occurs as a continuum and not as an all-or-none phenomenon. For example, apoptosis occurs prior to severe depletion in ATP and loss of membrane integrity but ultimately leads to cell death.[17,19] The phenomenon of apoptosis appears to commence during reperfusion with the formation of intracellular ROS and/or intracellular calcium overload[62–64] (Fig. 15-2). This process is initiated by translocation of the proapoptotic proteins Bad and Bax from the cytosol to the mitochondrial membrane. Heterodimerization of Bad or Bax with the antiapoptotic Bcl-2 or Bcl-xl can lead to the release of the mitochondrially localized cytochrome c into the cytosol.[65–67] Formation of a cytosolic complex consisting of cytochrome c, apoptosis-activating factor 1 (APAF-1), and caspase-9 leads to activation of caspase 3 and the cleavage of poly(ADP)-ribosylating (PARP) protein. Activation of PARP is the final step in apoptosis, leading to DNA fragmentation.[68]

As described earlier, the increased intracellular ROS and/or intracellular calcium overload collapse the mitochondrial membrane potential, leading to mitochondrial permeability transition pore (MPTP) opening, which, if not reversed, can result in the loss of mitochondrial proteins such as cytochrome c.[56]

The physiologic relevance of apoptosis during myocardial ischemia-reperfusion has yet to be determined. This is due to the fact that the majority of reports on apoptosis in this setting have been based on measurements of DNA fragmentation and laddering, the final steps in apoptotic cell death. Once DNA is fragmented, the cell's ability to synthesize new proteins to repair itself is severely compromised, and these cells, even if they survive a first ischemic episode, may die at an accelerated rate during subsequent stress or ischemia. However, studies conducted in other tissues and in isolated cells (including cardiomyocytes) indicate that the apoptotic program can be detected much earlier than these late stages. One of the earliest signs of apoptosis is the translocation of phosphatidylserine from the inner face of the plasma membrane to the cell surface, a process that can be detected by annexin V, which has a strong affinity for phosphatidylserine.[69,70] Apoptosis in cardiac myocytes can be demonstrated with fluoroscein isothiocyanate (FITC)-conjugated annexin V staining of the plasma membrane much earlier than DNA fragmentation (via the TUNEL assay and DNA laddering).[71–74.] There are also reports that this early stage of apoptosis does not irreversibly commit cells to programmed cell death in noncardiac tissue and that a significant proportion of myocytes, when submitted to simulated ischemia-reperfusion, exhibit signs of early apoptosis (positive annexin-FITC staining, intact membrane cell death, decreased cell width, and increased mitochondrial $[Ca^{2+}]$).[74–76]

Thus, it appears that ischemia-reperfusion injury (i.e., myocardial stunning, apoptosis, and infarction) manifests in a variety of interrelated ways. For example, apoptosis may proceed to necrosis when mitochondria are no longer able to withstand the intracellular Ca^{2+} overload and oxidative stress induced by ROS and when oxidative phosphorylation is unable to keep pace with energy demands. Due to the resulting decrease in the myocardial phosphorylation potential, energy-dependent ion pumps cannot maintain normal ion gradients. This results in cell swelling and, ultimately, loss of membrane integrity. These disturbances can be further exacerbated by the influx of macrophages and leukocytes, complement activation, and endothelial plugging by platelets and neutrophils. If cell death in ischemic-reperfused myocardium progresses from apoptosis to necrosis, and if early apoptosis is indeed reversible, then one therapeutic approach for the treatment or prevention of ischemia-reperfusion injury would be to target the early events in apoptosis. Regardless of which stage is being addressed, current cardioprotection strategies are designed to reduce cellular and subcellular ROS formation and oxidative stress, to enhance the heart's endogenous antioxidant defense mechanisms, and to prevent intracellular Ca^{2+} overload.

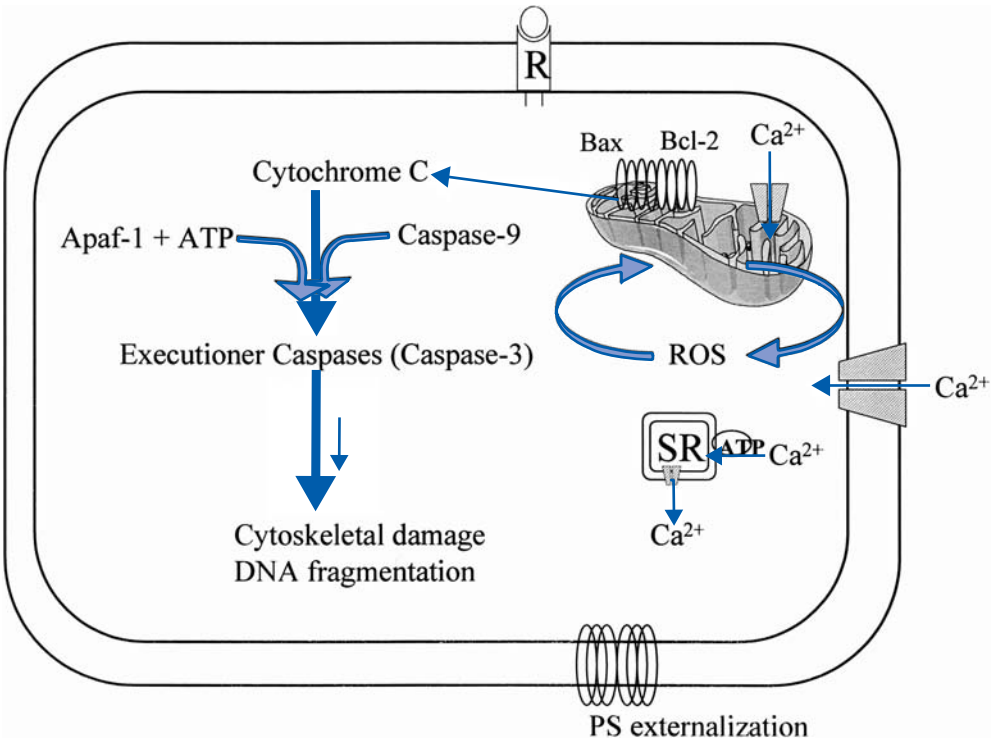

Figure 15-2. Proposed mechanisms of cardiomyocyte apoptosis following ischemia-reperfusion injury. Intracellular Ca^{2+} overload during ischemia and reperfusion and reactive oxygen species (ROS) formation during reperfusion are thought to be the primary mediators of the intrinsic pathway of apoptosis. The mechanisms of Ca^{2+} overload and ROS formation are described in detail in the text. Ischemia-reperfusion-associated effects on metabolism and decreased levels of the endogenous antioxidant glutathione lead to excess electron leak from the mitochondrial electron transport chain generating mitochondrial ROS. The mitochondrial Ca^{2+} uniporter can buffer increases in cytosolic Ca^{2+}, but increased mitochondrial Ca^{2+} can induce excess ROS formation. Likewise, ROS formation can induce intracellular Ca^{2+} overload. Through mechanisms that are not well defined, two families of closely related proteins (Bcl-2 and Bax) modulate the cell's response to apoptotic stimuli. Bcl-2 is an antiapoptotic protein that appears to be capable of inhibiting cytochrome c release either directly or by forming a complex with and inhibiting the proapoptotic family of proteins (Bax). Bax is thought to translocate from the cytosol to the mitochondrial membrane during the apoptotic process. Two early events in apoptosis are the externalization of phosphatidyl serine (PS) residues in the sarcolemma and the release of cytochrome c from the mitochondria. The significance of PS externalization is not clear; however, its occurrence can be detected with fluorescently tagged annexin-5, thus permitting the detection of the early stages of apoptosis. Cytochrome c released from the mitochondria complexes with an apoptotic protease-activating factor 1 (Apaf-1) and procaspase 9. In the presence of near-normal ATP levels, procaspase 9 is cleaved into the active caspase 9 with the resulting activation of the cytosolic protease caspase 3, often referred to as the *executioner caspase*. Caspase 3 protease activity leads to irreversible damage to cell morphology and DNA fragmentation and laddering.

NONCARDIOPLEGIC TECHNIQUES

Intermittent Cross-Clamping with Fibrillation

One of the earliest forms of cardioprotection, still used at some centers today, is known as *intermittent aortic cross-clamping with fibrillation and moderate hypothermic perfusion* (30 to 32°C). Using this approach, CABG can be performed on the unarrested heart with ascending aorta cannulation and generally a two-stage single venous cannula. This technique allows the surgeon to operate in a relatively quiet field (during ventricular fibrillation) and to avoid the consequences of profound metabolic changes that occur with more prolonged periods of ischemia. The duration of fibrillation is determined by how long it takes to perform the distal anastomoses. After completion of the last distal graft, the heart can be defibrillated and the proximal aortic-based graft anastomoses performed on the beating heart using an aortic partial occlusion clamp.

As a result of increasing pressures to reduce costs and yet maintain acceptable levels of myocardial protection, there has been a renewed interest in this approach. There are, in fact, a number of reports that indicate that satisfactory protection can be conferred using this technique. In 1992, Bonchek and colleagues reported a large clinical series in which the advantages and safety of using this technique were

meticulously analyzed.[77] In this study, the authors reviewed the outcomes of the first 3000 patients at their institution who underwent primary CABG using the intermittent aortic cross-clamping technique. Preoperative risk factors (e.g., age, gender, left ventricular dysfunction (LVD), preoperative intra-aortic balloon pumping (IABP), and urgency of operation) and operative deaths were analyzed as well. In this series, 29% of the patients were older than 70 years of age, 27% were females, 9.7% had an ejection fraction of less than 0.30, 13% had an MI less than 1 week preoperatively, and 31% had preinfarction angina in the hospital. Only 26% underwent purely elective operations. Using the noncardioplegic cardioprotective technique, the authors reported an elective operative mortality rate of 0.5%, an urgent mortality rate of 1.7%, and an emergency rate of 2.3%. Postoperatively, inotropic support was needed in only 6.6% of the patients, and only 1% required IABP. It is important to note, however, that this was a retrospective, single-center institutional experience. The findings would have been more enlightening if the analysis had included a similarly matched group of patients at the same institution in which cardioplegic arrest had been employed. Nevertheless, the findings do suggest that noncardioplegic strategies can provide satisfactory myocardial protection even in high-risk patients.

As a result, a minority of surgeons continues to use this technique.[78–80] In 2002, Raco and colleagues[81] reported the results of 800 consecutive CABG operations performed by a single surgeon using aortic cross-clamping in both elective and nonelective procedures. The patients were divided into three cohorts: (1) elective, (2) urgent, and (3) emergent. The mean age, number of distal grafts, and mortality in the elective group were 61.5 years, 3.2 grafts, and 0.6%, respectively. For the urgent group, they were 63.1 years, 3.2 grafts, and 3.1%. In the emergent group, they were 63.8 years, 2.9 grafts, and 5.6%. These findings support the contention that intermittent aortic cross-clamping is a safe technique in both elective and nonelective patients when performed by an experienced surgeon.[82,83]

Systemic Hypothermia and Elective Fibrillatory Arrest

Although used infrequently, this technique appears to be a safe approach to protecting the heart during CABG. In 1984, Akins and colleagues reported a low incidence of perioperative infarction and a low hospital mortality rate in 500 consecutive patients using this technique.[84] With this method, systemic hypothermia (28°C), elective fibrillatory arrest, and maintenance of systemic perfusion pressure at between 80 and 100 mm Hg are the key elements. On fibrillatory arrest, the local vessel can be isolated and myocardial revascularization performed. The limitations of this technique include (1) the surgical field may be obscured by blood during revascularization, (2) ventricular fibrillation is associated with increased muscular tone, which can limit the surgeon's ability to position the heart for optimal exposure, and (3) it is generally not applicable for intracardiac procedures.[85]

CARDIOPLEGIC TECHNIQUES

Cardioplegic solutions contain a variety of chemical agents that are designed to arrest the heart rapidly in diastole, create a quiescent operating field, and provide reliable protection against ischemia-reperfusion injury. In general, there are two types of cardioplegic solutions: crystalloid cardioplegia and blood cardioplegia. These solutions are administered most frequently under hypothermic conditions.

Cold Crystalloid Cardioplegia

There are basically two types of crystalloid cardioplegic solutions: the intracellular type and the extracellular type. The intracellular types are characterized by absent or low concentrations of sodium and calcium. The extracellular types contain relatively higher concentrations of sodium, calcium, and magnesium. Both types avoid concentrations of potassium >40 mmol/L, contain bicarbonate for buffering, and are osmotically balanced. In both types, the concentration of potassium used ranges between 10 and 40 mmol/L (for potassium 1 mmol/L = 1 mEq/L). Examples of some of the various crystalloid cardioplegic solutions used are shown in Table 15-2.

Operative procedure

While the degree of core cooling varies from center to center, patients undergoing cardiac surgery are placed on cardiopulmonary bypass (CPB) and often cooled to between 33 and 28°C. To initiate immediate chemical arrest, the solution is infused after cross-clamping the aorta through a cardioplegic catheter inserted into the aorta proximal to the cross-clamp. The catheter may or may not be accompanied by a separate vent cannula. The cold hyperkalemic crystalloid solution then is infused (antegrade) at a volume that generally does not exceed 1000 mL. One or more infusions of 300 to 500 mL of the cardioplegic solution may be administered if there is evidence of electrical heart activity resumption or if a prolonged ischemic time is anticipated. If myocardial revascularization (MR) is being performed, the aortic cross-clamp can be removed after completing the distal anastomoses, and the heart can be reperfused while the proximal anatomoses are completed using a partial occlusion clamp. Alternatively, the proximal grafts can be performed after the distal grafts have been completed with the cross-clamp still in place (the single-clamp technique). Another approach is to perform the proximal aortic grafts first and then to cross-clamp the aorta and infuse the cardioplegic solution. When valve repair or replacement is being performed, the crystalloid cardioplegia can be administered directly into the coronary arteries via cannulation of the coronary ostia. Crystalloid cardioplegia also can be administered retrograde via a coronary sinus catheter with or without a self-inflating silicone cuff.

Results

Numerous studies have been performed to determine the efficacy of using cold crystalloid cardioplegic solutions to protect the heart during cardiac surgery. While there is considerable controversy regarding the "ideal" solution and its components, there is evidence that in those centers in which crystalloid cardioplegia is used almost exclusively, excellent myocardial protection can be achieved. In many reports, the perioperative MI rate is less than 4%, and the operative mortality rate is less than 2%.

Cold Blood Cardioplegia

Cold blood cardioplegia, widely employed throughout the world, is the cardioplegic technique used most commonly in the United States today. Although there are a variety of formulations, it is usually prepared by combining autologous blood obtained from the extracorporeal circuit while the patient is on cardiopulmonary bypass with a crystalloid solution consisting of citrate-phosphate-dextrose (CPD), tris-hydroxymethyl-aminomethane (tham) or bicarbonate (buffers), and potassium chloride. The CPD is used to lower the ionic calcium, the buffer is used to maintain an alkaline pH of approximately 7.8, and the final concentration of potassium is used to arrest the heart (approximately 30 mmol/L).

Prior to administering blood cardioplegia, the temperature of the solution usually is lowered with a heat-exchanging coil to between 12 and 4°C. The ratio of blood to crystalloid varies among centers, with the most common ratios being 8:1, 4:1, and 2:1. This, in turn, affects the final hematocrit of the blood cardioplegia infused. For example, if the hematocrit of the autologous blood obtained from the extracorporeal circuit is 30, these ratios would result in a blood cardioplegia with a hematocrit of approximately 27, 24, and 20, respectively.

The use of undiluted blood cardioplegia, or "miniplegia" (using a minimum amount of crystalloid additives), also has been reported to be effective. In an acute ischemia-reperfusion canine preparation, Velez and colleagues tested the hypothesis that an all-blood cardioplegia (66:1 blood:crystalloid ratio) would provide superior protection compared with a 4:1 blood cardioplegia delivered in a continuous retrograde fashion.[86] They found very little difference between the animal groups with respect to infarct size or postischemic recovery of function. This is consistent with the findings by Rousou and colleagues years earlier that it is the level of hypothermia that is important in blood cardioplegia, not necessarily the hematocrit.[87]

The rationales for using blood as a vehicle for hypothermic potassium-induced cardiac arrest include:

1. It can provide an oxygenated environment.
2. It can provide a method for intermittent reoxygenation of the heart during arrest.
3. It can limit hemodilution when large volumes of cardioplegia are used.
4. It has an excellent buffering capacity.
5. It has excellent osmotic properties.
6. The electrolyte composition and pH are physiologic.
7. It contains a number of endogenous antioxidants and free-radical scavengers.
8. It can be less complex than other solutions to prepare.

With respect to efficacy, there are numerous preclinical studies as well as nonrandomized and randomized clinical trials that demonstrate that cold blood cardioplegia is an effective way to provide excellent myocardial protection. While many of these same studies also have suggested that cold blood cardioplegia is superior to cold crystalloid cardioplegia, it is important to note that other investigators have shown crystalloid cardioplegia to be just as cardioprotective and cost-effective, if not more so, and that crystalloid cardioplegia more reliably ensures a quiet, bloodless operative field. Unfortunately, many of the clinical trials that have compared the efficacy of blood and crystalloid cardioplegia have been single-center studies, involved a limited number of patients, focused on a specific subset of patients, and/or omitted details regarding the clinical management of the patients.

Warm Blood Cardioplegia

The concept of using warm (normothermic) blood cardioplegia as a cardioprotective strategy in humans dates back to the 1980s. In 1982, Rosenkranz and colleagues reported that warm induction with normothermic blood cardioplegia, with a multidose cold blood cardioplegia maintenance of arrest, resulted in better recovery of function in canines than a similar protocol using cold blood induction.[88] In 1986, Teoh and colleagues reported an experimental study demonstrating that a terminal infusion of warm blood cardioplegia before removing the cross-clamp (a "hot shot") accelerated myocardial metabolic recovery.[89] This was followed by a report in 1991 by Lichtenstein and colleagues that normothermic blood cardioplegia in humans is an effective cardioprotective approach.[90] They compared the results of 121 consecutive patients who received antegrade normothermic blood cardioplegia during MR operations with a historical group of 133 patients who received antegrade hypothermic blood cardioplegia. The operative mortality in the warm cardioplegic group was 0.9% compared with 2.2% for the historical controls. At about the same time, Salerno and colleagues reported a series of 113 consecutive patients in which continuous warm blood cardioplegia was administered via the coronary sinus.[91] In this series, 96% had spontaneous return of rhythm on reperfusion, 7% needed transient IABP circulatory support, 6% had evidence of a perioperative MI, and 3% did not recover. A control cohort was not provided for comparison.

Despite these encouraging reports, there are still concerns with this approach. For example, for any given patient, it is not known just how long the warm heart can tolerate an ischemic event, which may occur when the infusion is

interrupted, flow rates are reduced owing to an obscured surgical field, or a maldistribution of the cardioplegic solution occurs. Another concern is the report by Martin and colleagues that suggested that the use of warm cardioplegia is associated with increased incidence of neurologic deficits.[92] In their prospective, randomized study (conducted on more than 1000 patients), the efficacies of warm blood cardioplegia and cold oxygenated crystalloid cardioplegia were analyzed. While operative mortalities were similar between the warm blood group and the cold oxygenated crystalloid cardioplegia cohort (1.0 versus 1.6%, respectively), the incidence of permanent neurologic deficits was threefold greater in the warm blood group (3.1 versus 1.0%). Thus, it appears that warm blood cardioplegia offers no distinct advantage over cold blood or cold crystalloid cardioplegia, and it may be less than ideal if its delivery is interrupted for any reason.

Tepid Blood Cardioplegia

Both cold blood (4 to 10°C) and warm blood cardioplegic solutions (37°C) have temperature-related advantages and disadvantages. As a consequence, a number of studies were performed in the 1990s to determine the optimal temperature. Hayashida and colleagues were one of the first groups to study specifically the efficacy of tepid blood (29°C) cardioplegia.[93] In this study, 72 patients undergoing CABG were randomized to receive cold (8°C) antegrade or retrograde, tepid (29°C) antegrade or retrograde, or warm (37°C) antegrade or retrograde blood cardioplegia. While protection was adequate for all three, the tepid antegrade cardioplegia was the most effective in reducing anaerobic lactate acid release during the arrest period. These authors reported similar findings when the tepid solution was delivered continuously retrograde and intermittently antegrade.[94] Since then, other studies also have demonstrated that tepid blood cardioplegia is safe and effective. The majority of these studies, however, have been single-center studies and/or conducted in a relatively small cohort of patients. Whether tepid cardioplegia confers better protection over other current methodologies remains to be determined.

Methods of Delivery

In addition to a variety of solutions and temperatures, there are also many different ways of administering the solutions (Fig. 15-3). As one might expect with so many options, the optimal delivery method of a cardioplegic solution also remains controversial. The various methods include intermittent antegrade, antegrade via the graft, continuous antegrade, continuous retrograde, intermittent retrograde, antegrade followed by retrograde, and simultaneous antegrade and retrograde infusions. While all methods generally are good, comparisons are difficult because there are numerous confounding factors such as (1) the composition of the solution, (2) the temperature of the solution, (3) the duration of the infusion, (4) the infusion pressure, (5) the type and complexity of the operation, (6) the need for surgical exposure, and (7) the expected versus actual cross-clamp time. One method that is being used frequently is the retrograde technique. This approach originated with a concept developed by Pratt in 1898, who suggested that oxygenated blood could be supplied to the ischemic heart via the coronary venous system.[95] Sixty years later, Lillehei and colleagues used retrograde coronary sinus perfusion to protect the heart during aortic valve surgery.[96] Today, it is an accepted method for delivering a cardioplegic solution and is used frequently as an adjunct to antegrade cardioplegia.

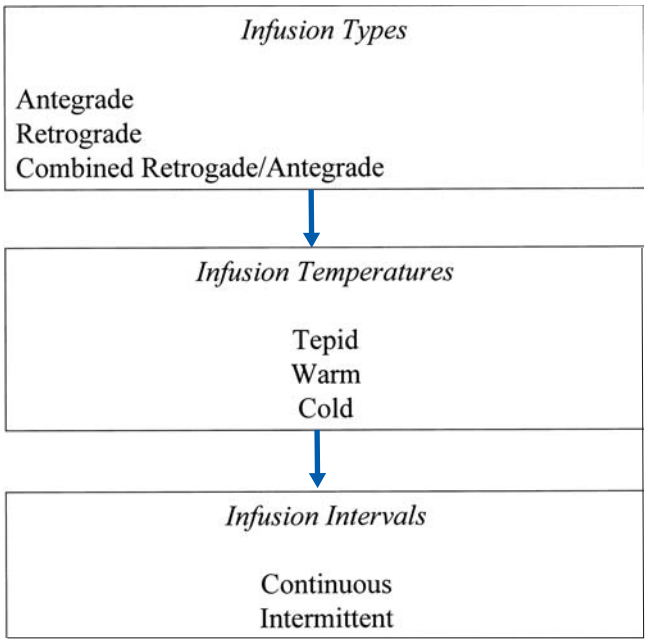

Figure 15-3. Methods and delivery of cardioplegic solutions.

In favor of the retrograde approach is the theoretical advantage of ensuring a more homogeneous distribution of the cardioplegic solution to regions of the heart that are poorly collateralized. It is also effective in (1) the setting of AR and valve surgery, (2) reducing the risk of embolization from saphenous vein grafts that could occur during antegrade perfusion during reoperative coronary artery surgery, and (3) delivering cardioplegia in a continuous manner.

Despite these advantages, retrograde cardioplegia is not without its limitations. Numerous experimental and clinical studies have shown that cardioplegia administered via the coronary sinus can result in a poor distribution of the solution to the right ventricle. This may be related to the variable venous anatomy of the heart. Because the anterior region of the right ventricle is not drained by the coronary sinus, and it is not uncommon for the heart to have a number of coronary sinus anomalies, these factors may result in the heterogeneous distribution of cardioplegic solutions and thus limit myocardial protection.

As a consequence, a technique for simultaneously delivering cardioplegia both antegrade and retrograde is

available. The feasibility and safety of this approach were reported in 1984 by Ihnken and colleagues.[97] In a more recent study, Cohen and colleagues used sonicated albumen and transesophageal echocardiography (TEE) intraoperatively to assess the effects of delivering a cardioplegic solution antegrade and retrograde simultaneously.[98] Compared with the antegrade or retrograde routes, the best and most consistent perfusion of the anterior left and right ventricles was achieved using the simultaneous technique. These investigators also reported that antegrade infusion resulted in superior perfusion of the left ventricle when compared with retrograde delivery alone and that right ventricular perfusion was inconsistent with both antegrade and retrograde delivery. Thus, it remains to be determined in which setting the simultaneous use of both methods is most appropriate.

With respect to intermittent cardioplegic infusions versus continuous infusions, the major advantage of the former is the ability to achieve and sustain a dry, quiescent operative field. While a continuous infusion, especially if it is oxygenated, has the theoretical advantage of minimizing ischemia, from a practical standpoint, it is unlikely that this can be achieved reliably. There is also the theoretical potential for an excessive infusion of cardioplegic solution.

PROTECTION STRATEGIES UNDER INVESTIGATION

Ischemic Preconditioning

Ischemic preconditioning is an adaptive biologic phenomenon in which the heart (and numerous other tissues) becomes more tolerant to a period of prolonged ischemia if first exposed to a prior episode of brief ischemia and reperfusion. This adaptation to ischemia was first described by Murray and colleagues and is referred to as *classic* or *early-phase preconditioning.*[99] This increased tolerance to ischemia is associated with a reduction in infarct size, apoptosis, and reperfusion-associated arrhythmias.[100–104] It has been demonstrated in every animal species studied and appears to persist as long as 1 to 2 hours after the ischemic preconditioning stimulus.[105,106] It becomes ineffective when the sustained ischemic insult exceeds 3 hours.[107] This suggests that the protection is conferred only when prolonged ischemia is followed by timely reperfusion.[108]

Subsequent studies have revealed that this endogenous defense mechanism can manifest itself in multiple ways. After the acute phase of preconditioning disappears, a second phase of protection appears 24 hours later and is sustained for up to 72 hours. This has been referred to as the *second window of protection, late-phase preconditioning,* or *delayed preconditioning.* Unlike classic preconditioning, which protects only against infarction, the late phase protects against both infarction and myocardial stunning.[101,109] Concurrent with these reports is an additional observation that ischemia induced in other organs could precondition the heart, a phenomenon referred to as *remote* or *interorgan preconditioning.*[110] Remote myocardial preconditioning, which has been reported by multiple investigators in various species, can be induced by brief occlusions of the renal and mesenteric arteries, as well as by skeletal muscle ischemia.[111–114] More recent studies indicate that multiple, brief coronary occlusions during the initial minutes of reperfusion following prolonged ischemia can reduce myocardial infarct size to a similar extent as ischemic preconditioning.[115,116] This adaptive response is referred to as *ischemic postconditioning.*

These observations have resulted in major investigative efforts to elucidate the intracellular mechanism(s) that underlie the heart's endogenous defenses against ischemia-reperfusion injury. The assumption is that a better understanding of these mechanism(s) could lead to the development of potent new therapeutic modalities that are more effective in treating or preventing the deleterious consequences of ischemia-reperfusion injury. One of the earliest hypotheses was that stimulation of cardiomyocyte adenosine A_1 and/or A_3 receptors was the primary mediator of acute ischemic preconditioning.[106,117,118] Subsequent studies have shown, however, that in addition to adenosine, there are multiple guanine nucleotide-binding (G) protein–coupled receptors that, once activated, can mimic the infarct-reducing effect of ischemic preconditioning (e.g., bradykinin, endothelin, α_1-adrenergic, muscarinic, angiotensin II, and delta-opioid receptors)[103,119] (Fig. 15-4). Transient infusion of exogenous agents that mimic ischemic preconditioning is referred to as *pharmacologic preconditioning.* Exactly which of these receptors is the most important in mediating endogenous preconditioning is unknown because there appear to be species differences and redundant pathways. Regardless, it is now thought that these triggers of ischemic preconditioning result in alterations in certain enzymes, such as tyrosine kinases, protein kinase C (PKC) isoforms, and mitogen-activated protein kinases [p38 and extracellular signal regulated kinase (ERK)] that, in turn, confer protection against irreversible injury prior to the onset of prolonged ischemia.[103,117–119] While the actual effector(s) of the protection has(have) yet to be determined, significant evidence has accumulated indicating that the cardiomyocyte mitochondria appear both to play a primary role in triggering this protection and to be a key target of preconditioning-induced protection.[103,117–121]

While early-phase preconditioning shares many of the same signaling mechanisms with late-phase preconditioning, the most obvious difference between the two is the apparent requirement for protein synthesis in the latter. Both late-phase ischemic and pharmacologic preconditioning have been shown to be associated with the upregulation of various proteins, including, but not limited to, heat-shock proteins, inducible NOS (iNOS), cyclooxygenase 2, and manganese superoxide dismutase.[110,124] There are, however, conflicting reports on what specific proteins are upregulated during late-phase preconditioning, which may be due to species differences, as well as stimulus-specific responses.[120–123]

The results of remote preconditioning studies indicate that this form of cardioprotection can be induced by

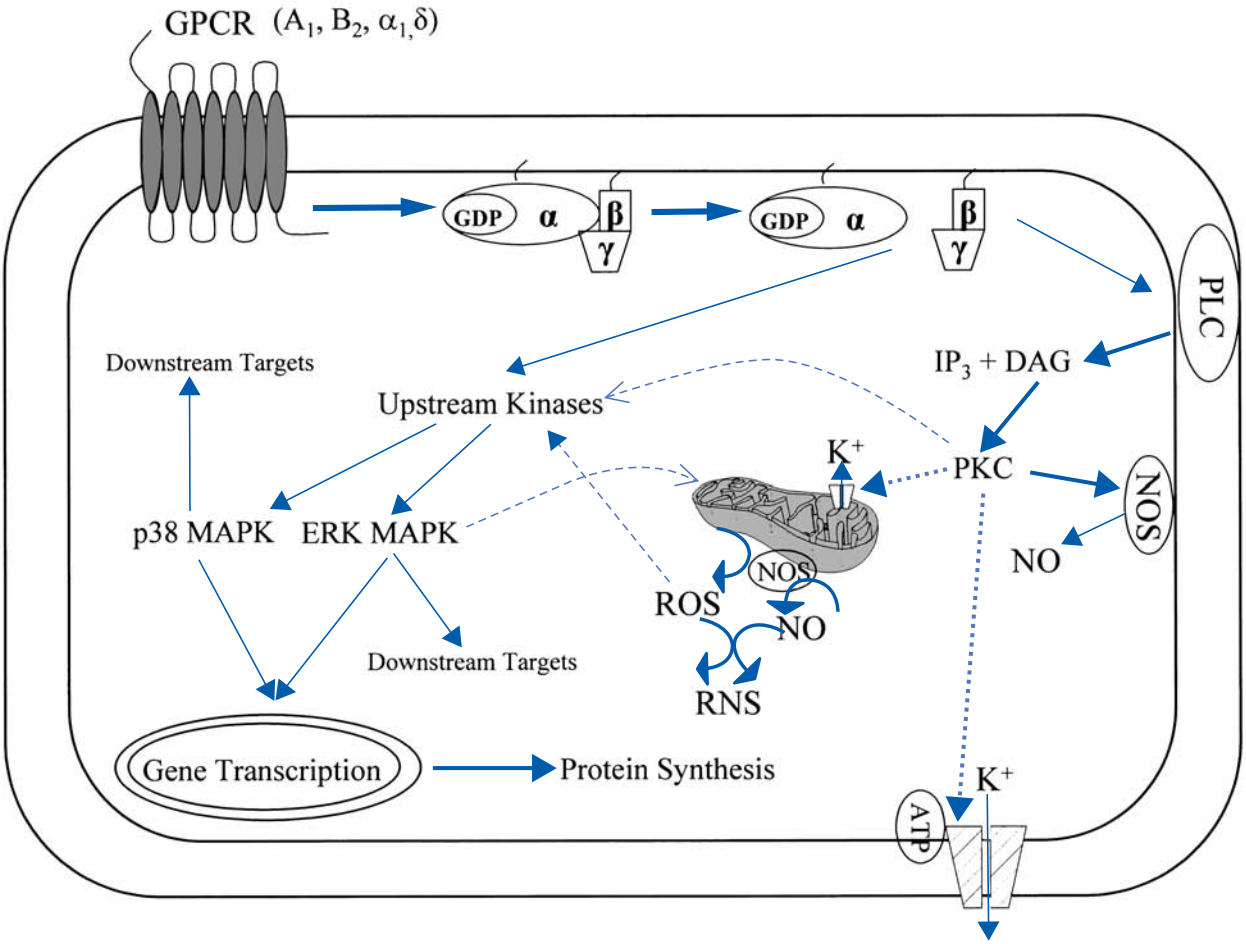

Figure 15-4. Proposed mechanisms of acute- and late-phase preconditioning. The stimulation of multiple G protein–coupled receptors (GPCRs), such adenosine A_1, bradykinin, α-adrenergic, and δ-opioid receptors, by endogenous ligands or by exogenous receptor agonists results in the activation of one or more G proteins. These initial events initiate the activation of several intracellular signaling pathways. Nitric oxide (NO) donors and reactive oxygen species (ROS) also can induce preconditioning. Significant evidence implicates the activation of one or more protein kinase C (PKC) isoforms and the mitogen-activated protein kinases (MAPKs) p38 and ERK in both acute and delayed preconditioning, although several other mechanisms may be involved. The complexities of these proposed signaling pathways are compounded by the subcellular compartmentation of these kinases and their downstream targets, as well as signaling crosstalk in either a stimulatory or an inhibitory manner or both. The identities of all the distal mediators and the effectors of protection have not been definitively established, but there is strong evidence that sarcolemmal and/or mitochondrial ATP-dependent potassium (K_{ATP}) channel opening may initiate both acute and delayed protection. Constitutive (or endothelial) nitric oxide synthase has been shown to be a downstream target of PKC and ERK, and there is significant evidence that NO plays a role in myocardial protection. There is also accumulating evidence that one or more nitric oxide synthase (NOS) isoforms are expressed in mitochondria. Although PKC, MAPKs, mitochondria, ROS, and NO appear to play primary roles in preconditioning, the definitive mechanisms have yet to be identified unambiguously. For example, it is well known that ROS are potent stimuli for MAPK activation, but it also has been hypothesized that MAPK activation induces mitochondrial ROS formation. The major difference between acute and delayed preconditioning is that de novo protein synthesis is required in the latter. The upregulation of multiple proteins has been implicated in delayed preconditioning, including, but not limited to, heat-shock proteins (HSPs), inducible iNOS, manganese-dependent superoxide dismutase (Mn-SOD), and cyclooxygenase 2 (COX-2). The upregulation of specific proteins may depend on the preconditioning stimulus and also may be species-dependent.

humoral factors and/or neurogenic mechanisms. Adenosine has been implicated as a mediator of remote myocardial preconditioning, an effect that was inhibited by the ganglionic blocker hexamethonium.[106] Given adenosine's rapid metabolism in the vascular endothelium and by erythrocytes, it is unlikely that this effect would be via a humoral mechanism. In fact, the results of a recent study indicate that preconditioning induced by intravenous adenosine was not associated with an increase in interstitial adenosine levels but was blocked by hexamethonium.[124] Alternatively, calcitonin

gene-related peptide (CGRP) has been implicated in remote preconditioning via a humoral, but not a neurogenic, mechanism.[125]

Ischemic postconditioning has been described only very recently, and thus there have been fewer studies examining potential mechanisms. Although there is evidence that adenosine A_{2a} receptors may play a role in mediating ischemic postconditioning,[126] it is unknown whether this is a direct effect on cardiomyocytes. Additional studies indicate that postconditioning may be mediated by some of the same protein kinase pathways that are involved in preconditioning.[127–130]

There is increasing evidence that ischemic preconditioning and postconditioning may occur in the human heart, although some of this evidence remains circumstantial. A number of investigators have reported that patients experiencing angina prior to an MI have better in-hospital prognoses and a reduced incidence of cardiogenic shock, fewer and less severe episodes of congestive heart failure, and smaller infarcts as assessed by cardiac enzyme release.[131–134] There are also follow-up studies that suggest patients who have had angina prior to an infarct have better long-term survival rates.[135–137] There are also a myriad of reports that patients who undergo percutaneous coronary interventions (PCIs) have an enhanced tolerance to ischemia after the first balloon inflation, provided that the first balloon inflation exceeds 60 to 90 seconds.[105] Chest pain severity, regional wall motion abnormalities, ST-segment elevation, QT dispersion, lactate production, and CK-MB release all have been reported to be attenuated in this setting as well.[138–143]

In patients undergoing PCIs, a preconditioning-like effect also has been mimicked by the administration of a variety of pharmacologic agents that are known to induce preconditioning in animal studies. For example, the administration of adenosine prior to PCI has been reported to attenuate myocardial ischemic indices during the first balloon inflation.[144,145] Administration of other agents, such as bradykinin and nicorandil (a K_{ATP} channel opener), also has been reported to produce similar effects.[146–148] Conversely, the administration of aminophylline (a nonselective adenosine receptor antagonist), glibenclamide (a K_{ATP} channel blocker), or naloxone reportedly abolishes the effects of ischemic preconditioning during PCI.[149–151]

Additional studies provide evidence of delayed pharmacologic preconditioning and postconditioning in the clinical setting. Leesar and colleagues reported that a 4-hour intravenous infusion of nitroglycerin (an NO donor) 24 hours prior to PCI decreased ST-segment changes and chest pain during the first balloon occlusion compared with patients treated with saline vehicle.[152] A subsequent report by this same group indicated that delayed preconditioning with nitroglycerin decreased exercise-induced ST-segment changes and improved exercise tolerance.[153] Two recent studies provided the first clinical evidence of ischemic postconditioning.[154,155] Patients receiving brief balloon inflations/deflations in the initial minutes of reperfusion during PCI exhibited reduced ST-segment changes and total creatine kinase release compared with control subjects.

Thus, there are many observational studies that support the hypothesis that myocardial protection conferred by ischemic preconditioning and its possible mediators in animal studies is translatable to humans. It is important to note, however, that classic or early ischemic preconditioning observed in animals is associated with a reduction in infarct size, not stunning, and that many of the clinical studies are either retrospective in nature or have used surrogate markers of injury as end points.

With respect to cardiac surgery, one of the first studies indicating that preconditioning may exist in humans was conducted by Yellon and colleagues in 1993.[156] In this study, patients undergoing cardiac surgery were subjected to a protocol that involved two cycles of 3 minutes of global ischemia. Cross-clamping the aorta intermittently and pacing the heart at 90 beats per minute were used to induce ischemia. This was followed by 2 minutes of reperfusion before a 10-minute period of global ischemia and ventricular fibrillation. Myocardial biopsies were obtained during a 10-minute period of global ischemia, and ATP tissue content was measured. The results showed that the ATP levels in the biopsies obtained from patients subjected to the preconditioning-like protocol were higher. However, since ATP content is not a marker of necrosis, a follow-up study was performed, and troponin T serum levels were used. In this study, the investigators reported that the release of this marker of necrosis also was less in patients subjected to the preconditioning protocol.[157]

It is unknown whether the phenomenon of ischemic preconditioning plays any role in conferring protection when using the intermittent cross-clamp technique. Teoh and colleagues, however, reported that ischemic preconditioning might confer additional myocardial protection beyond that provided by intermittent cross-clamp fibrillation in patients undergoing CABG.[158] The fact that other human studies have not shown additional protection when ischemic preconditioning was added to a myocardial protection protocol makes this less likely.[159,160] For the immediate future, the most promising strategy for developing new methods to protect the heart against ischemia-reperfusion injury lies with elucidation of the intracellular events underlying the phenomenon of late-phase ischemic preconditioning (see Fig. 15-4).

Adenosine

There is considerable experimental evidence that the preischemic administration of the nucleoside adenosine retards the rate of ischemia-induced ATP depletion, prolongs the time to onset of ischemic contracture, attenuates myocardial stunning, enhances postischemic myocardial energetics, and reduces infarct size.[161] As mentioned earlier, there is also evidence that adenosine may play a role in mediating the infarct size–limiting effects of ischemic preconditioning.[103,115,116] A transient infusion of adenosine or certain adenosine receptor

agonists prior to ischemia is associated with infarct size reduction similar to that of ischemic preconditioning.[103,161] There are, however, conflicting reports regarding the ability of adenosine receptor antagonists to block ischemic preconditioning.[115,162–165] When analyzing these studies, it is important to recognize a small but important difference between adenosine preconditioning and adenosine pretreatment. The former involves a brief infusion of adenosine that is terminated prior to the onset of ischemia, whereas the latter involves the continuous infusion of adenosine until the onset of ischemia. The significance of this difference lies with the observation that adenosine pretreatment, not adenosine preconditioning, attenuates myocardial stunning.[166,167] Myocardial stunning is the most common form of injury in patients after heart surgery. The beneficial effects of adenosine infusions prior to ischemia appear to be due to the direct effects of adenosine on the cardiac myocyte because (1) adenosine must be infused at a dose that reaches the interstitial fluid (ISF) space that surrounds the cardiac myocyte and (2) adenosine reduction of ischemic and hypoxic injury can be demonstrated in isolated myocyte preparations.[168–170]

Although the cardioprotective effects of adenosine have been recognized for some time, there are still many questions regarding its mechanism of action. Genetic, biochemical, and pharmacologic studies indicate that there are at least four distinct sarcolemmal adenosine receptor subtypes, designated A_1, A_{2a}, A_{2b}, and A_3, that couple to a variety of guanine nucleotide-binding (G) proteins (G_o, $G_{i\alpha 2}$, $G_{i\alpha 3}$, G_q, and G_s) depending on the receptor subtype and tissue studied. Currently, there is definitive evidence that two, and possibly three, of these receptors are expressed in the adult heart. Radioligand binding studies have verified the presence of A_1 and A_{2a} adenosine receptors in mammalian myocardium, and numerous studies since have reported the physiologic roles of these receptors.[171] More recent studies, using both pharmacologic approaches and receptor knockout mice, suggest that adenosine A_{2b} receptors may be expressed in the coronary vasculature.[172] Although there are some reports of A_3 receptor mRNA expression in cardiac tissue, presently there is no definitive evidence for the expression of this receptor in the normal mammalian heart.[173,174]

With respect to clinical studies, Lee and colleagues pretreated seven patients undergoing CABG with adenosine and compared their postoperative course with that of a similar group of untreated patients.[175] Adenosine was infused incrementally before the initiation of CPB at a rate of 50 μg/kg per minute every minute until a dose of 350 μg/kg per minute was reached. The total duration of the adenosine infusion lasted for 10 minutes, or until the patient developed systemic arterial pressures less than 70 mm Hg, at which time the infusion was discontinued. Five minutes after completion of the adenosine or the saline control infusion, patients were placed on CPB and underwent CABG. Cold blood cardioplegia was used to facilitate the arrest. The investigators reported that adenosine pretreatment was associated with improved postoperative myocardial function. Major limitations of this study were the small number of patients studied and the limited number of parameters used to assess ventricular function. In contrast, Fremes and colleagues reported the results of an open-label, nonrandomized adenosine study in which no effect was observed.[176] In this study, the patients also underwent CABG. Antegrade warm blood cardioplegia was used, with adenosine added to the initial 1-L dose and the final 500-mL dose of cardioplegia. The adenosine concentrations studied were 15, 20, and 25 μmol/L. These investigators found that adenosine could be added safely as a supplement to cardioplegic solutions, but the agent had no effect on myocardial function at the doses studied.

A similar lack of efficacy in humans was reported by Cohen and colleagues in a phase II double-blind, placebo-controlled trial performed in patients also undergoing CABG.[177] Patients were treated with placebo (saline) or warm blood cardioplegia supplemented with 15, 50, or 100 μM adenosine. These investigators also reported that the adenosine additive had no effect on survival, on the incidence of MI (as determined by CK-MB levels), or on the incidence of low cardiac output syndrome. A major limitation of this study was the use of low concentrations of adenosine in the setting of warm blood cardioplegia. The nucleoside is metabolized rapidly to inosine and hypoxanthine, and the half-life in blood is measured in seconds.

In contrast, Mentzer and colleagues reported a beneficial effect in an open-label, single-center study in which the safety, tolerance, and efficacy of high doses of adenosine were assessed.[178] As in the previous studies, adenosine was added to cold blood cardioplegia in patients undergoing CABG. In this study, 61 patients were randomized to receive standard cold blood cardioplegia or cold blood cardioplegia containing one of five adenosine doses (100 μM, 500 μM, 1 mM, 2 mM, or 2 mM with a preischemic infusion of 140 μg/kg per minute). Invasive and noninvasive studies of myocardial function were obtained at 1, 2, 4, 8, 16, and 24 hours postbypass. This included the recording of inotropic utilization rates for the postoperative treatment of low cardiac output. Blood samples were collected before and after the first, second, and last dose of cardioplegia, as well as at 1 and 24 hours after cessation of CPB, for the measurement of nucleoside levels. These investigators found that high-dose adenosine treatment was associated with a 249-fold increase in the plasma adenosine concentration and a 69-fold increase in the combined levels of adenosine and its degradation products inosine and hypoxanthine. The high-dose adenosine and associated high plasma levels of adenosine were associated with a reduction in postbypass inotropic drug utilization and improved regional wall motion and global function measured by transthoracic echocardiography (TTE).

Using a similar protocol, Mentzer and colleagues examined the effects of high-dose adenosine treatment in 253 patients randomized to one of three treatment arms.[179] This was a double-blind, placebo-controlled multicenter

trial. The three cohorts consisted of patients who were administered intraoperative cold blood cardioplegia, those administered cold blood cardioplegia containing 500 μM adenosine, and those receiving cold blood cardioplegia containing 2 mM adenosine. Patients receiving the adenosine cardioplegia also were given an infusion of adenosine (200 μg/kg per minute) 10 minutes before and 15 minutes after removal of the aortic cross-clamp. Invasive and noninvasive measurements of ventricular performance were obtained before, during, and after surgery. The results of this study revealed a trend toward a decrease in high-dose inotropic agent utilization rates and a lower incidence of MI. A composite outcome analysis showed that patients who received the high-dose adenosine were less likely to experience one of five adverse events: high-dose dopamine use, epinephrine use, insertion of an IABP, MI, or death. A major limitation of this study was the failure to demonstrate a reduction in dopamine use or overall inotropic use, the two primary end points of the study. Another factor was the relatively low adverse event rates of MI and death, namely, 5.1 and 3.6%.

In summary, there is preclinical and clinical evidence that adenosine is a cardioprotective agent. Its clinical use, however, is somewhat limited because large doses are associated with marked hypotension. Although this can be managed easily while the patient is on CPB, it would be preferable to use a more selective A_1 receptor agonist that would confer protection without peripheral vasodilation. The administration of such an agent prior to surgery (much in the same way that late-phase preconditioning has a salutary effect in limiting myocardial stunning, apoptosis, and infarction 24 hours later) could result in a reduction in the current rates of postoperative stunning and infarction and represent a significant advance in the field of myocardial protection.

Sodium-Hydrogen Exchange Inhibition

The sodium-hydrogen exchangers (NHEs) are a family of membrane proteins that are involved in the transport of hydrogen ions in exchange for sodium ions. The driving forces behind the exchange are the transmembrane Na^+ and Ca^{2+} gradients and the membrane potential.[224,225] The gradient is regulated by the intracellular pH through interaction of H^+ with a sensor site on the exchanger protein (Fig. 15-5). To date, nine NHE isoforms have been identified and are designated as NHE-1 through NHE-9.[180–183] While the exact role the exchanger plays in the normal excitation-contraction coupling process has yet to be determined, there is increasing evidence that these proteins perform an important role in many pathophysiologic conditions. They have been implicated in the etiology of arrhythmias, stunning, apoptosis, necrosis associated with acute myocardial ischemia-reperfusion injury, and postinfarction ventricular remodeling and heart failure.[184,185]

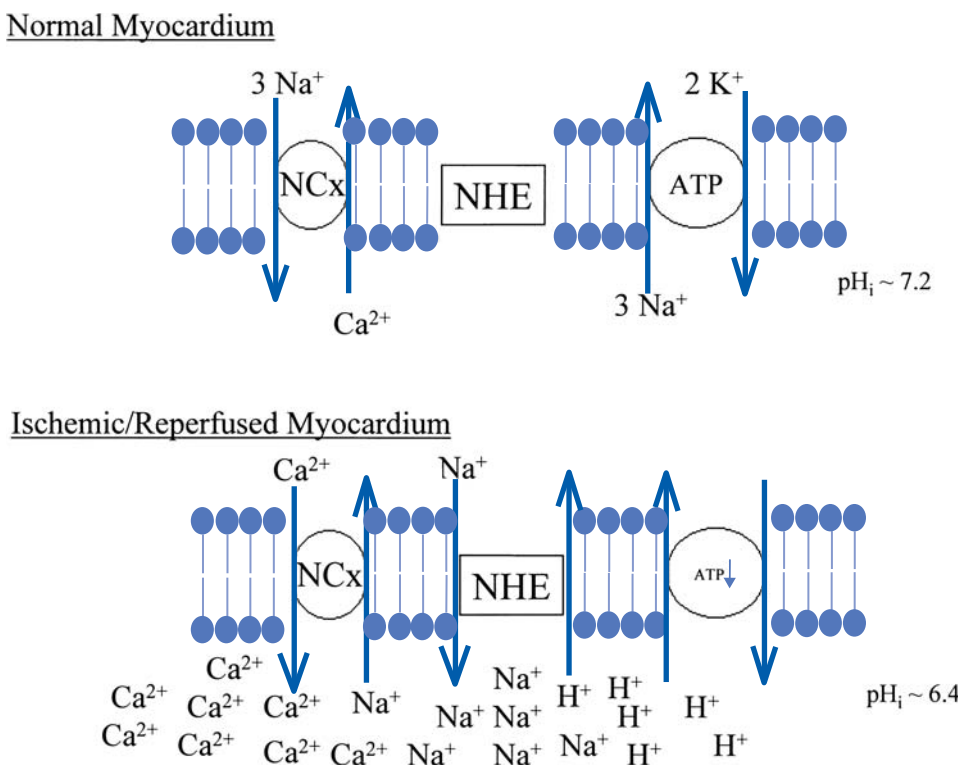

Figure 15-5. Sodium-hydrogen exchangers in the normal and ischemic myocardium.

One of the primary mechanisms of injury that all these conditions have in common is the deleterious effect of an excess accumulation of intracellular calcium.[184,185] Normally, sodium-hydrogen (Na^+ -H^+) exchange plays an important role in regulating cardiac myocyte physiology. The influx of extracellular Na^+ via its concentration gradient is coupled with the efflux of H^+, helping to maintain the intracellular pH (see Fig. 15-5). The Na^+ -Ca^{2+} exchanger uses the normal Na^+ gradient to extrude Ca^{2+} in order to maintain normal intracellular Ca^{2+} homeostasis. However, during ischemia, intracellular Na^+ accumulates owing to decreased activity of Na^+, K^+-ATPase and increased production of H^+ owing to anaerobic glycolysis. During the initial phase of reperfusion, the Na^+ -H^+ exchanger is accelerated in an attempt to restore intracellular pH. This results in even more Na^+ and ultimately more Ca^{2+} accumulating intracellularly. As a consequence of increased intracellular sodium, the Na^+ -Ca^{2+} exchanger operates in the reverse direction, resulting in a marked increase in the intracellular Ca^{2+} concentration (Ca^{2+} overload). This Ca^{2+} overload can result in the activation of various enzyme systems and signaling pathways that over time can lead to cell contracture, membrane rupture, gap junction dysfunction, and cell death.[186,187]

Accordingly, the EXPEDITION study was conducted to address the efficacy and safety of NHE inhibition by cariporide in the prevention of death or MI in patients undergoing CABG. High-risk CABG patients ($n = 5770$) were randomized to receive either intravenous cariporide (180 mg/h preoperative loading dose and then 40 mg/h over 24 hours and 20 mg/h over the subsequent 24 hours) or placebo. The primary composite end point of death or MI was assessed at 5 days, and patients were followed for up to 6 months. The results of this study indicated that there was an 18.3% relative risk reduction in the incidence of death or MI at 5 days ($p = .0002$). At day 30 and month 6, the relative risk reduction of death or MI was 16.1% ($p = .0009$) and 15.7% ($p = .0006$), respectively. When analyzed separately, the relative risk reduction in the incidence of MI alone at 5 days was 23.8% ($p = .000005$) and at month 6 was 25.6% ($p = .000001$). The mortality rate, however, increased at 5 days from 1.5% in the placebo group to 2.2% in the group with cariporide. This was associated with an overall increase in the incidence of cerebrovascular events, specifically 86 events (2.7%) in the placebo group versus 146 (5.2%) in the cariporide group. Thus, while cariporide treatment was effective in reducing the incidence of nonfatal MI, its efficacy was associated with toxicity, and the overall assessment of benefits and risks associated with cariporide indicated that the imbalances in the safety profile outweighed the reduction in the observed MI rate. Thus, it is unlikely that cariporide will be used clinically. The importance of the study should not be underestimated, however, because (1) EXPEDITION demonstrated that myocardial necrosis after CABG is higher than previously appreciated, and (2) these findings suggest that NHE-1 inhibition holds promise as a new class of drugs that could reduce myocardial injury associated with ischemia-reperfusion injury significantly.

Nitric Oxide

There is increasing evidence that the signaling molecule nitric oxide (NO) plays an important role in modulating the heart's tolerance to ischemia. However, the combination of the short half-life of NO, the multiple redox states in which it can exist, the subcellular compartmentalization of NOS isoforms, and the multiple targets of its actions has hindered determination of the specific role this molecule plays in modulating ischemia-reperfusion injury.[188–190] This explains, in part, why NO and related reactive nitrogen species have been reported to both exacerbate injury and exert a cardioprotective effect.[188, 191] For the most part, however, studies performed using in vivo preparations indicate that the administration of NO donors reduces infarct size.[191,192] There are also reports that the infusion of NOS inhibitors during reperfusion exacerbates ischemia-reperfusion injury.[191,192] These reports are consistent with evidence that NO modulates coronary blood flow and that the molecule can reduce neutrophil adherence to endothelium and inhibit platelet aggregation. There is also evidence that NO produced during reperfusion may scavenge the oxygen free-radical superoxide (O_2^-), an effect observed in oxidant-stressed cells exposed to constant low levels (1 to 2 μM) of NO.[193,194]

With respect to clinical studies, there is only a modest amount of evidence that the NO mechanism can be manipulated to confer myocardial protection in humans. Leesar and colleagues reported that the infusion of nitroglycerin (an NO donor) 24 hours prior to angioplasty mimicked the protection associated with the first balloon inflation in the control group in terms of ST-segment shifts, regional wall motion abnormalities, and chest pain scores.[155] Zhang and Galinanes studied the effects of arginine (a precursor to NO) on human myocardial specimens obtained from right atrial appendages of patients undergoing elective CABG.[195] The tissues were subjected to 120 minutes of simulated ischemia followed by 120 minutes of reoxygenation. Ischemic injury was assessed by measuring the leakage of lactate dehydrogenase (LDH) into the incubation medium and the capacity of the tissue to reduce MTT [3-(4-dimethylthiazol-yl)-2,5-diphenyltetrazolium bromide] to a formazan product. In this study, L-arginine (a precursor of NO) decreased LDH leakage but had no effect on MTT reduction or oxygen consumption. However, the effect of arginine was not reversed by L-NAME (an NO synthase inhibitor), nor was it mimicked by *S*-nitroso-*N*-acetylpenicillamine (an NO donor). These data suggested that L-arginine was effective but provided only a modest degree of protection against simulated ischemia-reperfusion injury in human myocardial atria tissue.

These studies are limited, however, because the demonstration of efficacy depended on the measurement of surrogate markers of injury and because sample sizes were small. Additional preclinical studies and clinical trials are needed to demonstrate whether NO plays an important role

in protecting the ischemic heart. As noted by Feng and colleagues, the potential cytoprotective role of iNOS-derived NO needs to be reconciled with the known detrimental actions associated with iNOS in the setting of septic shock, organ rejection, inflammation, autoimmune diseases, and ischemic brain injury.[196]

MYOCARDIAL PROTECTION DURING BEATING-HEART SURGERY

As many as 10 to 15% of the patients in the United States who undergo surgical MR have the operation performed on the beating heart, i.e., off-pump coronary artery bypass (OPCAB) surgery. The acceptance of this technique is due, in part, to the development and availability of better shunt appliances and mechanical stabilization devices, as well as the demonstration of satisfactory outcomes.[197,198] Overall, the incidence of death, perioperative MI, renal failure, and respiratory failure appears to be similar among patients undergoing either OPCAB or on-pump surgery.[1,199] If sensitive myocardial marker proteins are used to detect myocardial necrosis, it is possible that cell necrosis may be less in OPCAB patients. The fact that any necrosis occurs, however, suggests that OPCAB patients may be susceptible to ischemia-reperfusion injury. For the most part, the indications for OPCAB remain controversial, and long-term outcomes have yet to be determined. Likewise, there is a paucity of data regarding the extent to which the myocardium is reversibly or irreversibly damaged after OPCAB. This is due, in part, to the fact that the primary focus among beating-heart advocates has been the demonstration of feasibility, safety, and cost-effectiveness.

CONCLUSION

While considerable progress has been made in the field of myocardial protection, the ideal solution, technique, or delivery method has yet to be identified. This is due, in part, to our increasing awareness of the complexity of ischemia-reperfusion injury and recognition that the definition of ideal protection is no longer limited to the time that the patient is in the operating room. As long as the incidence of myocardial stunning ranges from 20 to 80%, postischemic ventricular dysfunction from 3 to 7%, severe dysfunction in high-risk patients from 15 to 20%, and non-Q-wave and Q-wave infarction nearly 20%, there is clearly a need to develop new therapeutic strategies to protect the heart during cardiac surgery. This need is even greater when one considers that long-term survival after heart operations is determined, in part, by adequate myocardial protection during the operation itself.

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CHAPTER 16

Postoperative Care of Cardiac Surgery Patients

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THE EVOLUTION OF CARE

Mortality and morbidity in cardiac surgery have continued to decline despite increases in patient age, comorbid conditions, and procedure complexity. Much of this success can be attributed to advances in critical care. This chapter will outline strategies and principles of modern postoperative care.

CARDIOVASCULAR CARE

Hemodynamic Assessment

Assessment and optimization of hemodynamics generally are the principal focuses of care following cardiac surgery. Appropriate management requires knowledge of preoperative cardiac function and an appreciation of the impact of intraoperative events. The goal of postoperative hemodynamic management is the maintenance of adequate oxygen delivery to vital tissues in a way that avoids unnecessary demands on a heart recovering from the stress of cardiopulmonary bypass, ischemia, and surgery.

A basic initial hemodynamic assessment includes a review of current medications, heart rate and rhythm, mean arterial pressure, central venous pressure, and electrocardiogram (ECG) to exclude ischemia and conduction abnormalities. The presence of a pulmonary artery catheter enables the measurement of pulmonary artery pressures, left-sided filling pressures [e.g., pulmonary capillary wedge pressure (PCWP)], and mixed venous oxygen saturation ($M\dot{V}O_2$). Cardiac output, as well as pulmonary and systemic vascular resistances, also can be calculated when a pulmonary artery catheter is present. Cardiac output is determined using thermodilution or the Fick equation. Cardiac output (CO), blood pressure (BP), and systemic vascular resistance (SVR) are related to each other using Ohm's law (Table 16-1). Reasonable minimum goals for most patients include an $M\dot{V}O_2$ of about 60%, a mean arterial pressure (MAP) of more than 65 mm Hg, and a cardiac index (CI) of more than 2 L/m^2 per minute. Goals should be individualized. Patients with a history of hypertension or significant peripheral vascular disease probably will benefit from higher blood pressure; patients who are bleeding or who have suture lines in fragile tissue are best served with tighter control. Strategies designed to produce a supranormal cardiac index or $M\dot{V}O_2$ have failed to demostrate a survival advantage.[1]

Failure to achieve adequate cardiac output and end-organ oxygen delivery can be caused by many, often codependent factors. These include volume status (preload), peripheral vascular tone (afterload), cardiac pump function, heart rate and rhythm, and blood oxygen-carrying capacity.

Volume status is determined readily by invasive monitoring. Central venous pressure (CVP), unless it is very low, is an unreliable indicator of left ventricular end-diastolic volume (LVEDV). (An elevated CVP can be seen in volume overload, right-sided heart failure, tricuspid and mitral regurgitation, pulmonary hypertension, tamponade, tension pneumothorax, and pulmonary embolism.) Plumonary artery diastolic pressure correlates with left-sided filling pressures when pulmonary vascular resistance (PVR) is normal (low). PCWP (or left atrial pressure if this is being measured directly) provides the most accurate assessment of left-sided filling pressures, and its correlation with pulmonary artery diastolic pressure should be noted to enable a more continuous assessment of left-sided pressures. Determination of optimal filling pressures generally is empirical; a wedge pressure of 15 mm Hg generally is adequate, but many patients require significantly higher pressures. Most patients arrive from the operating room with a significant net fluid gain, but much of this excess volume is extravascular owing to third space and pleural cavity accumulation. Vasoplegia often is created by a systemic inflammatory response to cardiopulmonary bypass (CPB), and it is common to have a

(*text continues on p. 04*)

Table 16–1.

Common Intensive Care Values and Formulas

Early postoperative hemodynamic parameters	Expected values
Mean arterial pressure (**MAP**)	60–90 mm/Hg
Systolic blood pressure (**sBP**)	90–140 mm/Hg
Right arterial pressure (**RAP**)	5–15 mm/Hg
Cardiac index (**CI**)	2.2–4.4 L/min/m^2
Pulmonary artery wedge pressure (**PAWP**)	10–15 mm/Hg
Systemic vascular resistance (**SVR**)	1400–2800 dyn-s/cm^5
Common hemodynamic formulas	**Normal values**
CO = SV × HR **CI** = CO ÷ BSA CO = cardiac output; HR = heart rate; SV = stroke volume; BSA = body surface area	4–8 L/min 2.2–4.0 L/min/m^2
$\textbf{SV} = \frac{\text{CO (L/min)} \times 1000 \text{ (mL/L)}}{\text{HR}}$	60–100 mL/beat (l mL/kg/beat)
SVI = SV ÷ BSA SVI = stroke volume index	33–47 mL/beat/m^2
$\textbf{MAP} = \text{DP} + \frac{(\text{SP} - \text{DP})}{3}$	70–100 mm/Hg
$\textbf{SVR} = \frac{\text{MAP} - \text{CVP}}{\text{CO}} \times 80$ CVP = central venous pressure; **Ohm's law**: voltage (***V***) = Current (***I***) × resistance (***R***); resistance is directly proportional to viscosity (hematocrit) and inersely proportional to the radius to the fourth power.	800–1200 dyn-s/cm^5
$\textbf{PVR} = \frac{\text{PAP} - \text{PCWP}}{\text{CO}} \times 80$ PVR = pulmonary vascular resistance; PAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure	50–250 dyn-s/cm^5
LVSWI = SVI × (MAP − PCWP) × 0.0136 LVSWI = left ventricular stroke work index	45–75 mg-M/beat/m^2
O_2 delivery = CO (Hb × %sat)(1.39) + (Pa_{O_2})(0.0031) 1.39 is milliliters of oxygen transported per gram of serum hemoglobin (Hb); 0.0032 is solubility coefficient of oxygen dissolved in solution (mL/torr of Pa_{O_2})	60–80%
AV O_2 difference = (1.34)(Hb) × (Sa_{O_2} − Sv_{O_2}) $\textbf{Fick cardiac output} = \frac{\text{estimated } O_2 \text{ comsumption}}{\text{AV } O_2 \text{ difference}}$ AV = arteriovenous oxygen difference; oxygen consumption is measured from a nomogram based on age, sex, height, height; Hb = serum hemologlobin (g/dL); Sa_{O_2} = arterial oxygen saturation (%) in arterial blood; Sv_{O_2} = mixed venous oxygen saturation (%) from the pulmonary artery in the absence of a shunt or calculated $M\dot{V}_{O_2}$ = (3 × SVC saturation + IVC saturation) ÷ 4, if a left-right shunt is present); 1.34 = mL O_2 per gram of Hb; 10 dL/L)	Normal Pv_{O_2} = 40 torr and Sv_{O_2} = 75% Normal Pa_{O_2} = 100 torr and Sa_{O_2} = 99%

Table 16–1.

Common Intensive Care Values and Formulas (*continued*)

Shunt fraction $= \frac{Q_p}{Q_s} = \frac{(Sao_2 - M\dot{V}o_2)}{(Pvo_2 - Pao_2)}$ Q_s = systemic flow (L/min); Qp = pulmonary flow (L/min)	Normal, < 5%
EF (%) $= \frac{\text{end-diastolic volume} - \text{end-systolic volume}}{\text{end-diastolic volume}}$ EF = ejection fraction (an index of ventricular activity)	60–70%
Respiratory formulas	**Normal values**
D(A–a)O_2 $= (FIO_2) \times (713) - PaO_2 - (PaO_2 \div 0.8)$ D(A–a)O_2 = alveolar-arterial oxygen difference, taking FIO_2 (inspired oxygen into consideration); a sensitive index of efficiency of gas exchange	Suboptimal oxygenation > 350 on 100% oxygen Or PaO_2 < 500 torr on 100% oxygen
Renal and metabolic values and formulas	
$C_{Cr} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{72 \times Cr} \times 0.8$ (for females) Cockroft & Gault equation for creatinine clearance (C_{Cr}) (an approximation to glomerular filtration rate, GFR) Or more precisely with 24- or 2-h urine specimen: $C_{Cr} = (U_{Cr} \div P_{Cr}) \times$ (volume/1440 min, or 120 min) U_{Cr} & P_{Cr} = urinary and plasma creatinine concentrations	C_{Cr} < 55 mL/min threshold below which surgical risk increases[159]

Evaluating oliguria (adapted from ref. 37)	**Prerenal**	**Renal**
BUN/Cr	> 20:1	< 10:1
U/*P* creatinine	> 40	< 20
U_{osm}	> 500	< 400
U/*P* osmolality	> 1.3	< 1.1
Urine specific gravity	> 1.020	1.010
U_{Na} (mEq/L)	< 20	> 40
FE_{Na}	< 1%	>2%
Urinary sediment	Hyaline casts	Tubular epithelial casts; granular casts
BUN = urea nitrogen, serum (7–18 mg/dL)		

$\mathbf{FE_{Na}} = \frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}} \times 100$ FE_{Na} = fractional excretion of sodium; *U* and *P* are urinary and plasma concentrations of sodium and creatinine, respectively	Normal, 1–3%
Anion gap $= (Na^+) - [(Cl^-) + HCO_3^-)]$ Elevated by ethanol, uremia (chronic renal failure), diabetic ketoacidosis, paraldehyde, phenformin, iron tablets, isoniazide, lactic acidosis (CN^-, CO, shock), ethanol, ethylene glycol, salicylates	Normal, 8–12

(continued)

Table 16–1.

Common Intensive Care Values and Formulas (*continued*)

$$C_{H_2O} = V - C_{osm}$$
$$C_{osm} = U_{usm} \times V/P_{osm}$$

C_{H_2O} = free water clearance; V = urine flow rate; P_{osm} and U_{osm} = plasma and urine osmolarity, respectively

P_{osm} = 275–295 mOsmol/kg

Capillary fluid exchange (Starling forces)

Net filtration pressure = $P_{net} = [(P_c - P_i) - (\pi_c - \pi_i)]$

K_f = filtration constant (capillary permeability)

Net fluid flow = (P_{net}) (K_f)

P_c = capillary pressure—tends to move fluid out of capillary

P_i = interstitial fluid pressure—tends to move fluid into capillary

π_c = plasma colloid oncotic pressure—tends to cause osmosis of fluid into capillary

π_l = interstitial fluid colloid osmotic pressure—tends to cause osmosis of fluid out of capillary

Edema

1. High P_c, heart failure
2. Low π_c, nephritic syndrome
3. High K_f, toxins, sepsis
4. High π_l, lymphatic blockage

Prosthetic heart valves: current anticoagulation regimens (adapted from ref. 160)	**Coumadin target INR/aspirin 81 mg**
AVR mechanical	2.5–3.0/yes, if high risk
AVR bioprosthetic (tissue)	2.5–3.0 (3 months) or none if aspirin used/yes
MVR mechanical	2.5–3.5 (indefinitely)/yes, if high risk
MVR bioprosthetic or MV repair	2.5–3.0 (3 months; continue 1 yr if history of embolism; indefinitely if AF and LA thrombus at time of surgery)/yes, after 3 months
AVR & MVR mechnical	2.5–3.0 (indefinitely)/yes
AVR & MVT bioprosthetic (tissue)	2.5–3.0 (3 months)/yes, after 3 months
Atrial fibrillation (with any of the above)	2.5–3.0 (indefinitely)/yes

AF = atrial fibrillation; AVR = aortic valve replacement; MVR = mitral valve replacement; High risk = AF, myocardial infarction, enlarged left atrium (LA), endocardial damage, low EF, history of systemic emobolism despite adequate anticoagulation.

significant ongoing volume requirement in the immediate postoperative period. Urine output and bleeding are common sources of ongoing fluid loss. Hypothermia promotes vasoconstriction. As patients rewarm, changes in peripheral vascular tone contribute to labile hemodynamics, which often are best treated with volume.

Peripheral vascular tone needs to be sufficient to provide the patient with adequate blood pressure; excess vasoconstriction can create dangerous levels of hypertension and decrease cardiac output. Decreased afterload can be caused, in part, by medications (e.g., anesthetic agents and preoperative angiotensin-converting enzyme inhibitors), increased temperature, and a systemic inflammatory response to CPB. Increases in afterload can be caused by medications, hypothermia, and increased sympathetic output (including pain and anxiety) or may be secondary to hypovolemia or pump failure.

Pump function can be influenced by levels of exogenous or endogenous inotropes, postoperative stunning, ischemia or infarction, valve function, acidosis, electrolyte abnormalities, hypoxia, or tamponade. Bradycardia, arrhythmias, and conduction defects also can adversely affect cardiac output. The

oxygen-carrying capacity of blood is a function of hematocrit and oxygenation. A hematocrit of 21% and a oxygen saturation of greater than 92% usually are adequate for a stable postoperative patient.

It is important not to allow evaluation of the patient to become obscured by too many numbers or theories, and an overall assessment of the patient is always more important than any single parameter. Trends in hemodynamic parameters usually are more important than isolated values. Patients generally do well if they have warm, well-perfused extremities, normal mental status, and good urine output (>0.5 mL/kg per minute). Acute changes in hemodynamic status are common postoperatively, and vigilant monitoring enables care to be more preemptive than reactive.

Hemodynamic Management

Fluid management

As emphasized previously, the goal of postoperative hemodynamic management is the maintenance of adequate end-organ perfusion without unnecessarily taxing the heart. Assessment and optimization of intravascular volume status generally are the first steps in this process. Most patients have ongoing fluid requirements in the immediate postoperative period that can be caused by persistent third spacing, warming, diuresis, vasodilation, and bleeding. Careful monitoring of fluid balances and filling pressures should guide volume resuscitation. Starling curves are highly variable; it is helpful to correlate cardiac output and $M\dot{V}O_2$ with changes in volume status. Patients with ventricular hypertrophy (e.g., those with a history of hypertension or aortic stenosis) or diastolic dysfunction usually need higher filling pressures. Patients with persistently low filling pressures despite aggressive fluid administration usually are either bleeding or vasodilated. Calculation of CO and SVR often can help to sort this out. In the case of significant vasodilation, judicious use of a pressor agent can help to decrease fluid requirements. Inotropes should not be administered for the treatment of hypovolemia. Fluid requirements often can be reduced following extubation; decreased intrathoracic pressure improves venous return.

The choice of an optimal resuscitation fluid is unresolved. In the acute setting, colloid infusions achieve comparable hemodynamic effects with less volume than crystalloid solutions. After 1 hour, 80% of 1000 mL of 5% albumin solution is retained intravascularly. In situations characterized by loss of vascular endothelial integrity (e.g., following CPB), albumin may redistribute into the interstitial space and increase third-space fluid accumulation.[2,3] One study has shown that the accumulation of extravascular pulmonary water is unaffected by the prime type or the type of fluid administered postoperatively.[4] The largest prospective, randomized, controlled study comparing colloid with crystalloid has been unable to demonstrate a difference in outcomes.[5] Albumin and hetastarch provide comparable hemodynamic benefits, although hetastarch should be avoided in bleeding or coagulopathic patients and in those with renal impairment.[6,7]

Although unusual in the immediate postoperative period, volume overload is a common problem in the days following surgery. If patients have normal cardiac function, they often diurese appropriately without intervention. Conversely, volume overload is a common cause of postoperative heart failure. Diuretics and vasodilators are required frequently in patients with impaired pump function before or following surgery or in those who received large volumes of fluid perioperatively. Patients with impaired renal function may require renal replacement therapy (e.g., ultrafiltration, continuous venovenous hemofiltration, or hemodialysis) to become euvolemic. Rapid diuresis accompanied by inadequate electrolyte repletion frequently is arrhythmogenic.

Pharmacologic support

Medications are used perioperatively to provide vasoconstriction, venous and arterial vasodilation, and inotropic support as well as to treat arrhythmias. As summarized in Table 16-2, many of the commonly used medications have multiple actions. Selection of appropriate agents depends on accurate hemodynamic assessment.

Pressors are indicated for vasodilated patients who have normal pump function and are unresponsive to volume. These agents include *alpha agents* (e.g., neosynephrine) and *vasopressin. Methylene blue* has demonstrated efficacy in vasopressor-resistant hypotension.[8,9] Pressors can contribute to peripheral ischemia and vasospasm of coronary arteries and arterial conduits. Careful monitoring of extremity perfusion and electrocardiographic changes is required when using these agents.

Vasodilators are indicated for hypertensive patients and for patients who are normotensive with poor pump function. *Nitroglycerin* and *sodium nitroprusside* are used commonly in the immediate postoperative period. Both have the advantage of being short acting and easy to titrate. Both can cause hypoxia by inhibiting pulmonary arterial hypoxic vasoconstriction and increasing blood flow through poorly oxygenated lung. Nitroglycerin is a stronger venodilator than an arterial dilator and can increase intercoronary collateral blood flow,[10] but patients quickly can become tachyphylactic. Prolonged nitroprusside use can lead to cyanide toxicity, and methemoglobin levels must be monitored. *Nicardipine* is a calcium channel blocker with minimal effects on contractility or atrioventricular (AV) nodal conduction; it appears to have the efficacy of nipride without its toxicity. *Nesiritide,* or brain naturetic peptide, promotes diuresis in addition to vasodilation and may have beneficial lusitropic effects in patients with diastolic dysfunction.

Hypertension also can be treated with *beta blockers.* These agents work by decreasing heart rate and contractility. Esmolol is useful in the presence of labile blood pressure because of its short half-life. Labetalol combines beta- and alpha-adrenergic blockade. Patients whose pump function is inotrope-dependent should not receive beta blockers.

Table 16–2.

Common ICU Scenarios and Management Strategies

Cardiac output syndromes

MAP	CVP	CO	PCW	SVR	Strategy
Normotensive	High	Low	High	Normal/high	Venodilator/diuretic/inotrope
Hypertension	High	Normal	High	High	Vasodilator
Hypotension	Low	Low	Low	Normal	Volume
Hypotension	High	Low	High	High	Inotrope/IABP/Vasodilator
Hypotension	Normal/low	Normal/high	Normal/low	Low	α-agent

CVP = central venous pressure; CO = cardiac output; SVR = systemic vascular resistance; iNO = inhaled nitric oxide; $iPGI_2$ = inhaled prostacyclin

Commonly used vasoactive drugs and hemodynamic effects

Pharmacologic agent	HR	PCW	CI	SVR	MAP	$M\dot{V}O_2$
Inotropic agents						
Dobutamine	↑↑	↓	↑	↓	↑↓	↑↔
Milrinone	↑	↓	↑	↓↓	↓	↑↓
Mixed vasoactive agents						
Epinephrine	↑↑	↑↓	↑	↑	↑	↑
Norepinephrine	↑↑	↑↑	↑	↑↑	↑↑	↑
Dopamine	↑↑	↑↓	↑	↑↓	↑↓	↑
Vasopressor agents						
Phenylephrine	↔	↑	↔	↑↑	↑↑	↑↔
Vasopressin	↔	↔	↔	↑↑	↑↑	↑↔
Methylene blue	↔	↔	↔	↑	↑	↑
Vasodilating agents						
Nitroglycerin	↑	↓↔	↔	↓	↓	↔↓
Nitroprusside	↑↑	↓↔	↔	↓↓	↓↓	↔↓
Nicardipine	↔	↔	↔	↓↓	↓↓	↔
Nesiritide	↔	↓↔	↔	↓	↓	↔

HR = heart rate; PCW = pulmonary capillary wedge; CI = cardiac index; SVR = systemic vascular resistance; MAP = mean arterial pressure; MVO_2 = mixed venous oxygen saturation

NASPE/BPEG pacemaker identification codes[161]
Code positions

I	*II*	*III*	*IV*	*V*
Chamber paced	**Chamber sensed**	**Response to sensing**	**Programmable functions**	**Antitachyarrhythmia functions**
V—ventricle	**V**—ventricle	**T**—triggers pacing	**P**—programmable rate and/or output	**P**—antitachyarrhythmia
A—atrium	**A**—atrium	**I**—inhibits pacing	**M**—multi-programmable	**S**—shock
D—double	**D**—double	**D**—triggers and inhibits pacing	**C**—communicating functions (telemetry)	**D**—dual (pacer and shock)
O—none	**O**—none	**O**—none	**R**—rate modulation	**O**—none
S—single chamber	**S**—single chamber	—	**O**—none	—

Table 16–2.

Common ICU Scenarios and Management Strategies (*continued*)

Postoperative mediastinal bleeding		
Bleeding Scenario	**Diagnosis**	**Strategy**
<50 mL/h Stable BP, coagulopathy	Post-CPB	Observation
>100 mL/h		
Hypothermic	Hypothermia (see above)	Rewarming strategies
Acute hypotension (MAP <50 mm Hg)		Fluid resuscitation (aim MAP 60–65 mm/Hg)
Diffuse bloody ooze	Borderline coagulopathy	
Coagulopathy:		PEEP trial (5–10 cm H_2O)
1. High PTT, PT	Rebound heparin effect	Coagulation screen
2. INR >1.4	Deficient clotting factors	Heparin level; protamine
3. Low fibrinogen	Deficient clotting factors	Fresh-frozen plasma
4. Platelets $<10^5/\mu L$	Thrombocytopenia	Fresh-frozen plasma
5. Platelets $>10^5/\mu L$	Platelet dysfunction	Platelet pool
6. Bleeding > 10 min	Fibrinolysis	DDAVP
7. Bleeding >30 min (High D-dimers, evidence of fibrinolysis)	Fibrinolysis	Tranexamic acid, ε-aminocaproic acid, aprothinin
> 200–300 mL/h (Adapted from ref 37) > 200 mL/h for 4 h > 300 mL/h for 2–3 h > 400 mL/h for 1 h	Surgical bleeding	Surgical reexploration

DDAVP = desmopressin (synthetic vasopressin); PTT = activated partial thromboplastin time; FDP = fibrin and fibrinogen degradation products; PEEP = positive end-expiratory pressure; PT = prothrombin time; BP = blood pressure; CPB = cardiopulmonary bypass

Inotropic agents are indicated when low cardiac output persists despite optimization of fluid status (preload) and vascular tone (afterload). These agents include beta-adrenergic agents (e.g., *dobutamine*) and cyclic nucleotide phosphodiesterase inhibitors (e.g., *milrinone*). Both these agents increase cardiac output by increasing myocardial contractility and reducing afterload through peripheral vasodilation. Dobutamine is shorter acting and easier to titrate; milrinone achieves increases in cardiac output with lower myocardial oxygen consumption.[11] Both are arrhythmogenic and can exacerbate coronary ischemia. Both *epinephrine* and *norepinephrine* combine beta- and alpha-adrenergic agonist effects; they are pressors in addition to positive inotropes. *Dopamine* in low doses causes splanchnic and renal vasodilation. Since perioperative beta blockade has been shown to improve mortality and morbidity following cardiac surgery, it seems reasonable to avoid the gratuitous use of inotropes, and efforts should be made to wean these agents rapidly when they are no longer required.

Heart Rate and Rhythm Management

Deviations from normal sinus rhythm can cause significant clinical deterioration, and optimization of heart rate and rhythm frequently is an effective way to improve hemodynamic status.

Pacing (see Table 16-2)

Within normal rate ranges, cardiac output increases linearly with heart rate, and pacing often is very helpful. It is important to monitor the response to pacing carefully, however. For example, sinus bradycardia often is more effective than ventricular pacing at a more normal rate. Ventricular pacing can cause ventricular dysfunction and dyssynchrony, and the loss of consistent filling from atrial contraction can lead to clinical deterioration. If possible, atrial pacing is preferred to AV pacing, which is preferred to ventricular pacing. Pacing too rapidly can have an adverse effect on cardiac performance by decreasing filling time or inducing ischemia. Internal pacemakers often can be reprogrammed to improve output.

Heart block can occur following aortic, mitral, and tricuspid valve surgery. It is also associated with inferior myocardial infarction and can be secondary to medications (e.g., digoxin, amiodarone, calcium channel blockers, and beta blockers). If a biatrial transseptal approach to the mitral valve is employed, the sinus rhythm can be lost owing to divi-

sion of the sinoatrial (SA) node.[12] Heart block frequently is transient. If the ventricular escape rate is absent or insufficient, pacing wire thresholds need to be monitored carefully and backup pacing methods employed (e.g., a transvenous wire or pacing pulmonary artery catheter or external pacing pads) if needed while waiting for placement of a permanent pacemaker.

Ventricular arrhythmias

Nonsustained ventricular tachycardia (VT) is common following cardiac surgery and typically a reflection of perioperative ischemia-reperfusion injury, electrolyte abnormalities (typically hypokalemia and hypomagnesemia), or an increase in exogenous or endogenous sympathetic stimulation. Generally, nonsustained VT is more important as a symptom of an underlying cause requiring diagnosis and correction than as a cause of hemodynamic instability.

Sustained VT (persisting for more than 30 seconds or associated with significant hemodynamic compromise) requires more aggressive treatment. Ongoing ischemia should be ruled out (with coronary angiography if necessary), electrolytes should be replaced, and inotrope should be minimized. Beta blockers, amiodarone, and lidocaine are useful therapies. Electrocardioversion should be employed if sustained VT causes significant compromise.

Atrial fibrillation and flutter

PROPHYLAXIS: Atrial fibrillation and flutter occur in 20 to 40% of patients undergoing coronary artery bypass grafting (CABG) and generally is more common in patients undergoing valve and combined procedures. Beta blockers are the most commonly used and effective prophylactic treatment and should be started or resumed as soon as they can be tolerated safely following surgery. Inotropic support, hemodynamic compromise, and AV block (e.g., PR interval $>$ 0.24 ms or, second- or third-degree block) are contraindications. Beta blockers appear to provide more effective prophylaxis when they are dosed with high frequency and titrated to produce an effect on heart rate and blood pressure. Sotalol and amiodarone are also effective for prophylaxis but not superior. Beta blockers confer benefits other than atrial fibrillation prophylaxis, are easy to titrate, and do not have the toxicities associated with amiodarone.

TREATMENT: There are many treatment strategies for the management of atrial fibrillation.[13] We have found that the use of a guideline reduces the incidence of atrial fibrillation and decreases the disruption and anxiety that it creates (Table 16-1). The principal premise of this strategy is recognition of the fact that for most patients with new-onset atrial

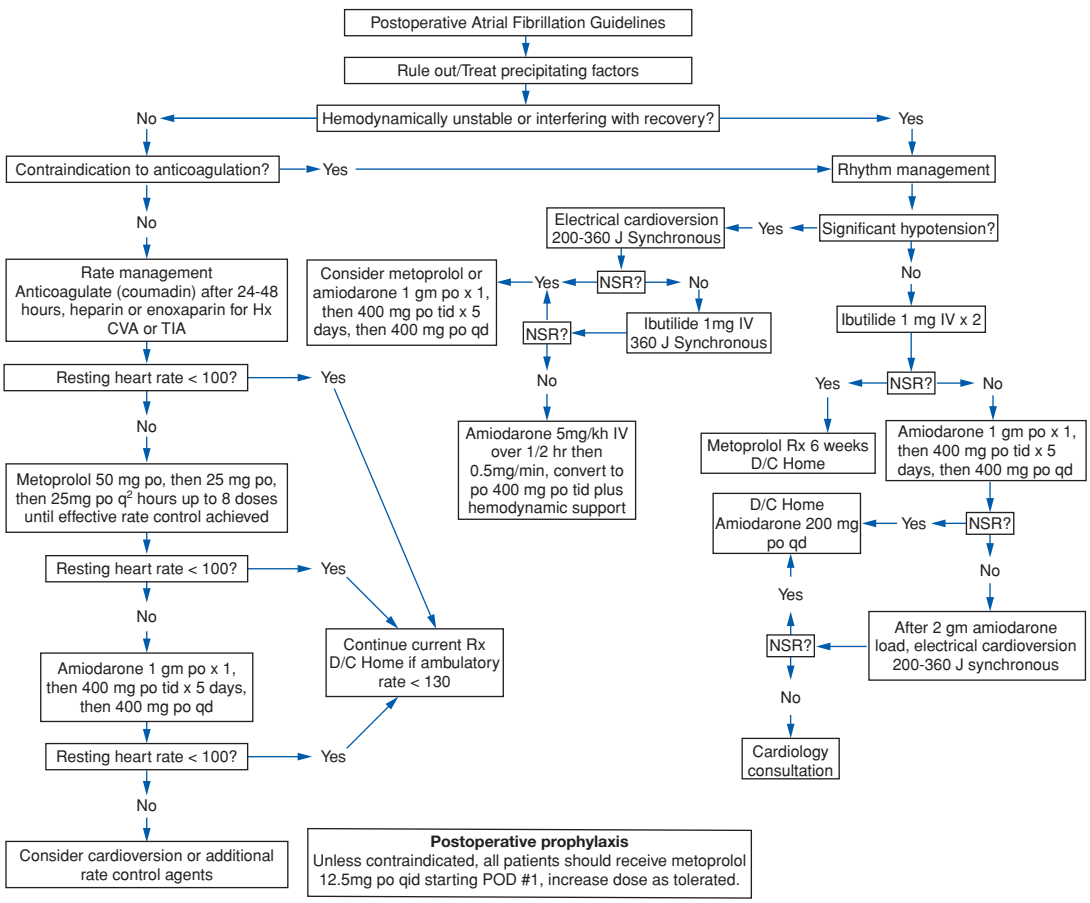

Figure 16-1. Postoperative atrial fibrillation guidelines. *(Adapted from Maisel WH, Rawn JD, Stevenson WG: Atrial fibrillation after cardiac surgery.* Ann Intern Med *2001; 135:1061.)*

fibrillation, the arrhythmia is self-limited (90% of patients are in sinus rhythm within 6 to 8 weeks independent of treatment approach). The pursuit of a rate control and anticoagulation strategy usually produces outcomes comparable with a rhythm-control strategy. Our prophylactic regimen begins with metoprolol 12.5 to 25 mg PO qid and is titrated upward as tolerated.

A. *Initial assessment.* The management of atrial fibrillation should be guided by the answers to the following three questions:
   1. *Is the patient symptomatic?* Atrial fibrillation generally is well tolerated, and overly aggressive management can cause significant morbidity. Nonetheless, the first step in the management of atrial fibrillation is an assessment of its hemodynamic significance. Significant symptoms may respond to rate control alone or may require chemical or electrical cardioversion. Evidence of compromise includes hypotension, changes in mental status, decreased urine output, impaired peripheral perfusion, anginal symptoms, and decreased cardiac output or increased filling pressures.
   2. *What are the precipitating factors?* Appropriate management of atrial fibrillation requires identification and treatment of potential risk factors. Atrial fibrillation can result from ischemia, atrial distension, increased sympathetic tone, electrolyte imbalances (particularly hypokalemia and hypomagnesemia precipitated by diuresis), acid-base disturbances, sympathomimetic medications (e.g., inotropes and bronchodilators), beta-blocker withdrawal, pneumonia, atelectasis, and pulmonary embolism.
   3. *What are the goals of therapy?* Hemodynamic stability is the primary goal. For most patients, rate control is sufficient because 90% of patients with new-onset atrial fibrillation following cardiac surgery will be in normal sinus rhythm in 6 weeks. Evidence of hemodynamic compromise or interference with recovery should prompt chemical or electrical cardioversion.

B. *Drug therapy.* Agents can be divided conveniently into rate-control and rhythm-control agents, although beta blockers are also effective in converting atrial fibrillation postoperatively. Monodrug therapy generally is better than polydrug therapy.
   1. *Rate-control agents:*
      a. *Beta blockers.* Metoprolol should be first-line therapy in most patients and can be given orally or intravenously. Metoprolol should be titrated to effect with a heart rate goal of less than 100 beats per minute at rest. The suggested treatment for new-onset atrial fibrillation is 50 mg PO, followed by 25 mg PO until normal sinus rhytum (NSR) or adequate rate control is achieved, up to eight doses. Some patients may require over 400 mg/d.
      b. *Calcium channel blockers.* Diltiazem is the agent of choice. It should be initiated as a bolus at 0.25 mg/kg IV, followed by 0.35 mg/kg IV, followed by a continuous infusion of 5 to 15 mg.
      c. *Digoxin* can be considered in patients with contraindications to beta blockers, in particular those with poor ejection fraction. There is some evidence that it increases atrial automaticity. It has a half-life of 38 to 48 hours in patients with normal renal function, significant potential toxicity, and a narrow therapeutic range. Levels must be monitored, particularly in patients with renal insufficiency. Many agents, including amiodarone, increase its serum level. Following chemical cardioversion, attempts should be made to minimize the number of rate-control agents used.
   2. *Antiarrythmics:*
      a. *Metoprolol* (diltiazem).
      b. *Ibutilide.* Ibutilide is given as a 1-mg intravenous bolus and repeated once if cardioversion fails to occur. Patients need to be monitored for a small but significant incidence of torsades de pointes that may be increased if given in conjunction with amiodarone.
      c. *Amiodarone* can cause myocardial depression and heart block; significant hypotension is associated most commonly with rapid bolus infusion. Significant toxicity can be associated with both short-term and prolonged use of amiodarone.
      d. *Adenosine* is helpful in the treatment of supraventricular tachycardia (SVT). (It should be avoided in transplant recipients, partially revascularized patients, and patients with atrial flutter.)

C. *Electrical cardioversion.* Electrical cardioversion should be used emergently for the treatment of hemodynamically unstable atrial fibrillation, starting at 200 J (synchronous). Sedation should be used. In patients with atrial wires who are in atrial flutter, overdrive pacing can be attempted.

D. *Anticoagulation.* Patients who remain in atrial fibrillation for more than 24 hours or have multiple sustained episodes over this period should be started on coumadin in the absence of contraindications. Heparin (intravenously, or low-molecular-weight heparin subcutaneously) should be considered after 48 hours in patients with a history of stroke or transient ischemic attacks (TIAs) or who have a low ejection fraction. Coumadin should not be initiated in patients who may require permanent pacer placement.

Postoperative Ischemia and Infarction

Postoperative ischemia and infarction can be caused by inadequate intraoperative myocardial protection; kinked, spasmed, or thrombosed conduits; thrombosed endarterectomized vessels; or embolization by air or atherosclerotic debris. It should be suspected in the presence of otherwise unexplained poor pump function, ST changes, new bundle-branch block or complete heart block, ventricular arrhythmias, or enzyme elevation. Electrocardiographic changes should be correlated with the anatomy of known atherosclerotic or revascularized territories. Air embolism preferentially involves the right coronary artery, and inferior ST-segment changes generally are

present in the operating room. It typically resolves within hours. It is worth noting that nonspecific ST-segment changes are common postoperatively and usually benign. Pericarditic changes generally are characterized by diffuse concave ST-segment elevations, accompanied by a pericardial rub and delayed in onset by at least 12 hours following surgery.

New wall motion abnormalities or mitral regurgitation diagnosed echocardiographically can help to determine the hemodynamic significance of suspected ischemia or infarction. Knowledge of the quality of conduits, anastomoses, and target vessels is critical in planning management strategy (e.g., there may be little to be gained and much to lose in attempting to improve flow to a small, highly diseased posterior descending artery with poor runoff). If there appears to be significant myocardium at risk, on the other hand, a timely trip to the operating room or the cardiac catheterization laboratory can improve outcomes dramatically. Ongoing ischemia should prompt consideration of standard strategies, including anticoagulation, beta blockade, and nitroglycerin as tolerated. Intra-aortic balloon placement should be considered to minimize inotrope requirements, decrease myocardial oxygen requirements, and/or minimize infarct size.

Right Ventricular Failure and Pulmonary Hypertension

Right ventricular failure can be a particularly difficult postoperative problem. It can be caused by perioperative ischemia or infarction or by acute increases in pulmonary vascular resistance (PVR). Preexisting pulmonary hypertension is caused commonly by left-sided heart failure, aortic stenosis, mitral valve disease, and pulmonary disease. Chronic pulmonary hypertension is characterized by abnormal increased vasoconstriction and vascular remodeling.[14] Acute increases in PVR are caused commonly by acute left ventricular dysfunction, mitral valve insufficiency or stenosis, volume overload, pulmonary edema, atelectasis, hypoxia, or acidosis. Pulmonary embolism also should be considered, but it is rare in the immediate postoperative period. As the right side of the heart fails, it becomes distended, central venous pressure increases, tricuspid regurgitation may develop, and pulmonary artery pressures and left-sided filling pressures become inadequate. Strategies for reversing this potentially fatal process begin with identifying potentially reversible etiologies. Volume status and left-sided function should be optimized. The right ventricle has its own Starling curve, and while the failing right ventricle often needs more volume to ensure adequate left-sided filling, overdistension will worsen function. Judicious use of positive end-expiratory pressure (PEEP) to recruit atelectatic lung and hyperventilation can decrease the impact of pulmonary vasoconstriction mediated by hypoxia and hypercarbia. Use of intravenous vasodilators [commonly, nitroprusside, nitroglycerin, tolazoline (PGI_2), hydralazine, prostacyclin, adenosine, and nicardipine] to reduce PVR frequently is limited by systemic hypotension. Inotropes (typically milrinone, which also provides vasodilatation) can be beneficial.[15] Since no intravenous vasodilator is selective for the pulmonary vasculature, topical administration can be significantly more effective in reducing PVR without causing systemic hypotension. Inhaled nitric oxide (NO) and PGI_2 have comparable efficacy. They also can improve oxygenation by shunting blood to ventilated lung.

Valvular Disease: Special Postoperative Considerations

Aortic valve replacement

The different pathophysiologies associated with aortic stenosis (primarily a pressure-overload phenomenon) versus aortic insufficiency (volume overload) can result in significantly different postoperative courses.

AORTIC STENOSIS: Aortic stenosis can lead to the development of a hypertrophied, noncompliant left ventricle. For some patients, replacement of a stenotic valve allows a ventricle conditioned to pumping against abnormally high afterload to easily achieve supranormal levels of cardiac output and blood pressure postoperatively. Meticulous blood pressure control frequently is required to avoid disrupting fresh suture lines. In some patients, the degree of ventricular hypertrophy can lead to dynamic outflow obstruction; the condition is treated most effectively with volume, beta blockers, and afterload augmentation. Even without dynamic outflow obstruction, reduced compliance (diastolic dysfunction) can create significant hemodynamic compromise if the patient becomes hypovolemic or loses normal sinus rhythm. (Up to 30% of stroke volume can be dependent on synchrony between atria and ventricle.) The placement of atrial wires in addition to ventricular wires can provide significant advantages in the event that the patient is bradycardic or experiences heart block postoperatively.

AORTIC REGURGITATION: The left ventricle in a patient with aortic regurgitation frequently is dilated without significant hypertrophy and often functions poorly postoperatively. Optimization of volume, afterload, inotropy, and rhythm in these patients often is challenging.

Mitral valve repair/replacement

MITRAL REGURGITATION: Following repair or replacement of an incompetent mitral valve, increased afterload and consequent greater wall stress unmask left ventricular dysfunction. Frequently, inotropic support and systemic vasodilatation are required to reduce the afterload mismatch seen following surgery.[16] Occasionally, left ventricular dysfunction can be the result of inadvertent suture placement over the circumflex coronary artery.

MITRAL STENOSIS: Unlike patients with mitral regurgitation, patients with mitral stenosis typically have preserved left ventricular function. Exacerbation of preexisting pulmonary

hypertension is common, however. Postoperative strategies focus on optimizing right ventricular function and decreasing pulmonary vascular resistance.

BLEEDING, THROMBOSIS, AND TRANSFUSION STRATEGIES

One of the principal challenges of cardiac surgery is to achieve sufficient anticoagulation while the patient is supported on CPB without experiencing excessive bleeding postoperatively. Not surprisingly, patients undergoing off-pump CABG experience a significant reduction in postoperative bleeding and blood product transfusion requirements.[17,18] Excessive bleeding and its complications, including blood product transfusions, cause significant morbidity and mortality.

Preoperative Evaluation

Preoperative evaluation includes documenting a history of abnormal bleeding or thrombosis and obtaining basic coagulation studies, a hematocrit, and a platelet count. A history of recent heparin exposure associated with thrombocytopenia should suggest a diagnosis of *heparin-induced thrombocytopenia* (HIT). Confirmation of the presence of IgG directed against platelet factor 4 (the prevalence of these antibodies in patients with previous heparin exposure can be up to 35%[19]) requires either a delay in surgery until the assay is negative (usually 3 months) or, if surgery is urgently required, an alternative anticoagulation strategy. Recent experience with the direct thrombin inhibitor *bivalirudin* appears promising in this scenario.

Preoperative medications that can increase bleeding risk are common. *Aspirin* inhibits cyclooxygenase, reduces the synthesis of thromboxane A_2 (TXA_2), and decreases platelet aggregation.[20] Preoperative aspirin use modestly increases postoperative bleeding,[21,22] but preoperative and early postoperative use (i.e., within 6 hours) is beneficial to outcome and ultimate survival.[23] Other antiplatelet agents have more profound impacts on platelet function. The *glycoprotein IIb/IIIa inhibitors* eptifibitatide (Integrillin) and tirofiban (Aggrastat) are sufficiently short acting that surgery can be conducted safely despite recent exposure. *Abciximab* (Reopro) usually requires a 24- to 48-hour delay of surgery, if feasible, to avoid catastrophic bleeding.[24] *Clopidogrel* (Plavix) is a thienopyridine derivative that blocks platelet ADP P_2Y_{12} receptors, inhibiting platelet activation by preventing ADP-mediated responses, decreasing alpha-granule release, and lowering TXA_2 and P-selectin expression with some anti-inflammatory effects.[25] Cessation of clopidogrel is preferred 5 days preoperatively but is not advisable in patients with drug-eluting coronary artery stents. Customarily, *coumadin* (which inhibits the vitamin K–dependent clotting factors II, VII, IX, and X) is discontinued 4 to 7 days preoperatively to allow gradual correction of the international normalization ratio (INR).

Intraoperative Strategies

Multiple *intraoperative strategies* have evolved to prevent unnecessary bleeding during blood product transfusion. Antithrombolytics *ε-aminocaproic acid* (Amicar) and *tranexamic acid* (Cyclokapron) inhibit plasminogen activation and limit fibrinolysis. Topical use of tranexamic acid intraoperatively prior to closure[26] may be a simple and effective way to reduce postoperative bleeding, particularly in patients with friable tissue who are having reoperations or have had previous exposure to chest irradiation. *Aprotinin* (Trasylol), a serine protease inhibitor, activates factor XII (Hageman factor), has antifibrinolytic properties (main hemostatic effect), and protects platelets. The drug is used primarily for patients who are at high risk for postoperative bleeding. A recent retrospective study has questioned aprotinin's safety.[27]

Retrograde autologous priming of the CPB circuit involves displacing circuit prime solution at the initiation of CPB with the patient's blood draining both antegrade through the venous cannula and retrograde through the arterial cannula.[28] This strategy has been shown to decrease the requirement for blood transfusion significantly following CABG. The use of heparin-bonded circuitry has enabled the safe use of lower anticoagulation targets while on bypass. Careful attention to hemostasis intraoperatively and avoidance of excessive use of a blood salvage device (e.g, cell saver®) (which depletes platelets and clotting factors) pays dividends postoperatively.

Postoperative Bleeding

Strategies for avoiding postoperative *hypothermia* are also very important. Hypothermia (≤35°C) on arrival to the ICU is associated with delayed extubation,[29] shivering and increased peripheral O_2 consumption,[30] hemodynamic instability, atrial and ventricular arrhythmias, and increased systemic vascular resistance and coagulopathy.[31,32]

Most patients are mildly *coagulopathic* postoperatively, but only a minority bleed excessively. Postoperative coagulopathy can be due to residual or rebound heparin effects following CPB, thrombocytopenia (qualitative and quantitative), clotting factor depletion, hypothermia, and hemodilution. Chest tube outputs persistently greater than 50 to 100 mL/h or other clinical evidence of bleeding demand attention.

The treatment of postoperative bleeding depends initially on making a judgment: Is bleeding surgical, coagulopathic, or both? Surgical bleeding is treated as soon as possible by reexploration; coagulopathies are corrected in the ICU. Coagulopathic patients rarely have significant clot formation in their chest tubes. Standard maneuvers include warming the patient, controlling blood pressure, extra PEEP, additional ε-aminocaproic acid, calcium gluconate, and blood products. In general, blood products should not be used to correct coagulation abnormalities unless the patient is bleeding significantly. All allogeneic blood products can contribute to transfusion-related lung injury and have other adverse effects. *Protamine* is indicated rarely and can increase bleeding. *Desmopressin* (DDAVP) is a synthetic vasopressin analogue that acts by increasing the concentration of von

Willebrand factor, an important mediator of platelet adhesion. It is of benefit in patients with von Willebrand's disease and in patients with severe platelet dysfunction secondary to uremia anitplatelet agents.[33]

Recombinant factor VIIa (rFVIIa) is a drug approved for use in hemophiliacs that has been used successfully in arresting bleeding in patients with life-threatening hemorrhage after cardiac surgery. On combination with tissue factor, it activates the extrinsic coagulation system via factor X, resulting in thrombin generation and prompt correction of the prothrombin time (PT) with no evidence of systemic thrombosis.[34–36]

Mediastinal Reexploration

Reexploration should be considered when CT outputs are greater than 400 mL/h for 1 hour, greater than 300 mL/h for 2 to 3 hours, and 200 mL/h for 4 hours[37] (see Table 16-2) or if signs of tamponade or hemodynamic instability develop. *Tamponade* should be considered in the presence of hypotension, tachycardia, elevated filling pressures, increasing inotrope requirements, pulsus paradoxus, and/or equalization of right and left atrial pressures.[38] An echocardiogram can be useful in this situation but cannot rule out tamponade. Chest x-rays are a necessary element of the evaluation for bleeding; look for a widening mediastinum or evidence of a hemothorax. Chest x-rays should be repeated on all patients with initial high chest tube output that later subsides to ensure that chest tubes have not clotted.

Autotransfusion

Autotransfusion of shed mediastinal blood remains controversial.[39] Red blood cell viability in unwashed shed mediastinal blood is comparable with that of autologous whole blood[40]; additionally, there is evidence indicating no apparent clinical coagulopathy (e.g., low fibrinogen levels but normal coagulation times at 1 and 24 hours) following reinfusion of shed blood.[41–43] This method of blood salvage is without allogeneic transfusion risks and possibly is immunostimulatory.

Blood Transfusions

Despite meticulous preoperative planning, correcting drug-induced coagulopathies, and employing intraoperative "cell saving" techniques with "bloodless" fields, bleeding is inevitable postoperatively. The adverse effects of blood transfusions are well defined. The benefits are not. There is considerable evidence to suggest that blood transfusion increases the risk of postoperative infection and mortality following cardiac surgery.[44] The Canadian Critical Care Trials group in a randomized trial restricted transfusion for hemoglobin to less than 7.0 g/dL versus 10.8 g/dL, with no change in mortality rate.[45] These findings are consistent which are NIH consensus recommendation. A National Institutes of Health (NIH) consensus conference concluded that patients with a hemoglobin level of greater than 10.9 g/dL do not require blood, whereas those with less than 7.0 g/dL hemoglobin benefited from blood.[46] Tissue perfusion depends on cardiac output and hemoglobin level. A marginal $M\dot{V}O_2$ or evidence of ischemia provides a rationale for increasing hematocrit.

Immunomodulation

It has become evident that blood transfusions have *immunomodulating effects* (by either alloimmunization or tolerance induction) that may increase the risk of nosocomial infections, transfusion-associated graft-versus-host disease (TAGVHD), transfusion-related lung injury (TRALI), cancer recurrence, and the possible development of autoimmune diseases later in life.[47] Furthermore, the risk of "newer" transfusion-transmitted diseases has become recognized. Proinflammatory mediators and cytokines have been associated with an increased risk of wound infection, sepsis, and pulmonary and renal insufficiency.[48]

RESPIRATORY CARE

Postoperative Pulmonary Pathophysiology

Following the introduction of CPB nearly 50 years ago, pulmonary complications were recognized and attributed to pulmonary vascular overload.[49] *Pump lung* is pulmonary dysfunction secondary to an inflammatory response provoked by the bypass circuit. Increases are seen in the alveolar-arterial (A-a) gradient, pulmonary shunt fraction, and pulmonary edema, with a resulting decrease in compliance. Many inflammatory mediators have been implicated. Complement is activated (e.g., C3a and C5b–C9) and can damage pulmonary endothelium directly, as well as sequester neutrophils. When activated, these neutrophils release oxygen free radicals and proteases, furthering injury. Macrophage cytokine production and platelet degranulation also have been demonstrated in models of bypass-induced lung injury.[50,51] Transfusion-related lung injury also may exacerbate lung dysfunction.

Despite increased knowledge of the mechanisms of injury, to date, there have been no interventions with clear clinical benefit. To the contrary, administration of methylprednisolone in a randomized, double-blind study significantly increased A-a gradient and shunt fraction, decreased both static and dynamic compliance, and delayed early extubation in a dose-dependent manner.

Assessment on Arrival

On arrival to the ICU, auscultation of the lungs should be performed to ensure equal breath sounds and the absence of bronchospasm. Ventilator settings usually are a mandatory mode such as synchronized intermittent mandatory ventilation (SIMV) or assist-control (AC) with an F_{IO_2} of 100%, a rate of 12 to 18 breaths per minute, a tidal volume (TV) of 6 to 10 mL/kg, PEEP of 5 cm H_2O, and pressure support (PS) of 8 to 10 cm H_2O if on intermittent mandatory ventilation (IMV). A review of the initial postoperative chest x-ray (CXR) confirms proper endotracheal tube position 2 to 3 cm

above the carina and proper nasogastric tube and intravenous line placement. Clinicians should be alert for pneumothoraces, hemothoraces, and a widened mediastinum. Arterial blood gas analysis should confirm adequate oxygenation and the absence of hypercapnea and metabolic acidosis. Arterial blood gas results should be correlated with pulse oximetry and minute ventilation.

Troubleshooting Hypoxia

As discussed earlier, oxygenation in all patients will be diminished compared with baseline. The inability to wean F_{IO_2} below 50% within the first few postoperative hours, however, should prompt a reevaluation because many causes can be treated. Sometimes simply replacing the pulse oximeter probe onto another finger or an earlobe will improve the reported oxygen saturation. This is particularly true in patients with peripheral vasoconstriction, and arterial blood gas analyses may be necessary for correlation. The use of vasodilators including nitroglycerin, milrinone, and particularly sodium nitroprusside can increase shunt fraction (by antagonizing hypoxic pulmonary vasoconstriction) enough to require a high F_{IO_2} to maintain adequate oxygenation. Increasing PEEP to improve alveolar recruitment may help,[52] or changing agents may be necessary. Nebulizer treatments may be necessary for bronchospasm, and repeat CXR may demonstrate pneumothorax, hemothorax, mediastinal hematoma, atelectasis, or a new infiltrate representing aspiration.

Atelectasis, particularly in the left lower lobe, is present to some degree in nearly all patients. Bibasilar atelectasis is believed to be the combined product of prolonged supine position and intraoperative muscle relaxation allowing upward displacement of abdominal contents and the diaphragm. This reduces functional reserve capacity (FRC) by up to 1 L.[53] On the left, this is compounded by pleurotomy for internal mammary artery (IMA) takedown, compression of the left lung, and decreased ventilatory tidal volumes to clear the field for IMA dissection. Left lower lobar atelectasis owing to phrenic nerve injury is not likely to resolve acutely with bronchoscopic aspiration. Lobar atelectasis in general, however, especially when associated with mucus plugging, is improved by bronchoscopic aspiration in approximately 80% of patients.[54] A prospective study comparing bronchoscopy with aggressive chest physiotherapy found the two techniques to be equally effective,[55] but only if the chest physiotherapy regimen is adhered to.[56]

Sedation

Sedation and pain relief in cardiac surgery "fast tracking" rely on short-acting agents, including propofol, fentanyl, and midazolam. Dexmedetomidine is a highly selective alpha$_2$-adrenoreceptor agonist that has anxiolytic, sympatholytic, and analgesic effects without contributing to respiratory depression, oversedation, or delirium. It may provide myocardial protection.[57] Hypotension and bradycardia can occur.

Early Extubation

Stable patients with a normal mental status often can be extubated either in the operating room or within a few hours following arrival in the ICU. Once an arterial blood gas analysis has confirmed adequate oxygenation and ventilation, pulse oximetry and monitoring of minute ventilation can guide extubation, often without the need for subsequent blood gas determinations.

Patients usually excluded from planning for early extubation include those with (1) preoperative pulmonary failure requiring intubation, (2) uncompensated congestive heart failure with pulmonary edema, (3) severe pulmonary hypertension or right-sided heart failure requiring hyperventilation or nitric oxide, (4) cardiogenic shock (including a requirement for intra-aortic balloon counterpulsion), (5) deep hypothermic circulatory arrest, (6) persistent hypothermia ($<$35.5(C), (7) persistent hypoxia (Pa_{O_2}:F_{IO_2} $<$ 200), (8) persistent acidosis (pH less than 7.30), (9) persistent mediastinal bleeding, or (10) a cerebrovascular accident or reduced mental status (inability to follow commands or protect airway).

Ventilator Weaning and Extubation

For patients unable to wean from the ventilator immediately following surgery, a spontaneous breathing trial (30 minutes of spontaneous breathing with 5 cm H_2O of pressure support or unassisted breathing through a T-tube) has been shown to be the most accurate predictor of successful extubation. Breathing trials typically are discontinued for such signs of distress as respiratory frequency more than 35 breaths per minute, O_2 saturation less than 90%, heart rate greater than 140 beats per minute, systolic blood pressure greater than 180 mm Hg or less than 90 mm Hg, agitation, diaphoresis, or anxiety.[58,59] Yang et al. introduced the concept of a rapid-shallow breathing index (RSBI, f/VT, breaths per minute per liter). In their study of medical patients, the RSBI was calculated over 1 minute of unassisted spontaneous breathing through a T-tube. An RSBI of greater than 105 indicated a 95% likelihood that a subsequent weaning trial would not lead to successful extubation, and an RSBI of less than 105 indicated an 80% likelihood of subsequent success. The minute ventilation $\dot{V}_E$ and Mean Inspiratory Pressure (MIP) were significantly less predictive.

The strategy of daily or intermittent spontaneous breathing trials (SBTs) also was compared directly with weaning strategies based on stepwise reduction of the frequency of intermittent mandatory ventilation (IMV) or stepwise reduction of the level of pressure-support ventilation (PSV). Daily or intermittent SBTs lead to successful extubation two to three times earlier than either IMV or PSV weaning.[58]

In a prospective series of ICU patients,[60] the 20% false-positive predictive value of an RSBI of less than 105 is overwhelmingly due to newly acquired problems, with only 7% of failures being referable to the process that initially required intubation. No direct study of the outcome of these strategies exists in the cardiac surgery population, but they are in broad clinical use, and we recommend at least daily SBTs, as quided by the SBI.

The decision to extubate must take into account the combined factors of mechanics, as described earlier, as well as an estimation of the patient's ability to manage secretions and protect his or her airway.[61]

Extubation Failure

Overall, approximately 5% of cardiothoracic patients require reintubation.[62,63] Patients with chronic obstructive pulmonary disease (COPD) have a 14% incidence,[64] whereas those with a past history of stroke have a 10% incidence.[65] Other risk factors include New York Heart Association (NYHA) class IV functional status, renal failure, need for intra-aortic balloon counterpulsion, reduced Pa_{O_2}:F_{IO_2}, reduced vital capacity, longer operating room time, a longer CPB run, and longer initial ventilatory requirement.[63] Unfortunately, in ICU patients overall, reintubation is an ominous predictor of increased length of stay and increased mortality.

Chronic Ventilation and Tracheotomy

In the early 1960s, translaryngeal intubation was associated with a prohibitively high rate of tracheal stenosis. As a result, a consensus existed that tracheotomy should be performed on patients requiring mechanical ventilation for longer than 3 days.[66] Low-pressure cuffs and soft tubes since have muddled this question of timing. A consensus subsequently evolved in that patients who continue to require mechanical ventilation at 2 weeks should undergo tracheotomy. Data surrounding this practice have been soft.[67] Several trials suggest earlier discontinuation of mechanical ventilation and reduced complications associated with earlier tracheotomy.[67,68] Causation is not clear, but compelling arguments for reduced dead space and airway resistance, as well as facilitated pulmonary toilet, are made in favor of early tracheotomy. Additionally, less sedation is required. It is also strongly suggested that clinician behavior is positively affected by the presence of a tracheostomy tube. That is, more aggressive attempts at weaning and discontinuation of mechanical support are made because reconnecting the ventilator is easy.[68]

Percutaneous dilatational tracheotomy (PDT) performed in the ICU is becoming recognized increasingly as a safe procedure.[68] A recent randomized, prospective study of medical patients projected to require more than 14 days of mechanical ventilation[69] compared two groups: PDT within 48 hours and PDT within 14 to 16 days. One hundred and twenty patients were enrolled. In the early PDT group, there was a strongly significant reduction in duration of mechanical ventilation (7.6 $\pm$ 4.0 versus 17.4 $\pm$ 5.3 days; $p < .001$), incidence of pneumonia (5% versus 25%; $p < .005$), and mortality (31.7% versus 61.7 %; $p < .005$). There was no difference in incidence or severity of tracheal stenosis identified in-hospital and at 10 weeks. With hope and with increasing evidence, early tracheotomy will come to be viewed more widely as beneficial to patient recovery rather than as an admission of defeat.

Pleural Effusion

Accumulation of fluid in the pleural space is common after cardiac surgery, particularly on the left side, and usually resolves with time and diuresis. The specific cause often is unknown, but a combination of factors can contribute, including fluid overload, hypoalbuminemia, pericardial and pleural inflammation (i.e., postpericardiotomy syndrome), atelectasis, pneumonia, and pulmonary embolism. Pleural effusion can cause chest pain or heaviness, shortness of breath, and hypoxia. Symptomatic effusions should be tapped, and usually thoracentesis does not have to be repeated. Nonsteroidal anti-inflammatory agents are used to treat postpericardotomy syndrome. Occasionally, tube thoracostomy drainage may be necessary until resolution of the inciting process. In contrast, retained hemothorax should be evacuated to avoid delayed development of fibrothorax requiring decortication.

Pneumonia

Nosocomial pneumonias have high associated mortality, and the incidence of ventilator-associated pneumonia increases approximately 1% per day.[70] Clinical diagnosis involves identification of a new or progressive infiltrate on CXR, change in character of sputum, leukocytosis, and fever.[71,72] Expectorated sputum cultures are considered to be very inaccurate, and directed bronchosopic sampling is preferred. Proper bronchoalveolar lavage requires large volumes of irrigant (>100 mL) and is performed infrequently. More commonly, tracheobronchial aspiration is performed using several milliliters of normal saline. Gram stain containing 25 or more squamous epithelial cells per low-power field indicates oral contamination. More than 25 neutrophils per low-power field suggests infection. Quantitative culture of 10^5 to 10^6 colony-forming units per milliliter (i.e., "moderate to numerous" or "3 to 4+") is indicative of infection, whereas 10^4 or fewer colony-forming units per milliliter (i.e., "rare to few" or "1 to 2+") is more suggestive of colonization. Gram-negative organisms are seen most commonly and should be the target of first-line empiric antibiotic coverage. Specific patient factors and culture results and sensitivities will further refine antibiotic therapy.[73]

The important role of pulmonary toilet in both the prevention and the treatment of nosocomial pneumonias cannot be overemphasized. All patients should be encouraged to get out of bed and ambulate (even if attached to the ventilator), turn, cough, and deep breathe with chest physiotherapy and bronchodilators. Sterile in-line suctioning should be performed in ventilated patients to aid in secretion clearance. Nasotracheal suctioning is extremely effective in unintubated patients in that the procedure stimulates very strong coughing and secretion clearance. Therapeutic fiberoptic bronchoscopy also can be performed.

Pulmonary Embolism

Deep venous thrombosis (DVT) and pulmonary thromboembolism (PE) are considered uncommon in the cardiac

surgery population.[74] Reported incidence of PE ranges from 0.5 to 3.5%, accounting for only 0.3 to 1.7% of perioperative deaths. This is believed to be due to large intraoperative doses of heparin, both a quantitative and qualitative thrombocytopenia after CPB, and increased use of antiplatelet agents and anticoagulants, as well as early ambulation. A recent autopsy study[75] demonstrated a 52% incidence of DVT, that 20% of deceased patients have minor PE, and that PE is identified as the cause of death in 7%. Unfortunately, risks of bleeding and heparin-induced thrombocytopenia make the choice of heparin DVT prophylaxis problematic. Intermittent pneumatic compression devices are effective if patients and staff are compliant with their use.

The diagnosis of PE requires a high index of suspicion and should be considered in any patient who postoperatively acquires a newly increased Pa_{O_2}:F_{IO_2} gradient, shortness of breath, or reduced exercise tolerance, particularly in the setting of a clear or unchanged CXR. Diagnosis is fairly reliably obtained by PE-protocol thin-cut high-speed helical computed tomography of the chest,[76] although accuracy is still influenced by pretest probability.[77]

RENAL AND METABOLIC SUPPORT

Perioperative Renal Dysfunction/Insufficiency

The new onset of renal dysfunction following cardiac surgery is correlated with significant morbidity and mortality. The incidence of acute renal failure (ARF) in CABG patients in the 1997 STS database was 3.14%, and 0.87% of these patients required dialysis.[78] Chertow[79] studied 43,642 Veterans Administration (VA) patients undergoing CABG or valve surgery. The overall risk of acute renal failure requiring dialysis was 1.1%. The mortality rate in this group was 63.7% versus 4.3% in patients without ARF. Decreased myocardial function and advanced atherosclerosis were independent risk factors for the development of dialysis-dependent renal failure.

Patients with preoperative renal dysfunction (serum creatine >1.5 mg/dL) have a higher incidence of stroke, bleeding complications, dialysis, prolonged mechanical ventilation, length of stay, and death.[80] Chertow found that preoperative renal function correlated with postoperative renal failure. The risk of ARF was 0.5, 0.8, 1.8, and 4.9% with baseline serum creatinine concentrations of less than 1, 1.0 to 1.4, 1.5 to 1.9, and 2.0 to 2.9 mg/dL, respectively. Chronic dialysis patients undergoing cardiac surgery have an 11.4% operative mortality rate, a 73% complication rate, and 32% 5-year actuarial survival rate.[81] Cardiac surgery following renal transplantation has an associated operative mortality rate of 8.8%.[82]

Patients with recent or long-standing hypertension should undergo renal angiography at the time of catheterization to assess renal artery stenosis, which, if significant, can be treated preoperatively in hope of improving postoperative renal function. To optimize preoperative renal function, contrast loads should be minimized, and patients should be well hydrated and receive renoprotective agents (e.g., *N*-acetylcysteine).[83]

Effects of CPB on Renal Function

Operative considerations include limiting the duration of CPB and maintaining mean arterial pressures at greater than 60 mm Hg.[84,85] Additional effects of CPB include trauma to the blood constituents, especially erythrocytes, with increased free hemoglobin levels and microparticle embolic insults to the kidneys. Hypothermia (during rewarming, vasodilatation and hyperemia of tissue beds result in third spacing of fluid), hemodilution (reduces viscosity of blood and plasma oncotic pressure), and ischemia-reperfusion injury can influence renal function; additionally, CPB leads to an increased release of catecholamines, hormones (e.g., rennin, aldosterone, angiotensin II, vasopressin, atrial natriuretic peptide, and urodilan[86]), and inflammatory cytokines (e.g., kallikrein and bradykinin) that also affect renal function adversely. These adverse stimuli cause decreased renal blood flow, a decreased glomerular filtration rate (GFR), and an increase in renal vascular resistance. Hypotension and pressor agents accentuate this response. Ultrafiltration is used in long pump runs to decrease volume overload in patients with renal dysfunction.

Independent of preoperative renal function, the primary postoperative goal is the maintenance of adequate renal perfusion pressure and a urine output greater than the 0.5 mL/kg per hour. Brisk diuresis (>200 to 300 mL/h) is common following CPB. Volume replacement and maintenance of adequate blood pressure and cardiac output are required for adequate renal perfusion. The best measure of kidney perfusion is adequate urine output independent of diuretics. Beyond optimizing hemodynamics and avoiding nephrotoxic medications, there is no convincing evidence that treatment with diuretics, mannitol, dopamine, fenoldapam, nesiritide, or any other agent is renoprotective. This is not to say, however, that these agents are of no benefit in promoting diuresis and avoiding renal replacement therapies in the event of renal dysfunction.

Electrolyte Disturbances

Calcium

Levels of ionized calcium (normal 1.1 to 1.3 mmol/L) are critical for myocardial performance and are involved in reperfusion injury. Hypocalcemia causes a prolonged QT interval. Hypocalcemia is common following CPB or an episode of hemodilution, sepsis, or citrated blood transfusions. The concentration of calcium ion is greatest in the intracellular space, with small amounts in the extracellular fluid (ECF). Calcium levels bound to albumin change with the levels of serum albumin, whereas ionized levels remain unchanged.[87]

Potassium

Potassium fluxes during cardiac surgery can be significant and may affect cardiac automaticity and conduction. Cardioplegia, decreased urine output, decreased insulin levels, and red blood cell (RBC) hemolysis all contribute to hyperkalemia.[88] Brisk diuresis, insulin, and alkalosis can cause hypokalemia.[89] Aggressive treatment of hypokalemia decreases the incidence

of perioperative arrhythmias. Serum potassium levels and replacement protocols are an integral part of the early postoperative management. Serum potassium rises logarithmically with replacement; larger quantities are required to treat significant hypokalemia.

Magnesium

Magnesium (normal 1.5 to 2 mEq/L) is the second most common intracellular cation after potassium. It is involved in endothelial cell homeostasis,[90] cardiac excitability, and muscle contraction through its role as an ATP cofactor and calcium antagonist; it is also closely involved in the regulation of intracellular potassium.[91] Following hemodilution and CPB, hypomagnesemia is common (>70% of patients) and is associated with an increased risk of atrial fibrillation and torsades de pointes.[92–94]

Endocrine Dysfunction

Diabetes mellitus

Up to 30% of patients have diabetes (type I or II) in the cardiac surgery population. Following CPB, the hormonal stress response (i.e., increased growth hormone, catecholamines, and cortisol) causes hyperglycemia (even in nondiabetics) with a decrease in insulin production; this may persist for up to 24 hours postoperatively and is exacerbated by exogenous catecholamine administration. Tight control of blood glucose levels with continuous insulin infusions has been shown to reduce the incidence of sternal wound infection by an order of magnitude.[95] Although a trial in critically ill ICU patients found a survival benefit in patients those blood sugars were kept below 110 mg/dL, only patients with an ICU length of stay greater than 3 days were shown to benefit, and hypoglycemia was shown to be an independent risk factor for mortality. It is not clear whether such aggressive control will benefit the majority of cardiac surgery patients. A recent study has shown an increase in stroke rate and mortality from intraoperative targets between 80 and 100 mg/dL.[96]

Adrenal dysfunction

The stress of cardiac surgery activates the hypothalamic-pituitary-adrenal (HPA) axis and increases plasma adrenocorticotropic hormone (ACTH) and cortisol levels. Subclinical adrenal insufficiency is present in up to 20% of the elderly population and can be unmasked by the stress of surgery. Any patient taking exogenous steroids within 6 months of surgery should receive stress-dose steroids perioperatively. Any patient exhibiting prolonged, unexplained vasodilatory shock should be suspected of having adrenal insufficiency. In a stressed patient, a low or normal cortisol plasma level can be assumed to be associated with adrenal insufficiency. In a stressed patient, a low or normal plasma cortisol leval can be assumed to be associated with adrenal insufficiency. A cosyntropin stimulation test can also be performed for diagnosis. In the interim, dexamethasone may be administered intravenously without interfering with the test.

RELEVANT POSTOPERATIVE COMPLICATIONS

Neurologic

Central nervous system

The incidence of *stroke* following cardiac surgery is procedure-specific and varies between 1 and 4%. Ricotta and colleagues[97] showed that associated carotid stenosis (>50%), redo heart surgery, valve surgery, and prior stroke are associated with an increased postoperative risk of stroke. John and colleagues[98] reviewed 19,224 patients in New York State. The stroke rate was 1.4% following CABG, with a 24.8% mortality rate in that group. Multivariable logistic regression identified the following predictors: calcified aorta, prior stroke, age, carotid artery disease, duration of CPB, renal failure, peripheral vascular disease, smoking, and diabetes. Intraoperative factors that may cause postoperative neurologic deficits include particulate macroembolization of air, debris, or thrombus[99]; microembolization of white blood cells, platelets, or fibrin[100]; duration of CPB[101]; cerebral hypoperfusion during nonpulsatile CPB; and hypothermic circulatory arrest.[102]

Up to 50% of cardiac surgery patients experience *delirium,* particularly those with preexisting organic mental disorders, significant prior alcohol consumption, advanced age, or intracranial cerebral artery disease.[107] Perioperative anesthetic and sedative administration are significant contributing factors. Causes of postoperative delirium in the cardiac intensive-care patient include sleep deprivation, renal failure, hepatic failure, and thyroid abnormalities. Electroencephalograms (EEGs) on these patients usually are abnormal, whereas in primary psychiatric diseases they are normal. Treatment involves correcting metabolic abnormalities, establishing a normal sleep-wake cycle, and minimizing medications likely to cause delirium.

Brachial plexus injury/peripheral nerve injury

Excessive *sternal retraction* during a median sternotomy may cause a brachial plexus injury because the first rib may impinge on the lower trunk and branches.[108,109] IMA harvesting also may cause damage to the brachial plexus.[110] *Malpositioning* of the upper limbs during surgery may result in a neurapraxia owing to compression of the ulnar nerve.[111] Palsy or plegia of dorsiflexion and eversion of the foot can be caused by common peroneal nerve stretch or compression at the level of the head of the fibula.[112] Saphenous neuropathy (i.e., sensory changes on the medial side of the calf to the great toe) following open vein graft harvesting (less so with endoscopic harvest) is also a potential complication secondary to the avulsion of pretibial or infrapatellar branches of the nerve.[113]

Gastrointestinal

Mesenteric ischemia following cardiac surgery is infrequent but usually catastrophic.[114,115] Risk factors include duration of bypass (i.e., hypoperfusion), use of pressor support (i.e.,

sympathetic vasoconstriction), use of the intra-aortic balloon pump (IABP) or other sources of atherosclerotic embolism, atrial fibrillation, peripheral vascular disease, and heparin-induced thrombocytopenia. Early surgical intervention (<6 hours) is associated with a 48% mortality rate, and this rises to 99% with delays (>6 hours) in surgical intervention. Gastrointestinal bleeding is common and can cause significant morbidity. The incidence of gastrointestinal bleeding can be reduced with the use of H_2 inhibitors, proton pump inhibitors, and sucralfate.[116] Other pertinent complications affecting the gastrointestinal system include pancreatitis (hyperamylasemia, 35 to 65% leads to 0.4 to 3% with overt pancreatitis)[117,118,119] acute acalculous cholecystitis (2 to 15% of all acute cholecystitis patients,[120] likely owing to hypoperfusion, narcotics, or parenteral nutrition that promote biliary stasis[121]), swallowing dysfunction or oropharyngeal dysphasia secondary to tracheal intubation or perioperative use of transesophageal echocardiography),[122] and small or large bowel ileus (i.e., Olgilvie's syndrome is associated with long-term ventilation).[123] Preoperative liver dysfunction (noncardiac cirrhosis) is associated with a high incidence of postoperative morbidity and mortality (Child class A cirrhosis: 20% morbidity, 0% mortality; Child class B cirrhosis: 80% morbidity, 100% mortality).[124] Although 20% of patients develop a transient hyperbilirubinemia, fewer than 1% have significant hepatocellular damage that progresses to chronic hepatitis or liver failure.[125]

Infections

Nosocomial infections

Between 10 and 20% of cardiac surgery patients develop a nosocomial infection. Infections may be related to the surgical wound, lung, urinary tract, invasive lines or devices, or the gastrointestinal tract. Prolonged mechanical ventilation is associated with nosocomial pneumonia. These are second only to urinary tract infection in frequency and carry the highest mortality rate.[126] Smokers and COPD patients are most likely to be colonized preoperatively and have a higher incidence of pneumonia (15.3% versus 3.6% in controls).[127]

Catheter-related infections (i.e., bladder and vascular-related) are common in the ICU. The most common pathogens are *Staphylococcus aureus* (12%), coagulase-negative staphylococci (11%), *Candida albicans* (11%), *Pseudomonas aeruginosa* (10%), and *Enterococcus* spp.[128,129]

Fever

Fevers are common in the ICU setting but are an insensitive indicator of postoperative bacteremia (3.2% incidence in 835 febrile CABG patients).[130] The yield of true-positive bacteremia ranges from 4 to 5%, with a contamination rate ranging from 32 to 47%.[131] Noninfectious causes of fever relative to cardiac surgery include myocardial infarction, postpericardiotomy syndrome, and drug fever. Infectious causes include wound infection, urinary tract infection, pneumonia, catheter sepsis, and loculated areas of contaminated blood accumulation (e.g., pericardial, pleural, retroperitoneal, and leg wound spaces).

Sepsis/septic shock

Septic shock following cardiac surgery can have devastating consequences. Pathophysiologic features of sepsis include systemic inflammation, coagulation changes, impaired fibrinolysis, and subsequent target-organ failure, with overall multiorgan failure, irreversible shock, and death (20 to 50%).[132,133] Mixed venous oxygen saturation can be abnormally high secondary to shunting and a failure to extract oxygen at the cellular level. In vasodilatory shock, the maintenance of end-organ tissue perfusion is critical; treatment includes aggressive fluid management and vasopressin.[134–137] Methylene blue (which inhibits NO synthesis)[138] has been used successfully in refractory hypotension. Bernard and colleagues[139] for the PROW/ESS study group showed a distinct survival advantage in the treatment of severe sepsis using drotrecogin alfa (activated) or recombinant human activated protein C (Zigris). The mechanism of action is a modulation of the systemic inflammatory, procoagulant, and fibrinolytic reaction to infection. In a randomized study of 1690 patients, the mortality rate was 30.8% in the placebo group versus 24.7% in the treatment group.

Wounds

DELAYED STERNAL CLOSURE/STERNAL INFECTION: Complicated operations with persistent bleeding and hemodynamic instability (owing to tissue edema) may preclude primary sternal closure. Delayed sternal closure allows hemodynamic stabilization and diuresis.[140] Anderson and colleagues[141] outlined the recent BWH experience; 1.7% (87 of 5177) open chests were managed with a hospital survival rate of 76%. Complications included deep sternal infection ($n = 4$), stroke ($n = 8$), and dialysis ($n = 13$). Multivariate analysis revealed mechanical ventricular assistance and reoperation for bleeding as independent predictors of in-hospital mortality.

SUPERFICIAL AND DEEP STERNAL WOUNDS: Superficial and deep sternal wound infections are significant complications of cardiac surgery. Deep sternal infection with associated mediastinitis occurs in 1 to 2% of cardiac operations, with a resulting mortality rate approaching 10%.[142] Common organisms are *Staphylococcus epidermidis*, *Staphylococcus* [including methicillin-resistant *S. aureus* (MRSA)], *Corynebacterium,* and enteric gram-negative bacilli.[143] Patients predisposed to sternal infections include those with significant comorbidities (e.g., obesity, diabetes, COPD, renal dysfunction, and low serum albumin), prolonged CPB, reoperations, diabetics with bilateral IMA harvests,[144,145] and patients with hyperglycemia.[146] Simple preoperative measures such as clipping of chest hair,[147] using Hibiclens washes,[148] administering adequate prophylactic antibiotics prior to skin incision, ensuring good intraoperative hemostasis without the use of bone wax,[149] and closure with subcuticular sutures and a topical adhesive (e.g., DERMABOND®) rather than

skin staples are helpful; additionally, tight glucose control during surgery and in the days following surgery results in a significantly lower sternal wound infection rate.[95]

Minor infections frequently respond to intravenous antibiotics, opening of the wound, and local wound care. Deeper infections require intravenous antibiotics (6 weeks); initial empirical therapy should consist of broad coverage against gram-positive cocci and gram-negative bacilli, with the regimen adjusted when cultures (i.e., blood or mediastinal or deep sternal wound drainage) have been speciated. The mainstay of treatment is surgical exploration and extensive débridement, which may require removal of the sternum with primary or secondary closure with muscle or an omental flap.[150] Postoperative vacuum-assisted closure (VAC)[151] of mediastinal wounds improves wound healing and reduces hospital length of stay.[152]

Nutrition

Preoperative debilitated or cachectic patients (i.e., more than 10% weight loss over 6 months) with albumin levels of less than 3.5 g/dL[153] are exceptionally prone to complications, such as infections, following surgery. There is no evidence to support a role for preoperative hyperalimentation.[154] Body mass index (a good nutritional index) of less than 15 kg/m^2 is associated with increased morbidity.[155] Postoperative patients have accelerated catabolic protein loss, usually requiring 25 to 40 kcal/kg per day. Advances in immunonutritional pharmacology (i.e., arginine, glutamine and *n*-3 fatty acids) in complex postoperative cardiac surgery patients may have a defined role in the future.[156–158]

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CHAPTER 17

Cardiopulmonary Resuscitation

Mark P. Anstadt • James E. Lowe

Cardiovascular disease remains the leading cause of death in the United States.[1,2] In 2002, 696,947 people died of heart disease, the majority attributed to coronary artery disease (CAD).[1] It is estimated that over 500,000 ST-elevation acute myocardial infarctions occur annually in the United States.[3] and ischemic heart disease accounts for the majority of sudden cardiac deaths.

Sudden cardiac death is the unexpected, nontraumatic, abrupt cessation of effective cardiac function associated with absent or acute symptoms of less than 1 hour.[4,5] Prodromes such as chest pain, palpitations, or fatigue may occur within the preceding 24 hours.[4] The majority of deaths occur suddenly, usually within 2 hours of the onset of symptoms.[1,2,6–8] Most victims die before reaching a hospital.[1,2] Although most sudden deaths in the United States result from CAD, other etiologies may be responsible.

Cardiopulmonary resuscitation (CPR) describes the emergency measures used to restore cardiovascular and respiratory function. Clinical interventions for treating cardiopulmonary arrest have been formulated in advanced cardiac life support (ACLS) guidelines.[19] The recommendations are based on scientific data established by the American Heart Association (AHA) and International Liaison Committee on Resuscitation.[9]

CPR and/or ACLS are performed in 1 to 2% of patients admitted to teaching hospitals (including approximately 30% of patients who die).[10,11] The goal is to achieve restoration of spontaneous circulation (ROSC), and ultimately, survival. Early defibrillation is the single most effective means for ROSC. When initial attempts fail, ROSC depends on improving myocardial perfusion and treating underlying disorders. Novel CPR techniques, mechanical circulatory support devices, antiarrhythmic agents, and therapeutic hypothermia can all play a role in these life-saving efforts. Overall survival rates remain low (Table 17-1),[12–14] and successful resuscitation frequently results in neurologic impairment.[15–17] Appropriate integration of rapid response, defibrillation, adjunctive devices, hypothermia, and pharmacologic agents has promise for improving resuscitation results.

TECHNIQUES IN CARDIOPULMONARY RESUSCITATION

Basic life support (BLS) defines the methods used to sustain ventilation and blood flow. BLS measures are recommended until ACLS can restore spontaneous circulation. Airway, breathing, circulation, and defibrillation (ABCD) algorithms describe standardized approaches to cardiac arrest (Fig. 17-1).[3]

Airway Management

Initial management of unresponsive patients is directed toward ensuring a patent airway.[19] The airway is opened using the head-tilt–chin-lift maneuver. The jaw-thrust technique is an alternative for suspected neck trauma; however, it is more difficult to perform.[20] Both relieve posterior displacement of the tongue, which is the most common cause of airway obstruction.[20–22] If signs of respiration are absent, rescue breathing is initiated. Difficult ventilation should be addressed by repositioning and considering foreign body obstruction. The Heimlich maneuver, or *subdiaphragmatic abdominal thrust,* is recommended for relieving obstruction from foreign bodies.[23] Rapid thrusts to the subxiphoid region dislodges a foreign body by increasing expiratory pressure.[24] This is repeated until ventilation is established. Chest thrusts are an alternative for obese patients and women in late stages of pregnancy. Magill forceps can be used to retrieve foreign bodies when necessary. Back blows are only recommended for pediatric patients.[24]

Masks and oral and nasal airways may be used with mouth-to-mask ventilation or bag-valve devices. Mouth-to-mask breathing more reliably provides adequate tidal volumes

Table 17–1.

Published Clinical Series in Which Cardiopulmonary Bypass was Utilized for Resuscitation of Patients Suffering Refractory Cardiac Arrest

Author	Hospital setting	No. treated	No. (%) ROSC	No. (%) survival	CPR duration (min) median (range) or mean +/– SD
Chen[195]	In	57	38 (67)	18 (32)	47+/–13
Conrad[200]	Voluntary registry	43	NR	9 (21)	NR
Kurose[202]	In	9	2 (22)	2 (22)	80 (35–130)
Mair[203]	ED	5 (cannulated 7)	4 (57)	3 (43)	20–60
Martin[196]	ED and witnessed Out	10 (cannulated 13)	6 (46)	0 (0)	32+/–13.6
Massetti[193]	In and Out	40	18 (45)	8 (20)	105+/–44
Raithel[204]	In	29	NR	6 (21)	NR
Rousou[205]	Cardiac surgical ICU	16	NR	9 (56)	Survivors: 50+–7 Deaths: 51+/–6
Schwarz[192]	In and Out	17 (cannulated 21)	9 (43)	3 (14)	NR
Silfvast[198]	Out, hypothermia	23	NR	14 (61)	67.25 (43.75–109)
Younger[194]	ED and In	21 (cannulated 25)	14 (57)	9 (36)	Survivors: 21+/–16 Deaths: 43+/–32

ED = emergency department; NR = not reported; ROSC = restoration of spontaneous circulation. Outcomes represented as percent of patients in which cannulation was attempted.

than bag-valve-mask respiration.[25–27] Bag-valve devices reduce exposure to potential infection, but require two rescuers.[9] Nasopharyngeal airways are considered for nonintubated patients. Oropharyngeal airways are only for unconscious patients; otherwise they add risk for laryngospasm and regurgitation.[9]

Endotracheal tube (ETT) intubation is the preferred method of airway management. Use of an ETT maintains an open airway, decreases risk of gastric distention and aspiration, and is an alternative drug administration route.[28] Orotracheal intubation is ideal unless a neck injury is suspected, in which case nasotracheal intubation is recommended. End-tidal CO_2 ($ETCO_2$) is an adjunct to confirm tube placement; esophageal intubation is likely with low $ETCO_2$.[29,30] ETT placement can be complicated by esophageal intubation, oral trauma, pharyngeal laceration, vocal cord injury, pharyngeal-esophageal perforation, main stem bronchus intubation, and aspiration.[31–33]

Transtracheal catheter (TTC) ventilation is instituted when routine methods fail. A catheter passed through the cricothyroid membrane attaches to a pressurized oxygen tank (30 to 60 lb/in^2), regulated by a triggered valve. Use of a TTC may provide suboptimal ventilation, leading to a respiratory acidosis.[34] Other problems include pneumothorax, hemorrhage, and esophageal perforation.[35] Cricothyroidotomy is considered when ETT ventilation is not possible.[36] Complications may include hemorrhage, esophageal perforation, and mediastinal and subcutaneous emphysema.[37] Tracheostomy is indicated when ventilation cannot otherwise be achieved.

Mouth-to-mouth ventilation is used in the absence of airway devices and generally results in alveolar partial oxygen pressure (P_{O_2}) of 80 mm Hg.[38] Respiratory rates of 10 to 12 per minute are recommended.[9] Cricoid pressure (Sellick maneuver), maintaining a patent airway, and slow breaths decrease risk for gastric distention, regurgitation, and aspiration.[27,37,39,40] Mouth-to-nose breathing is performed when the mouth-to-mouth is problematic.

Concern of transmissible diseases during resuscitation has reduced enthusiasm for CPR. Barrier devices (face shields and masks) have been developed to protect from exposure. Studies indicate minimal risk of hepatitis B virus, hepatitis C virus, or human immunodeficiency virus transmission during CPR.[41,42] Inadvertent exchange of blood with an

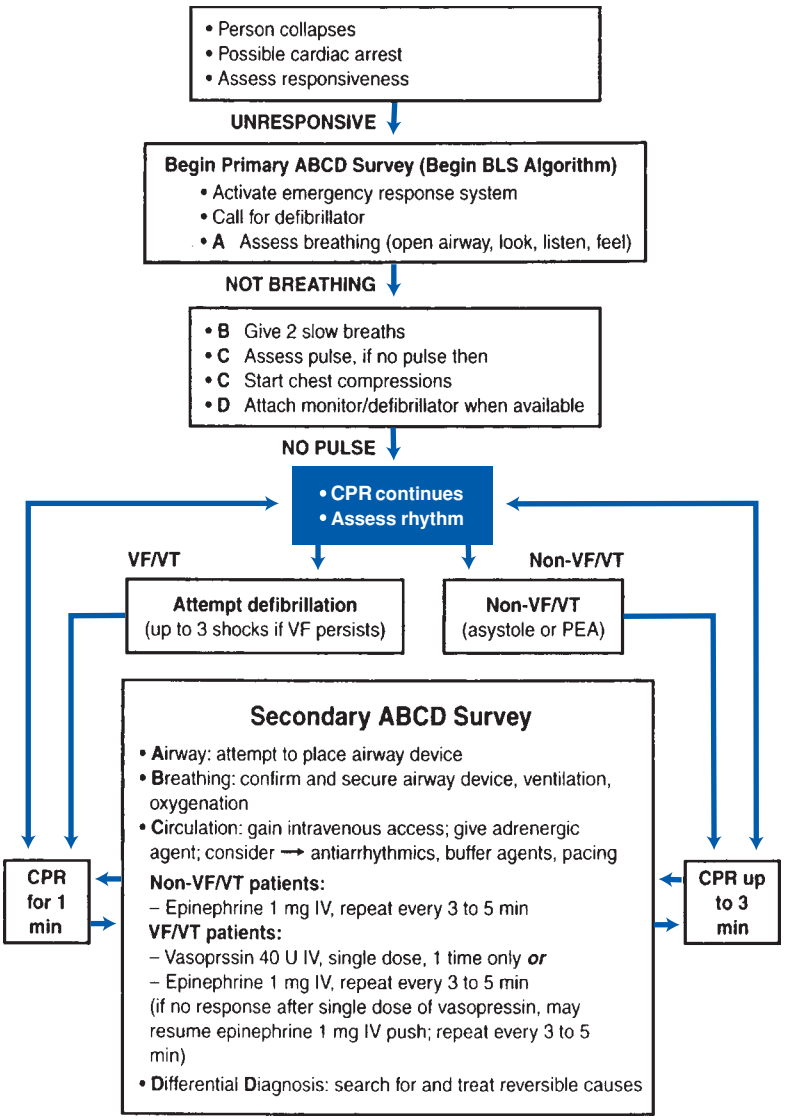

Figure 17-1. Universal treatment algorithm for adult emergency cardiac care. BLS = basic life support; CPR = cardiopulmonary resuscitation; VF/VT = ventricular fibrillation/ventricular tachycardia; PEA = pulseless electrical activity.

infected victim is always a risk.[43] Therefore, universal precautions should always be observed.[41] Rarely, herpes[44] and tuberculosis[19,45] have been transmitted. Chest compressions alone are better than no resuscitation attempt if one is reluctant to perform mouth ventilation. Chest compressions alone may result in survival rates comparable to CPR with ventilation.[46]

Closed Chest Cardiac Massage

Closed chest cardiac massage (CCM) is the principal means of restoring blood flow during CPR. CCM is performed with the victim supine on a firm surface (Fig. 17-2). Compressions are recommended over the lower sternum at 100/min. Compressions of 4 to 6 cm should occupy 50% of the cycle.[47] Complete release after compression allows ventricular filling, while light hand contact avoids repositioning between compressions.[9] In the best circumstances, CCM generates 25 to 30% of normal cardiac output.[48–51] Systolic blood pressure can range from 60 to 80 mm Hg; however, diastolic pressure is typically less than 20 mm Hg.[52] Organ perfusion is poor; cerebral flow is 10 to 15%[52] and coronary perfusion 1 to 5% of normal.[53–55] Clearly, CCM is a temporary means for providing flow to vital organs. In the absence of interventions (e.g., defibrillation), CCM is unable to sustain life and survival becomes unlikely. ROSC is exceedingly low with more than 30 minutes of CCM.

ROSC is dependent on proper CCM techniques. Recent studies examining CCM quality have demonstrated that CCM techniques are frequently suboptimal.[48,49] Inadequate compressions were observed in over $^1/_3$ of cases. Suboptimal compression rates have since been correlated with decreased ROSC.[50] Attention to detail deserves emphasis when performing life-sustaining methods.

Discontinuation of CPR remains controversial with no clearly defined criteria. Simply determining the adequacy of CCM can be quite subjective. Palpable pulses signify differences between systolic and diastolic pressures,[56] not forward flow. Venous pulse pressures may be similar.[57] Reactive pupils and/or spontaneous respirations indicate cerebral perfusion, but these are frequently absent and correlate

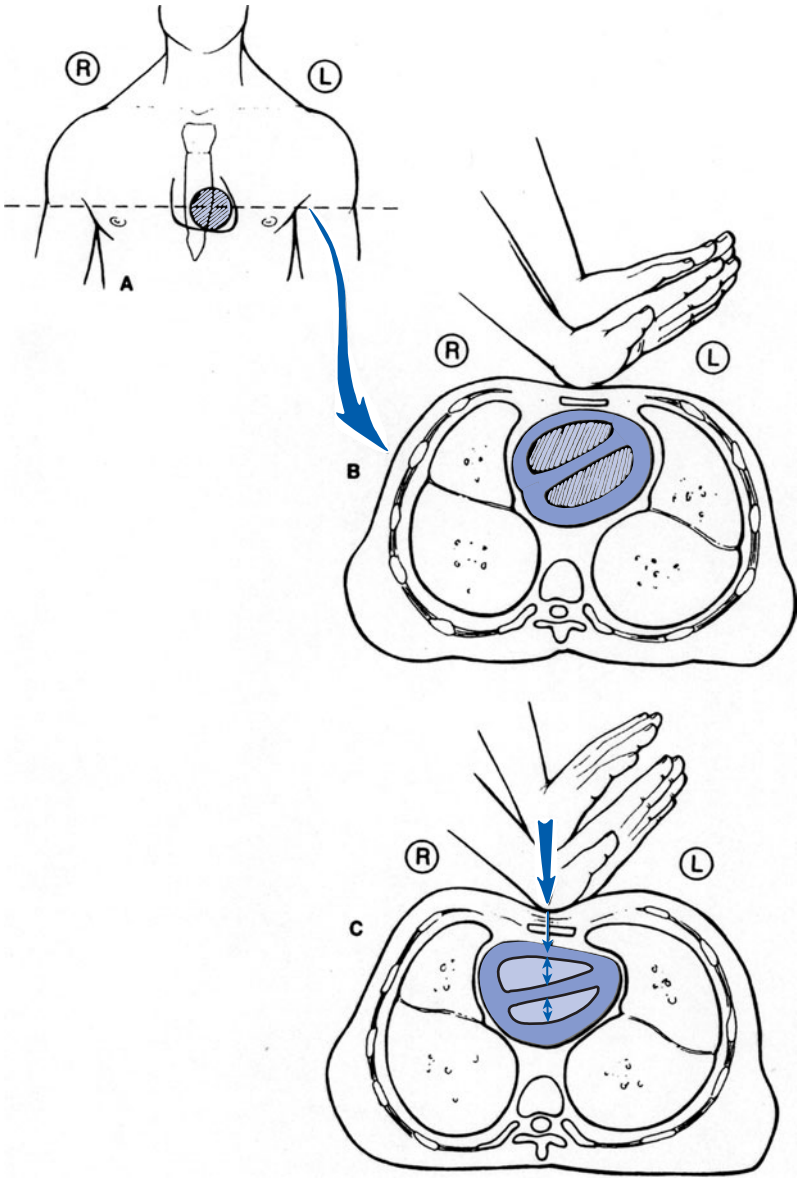

Figure 17-2. Cross-sectional view of closed cardiac massage. Compressions are delivered with high velocity and moderate force, resulting in cardiac compression.

poorly with outcome.[58] Aortic diastolic pressure is a measure of CPR's effectiveness[59] because it best correlates with coronary perfusion.[18] This measurement is usually not available.

Measuring $ETCO_2$ can provide useful information.[30,60,61] Low $ETCO_2$ suggests low blood flow, esophageal intubation, airway obstruction, massive pulmonary embolus, or hypothermia.[62] $ETCO_2$ can predict ROSC.[63,64]

Successful ROSC and survival are influenced by many factors. Ventricular fibrillation (VF), early defibrillation, rapid onset of CPR or ACLS, witnessed arrest, and younger age all have favorable implications.[82,230–232,234] These factors, proper CPR technique, and response are all considered before abandoning resuscitation.

Complications of CPR

Common complications associated with CPR are CCM rib and sternal fractures.[65] Others include aspiration, gastric dilatation, anterior mediastinal hemorrhage, epicardial hematoma, hemopericardium, myocardial contusion, pneumothorax, air embolus, hemothorax, lung contusion, and oral/dental injuries.[65–67] The liver and spleen are the most commonly injured intra-abdominal organs, reported in 1 to 2% of cases.[65] Rarely, significant injuries can involve the trachea, esophagus, stomach, cervical spine, vena cava, retroperitoneum, and myocardium.[65]

SUDDEN DEATH TREATMENT CONSIDERATIONS

Sudden death generally presents as ventricular fibrillation/tachycardia (VF/VT), asystole, or electromechanical dissociation (EMD), also called *pulseless electrical activity* (PEA). VF may continue after defibrillation attempts (*shock-resistant*) or persist despite other therapeutic interventions (*persistent*

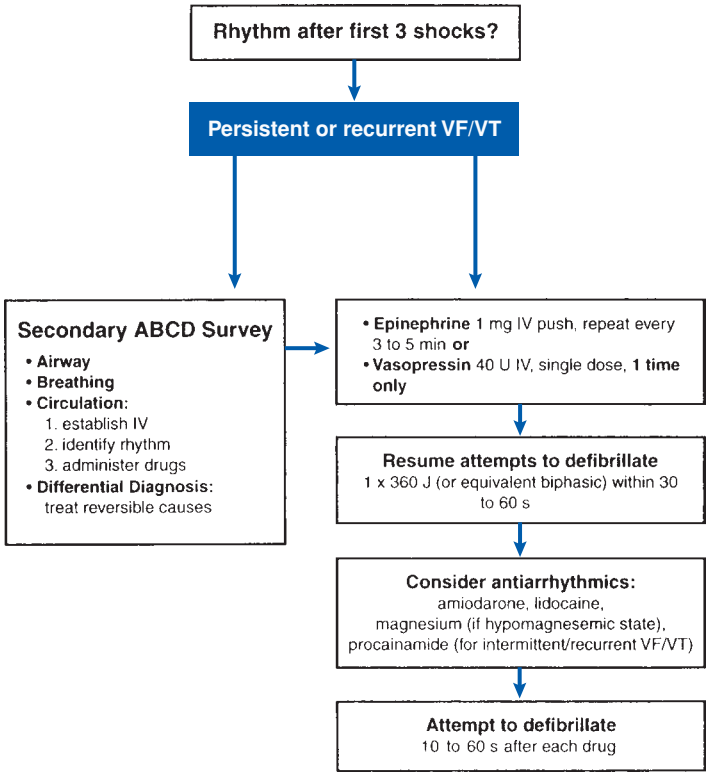

Figure 17-3. Treatment algorithm for persistent ventricular fibrillation and pulseless ventricular tachycardia (VF/VT).

or *refractory*). Also, successfully treated VF may recur (*recurrent*). These patterns are believed to have different etiologies, priorities of treatment, and prognoses. Early identification of the underlying rhythm is important for selecting the recommended treatment algorithm (see Fig. 17-1).

Ventricular Tachycardia

Ventricular tachycardia is an arrhythmia characterized by premature ventricular depolarizations (>100/min). Cardiac arrest occurs with rapid, sustained VT. VF is uncoordinated, continuous contraction of the ventricles. Over 80% of monitored cardiac arrests originate with VF/VT.[49,68] Most survivors have VF/VT as the initial rhythm.[69,70,82,232,233] Rapid defibrillation is the key determinant for survival[71–74,82] and should precede all other therapy if immediately available.[9,19] Delay negatively impacts successful defibrillation.[75,76] Mortality increases 4 to 10% for every minute preceding defibrillation attempts.[73,75,77] Survival rates approach zero when countershocks are attempted more than 10 to 12 minutes after arrest.[78] Current guidelines therefore emphasize early defibrillation and use of automated external defibrillation systems.[9]

Optimal treatment VF or pulseless VT begins with immediate defibrillation when possible. Energy for initial defibrillation is 200 J. Electrodes should remain in place between defibrillation attempts. If VF continues, a second shock (200 to 300 J) is given immediately. A third countershock (360 J) is given if the second fails. It is vital that three consecutive shocks are given without delay for other interventions. CPR is performed whenever defibrillation attempts fail. Figure 17-3 outlines treatment algorithms for persistent VF/VT. Epinephrine or vasopressin is given IV or via the endotracheal tube. Vasopressin should only be given once. Subsequent defibrillation attempts (360 J) may be stacked at this point. Epinephrine is given every 3 to 5 minutes. Refractory VF is treated with antiarrhythmics (see Fig. 17-3). Amiodarone may be the most efficacious in this setting.[12,79–81] Lidocaine is also acceptable for recurrent VF or pulseless VT; however, it is not recommended over amiodarone.[82] Magnesium and procainamide are recommended for recurrent VF/VT. Defibrillation should be attempted 30 to 60 seconds after administration of each drug.[9]

Prognosis for VF or pulseless VT is better than for asystole or PEA. Up to 30% of patients with witnessed VF/VT arrest are successfully resuscitated.[83,84,172,232,233] Early defibrillation conclusively improves survival in out-of-hospital arrests and increases when defibrillation is provided in the field.[71,72] Failure of initial defibrillation attempts is a poor prognostic sign. Underlying disorders, effective CPR, antiarrhythmic therapy, and further defibrillation attempts are considered before discontinuing CPR.[9]

Asystole is absence of electrical and mechanical cardiac activity and frequently indicates a terminal event. ACLS is indicated while other treatable causes are considered. Priorities (Fig. 17-4) include effective CPR and rhythm confirmation.[85] Low-amplitude VF may masquerade as asystole.[86] This scenario is rare in clinical practice.[87] Incorrect lead placement or equipment malfunction should be considered.[87] Confirming asystole is important, as countershocks do not benefit *true* asystole;[88,89] they induce parasympathetic

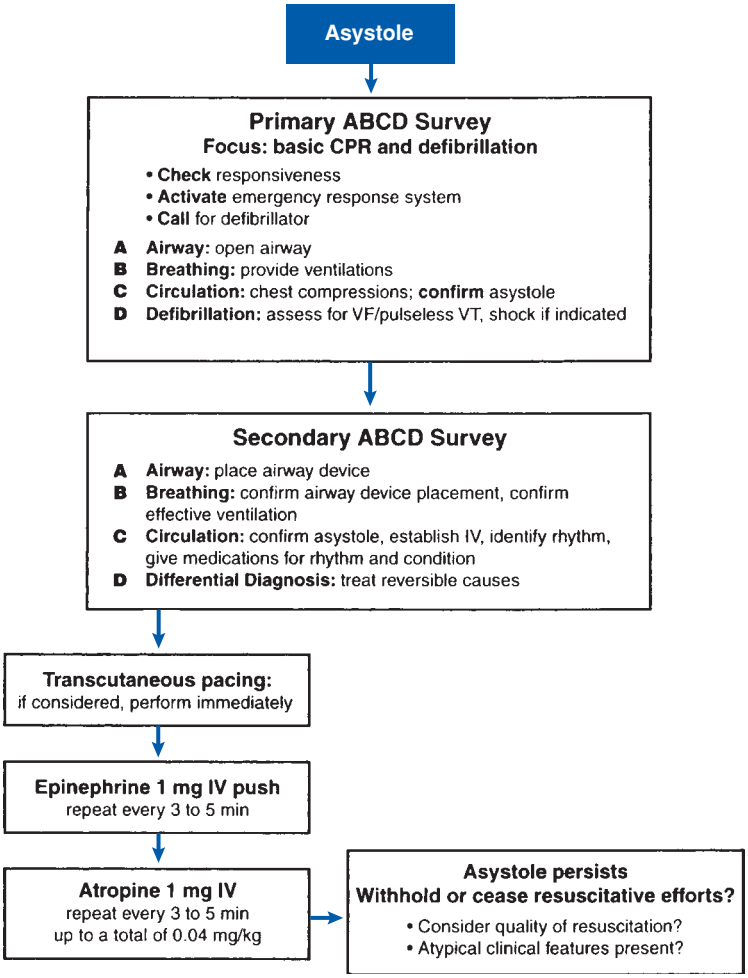

Figure 17-4. Treatment algorithm for asystole.

discharge and diminish chances of ROSC.[90,91] When VF is suspected, defibrillation should be attempted.

Once verified, asystole is managed by ABCD guidelines (see Fig. 17-4). Epinephrine raises perfusion pressures[9,92] and is repeated every 3 to 5 minutes. Atropine treats the high parasympathetic tone underlying severe brady-asystolic arrests.[90,91,93] Transcutaneous or transvenous pacing may be effective if applied early.[94] Timely pacing can result in successful capture and effective cardiac contraction.[95] Unfortunately, the prognosis of asystole remains grim. Less than 2% of patients survive.[96] Asystole following VF has a better prognosis than asystole after prolonged CPR.[97]

Pulseless electrical activity generally carries a very poor prognosis. Characterized by organized electrical activity without effective cardiac contractions, PEA is synonymous with EMD and includes pulseless idioventricular bradycardia, and ventricular escape rhythms.[9] These dysrhythmias have an extremely poor prognosis,[98,99] and are common proximate causes of death in delayed or difficult resuscitations.[85] As with asystole, PEA mandates assessment for reversible causes (Fig. 17-5). Rapid, narrow-complex activity increases the probability of treatable conditions.[85,100] Effective CPR and vasopressors are important for treatment.[99,101–103] Atropine is indicated for bradycardia.[9] Trauma is an indication for emergency left anterolateral thoracotomy[104] to address cardiac tamponade of cardiovascular injury. Thoracotomy allows cardiac massage and aortic occlusion, which may be life-saving. PEA following open heart surgery has a more favorable prognosis and chest reopening is recommended.[188]

Cardioversion is the *only* effective treatment for VF. Defibrillation depolarizes and results in temporary asystole;[91,105] pacemaker cells then restore myocardial activation. Myocardial contraction resumes if high-energy phosphates depleted by CPR[106] are sufficient.[107,108] The probability of successful defibrillation approaches 90% immediately following witnessed arrests.[106,109,110] Success rates decline rapidly, as ROSC decreases 7 to 10% every minute.[78] At best, CPR only slows the deteriorating state. Once available, a defibrillator should be positioned with quick-look paddles for rhythm evaluation. VF or pulseless VT is treated immediately. Blind defibrillation is rarely indicated. Asynchronous shocks are given for VF or pulseless VT. Synchronous shocks are given for stable rhythms (e.g., atrial fibrillation/flutter or monomorphic VT)[9] to avoid impinging on the relative refractory period.[111]

Energy levels for cardioversion impact success. Low currents may be ineffective and excessive energy levels cause

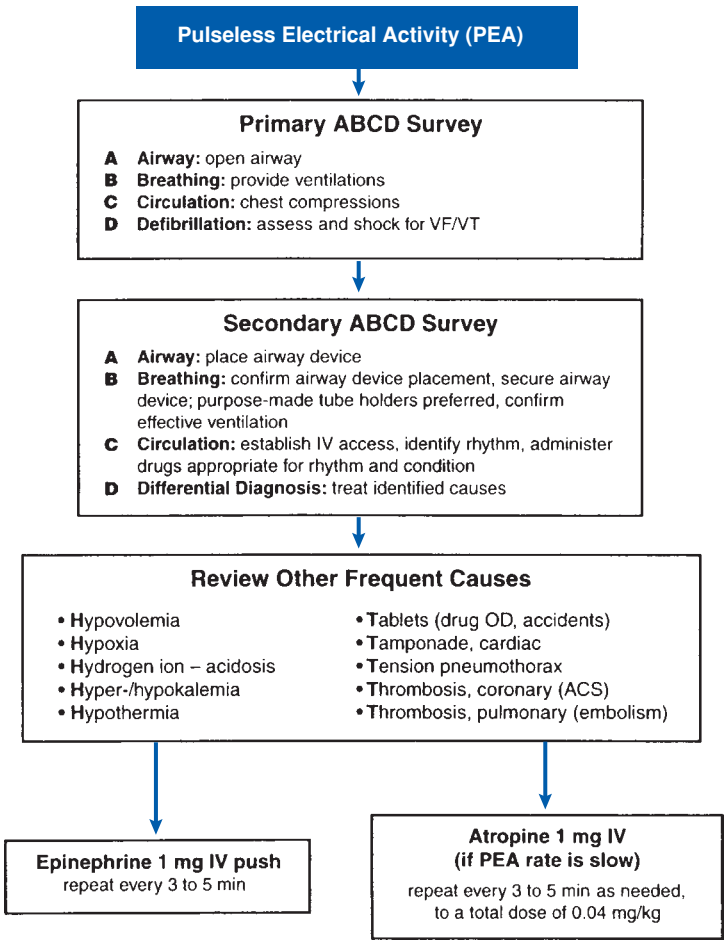

Figure 17-5. Treatment algorithm for pulseless electrical activity (PEA). ACS = acute coronary syndrome; OD = overdose.

myocardial injury.[112,113] The lowest energy that accomplishes defibrillation is desired. A prospective study demonstrated that 175 J and 320 J were equally effective for initial defibrillation attempts.[114] Therefore, 200 J is recommended for initial defibrillation attempts.[9] Most adults can be defibrillated with a 200-J shock delivered promptly.[115,116] The range for second countershocks is 200 to 300 J. Transthoracic impedance decreases with repetitive shocks, explaining why serial countershocks deliver greater energy to the heart.[117,118]

Body size impacts defibrillation energy requirements.[9] The optimal *current* for defibrillation is 30 to 40 A.[119–121] Adult transthoracic impedance is 70 to 80 gV, requiring a 200-J countershock for a 30-A current.[122] However, impedance varies significantly depending on energy delivery, chest size, electrode size, inter-electrode distance, paddle-skin coupling, respiration, and antecedent countershocks.[117-121,123,124] Therefore, the defibrillation techniques are critical. Electrodes are positioned to maximize current flow. Usually, one electrode is placed on the right parasternal border below the clavicle and the other in the left midaxillary line, level with the nipple.[9] Electrodes must not touch so current passes through the heart. During open chest resuscitation, one paddle is placed over the right ventricle, and the other behind the apex. Larger paddles are preferred for lower resistance;[117,124] small paddles should only be used if required to fit in the chest.[125] It is also noteworthy that compression of the heart reduces the defibrillation threshold.[133]

Defibrillation threshold (DFT) describes the amount of current required to defibrillate the heart. DFT increases during CPR and is primarily affected by coronary perfusion pressure. Catecholamines decrease the DFT.[126–128] It was thought that epinephrine decreased the DFT through beta-adrenergic effects; instead, this is due to alpha-adrenergic increases in systemic pressure.[129] Time-dependent increases in DFT observed during CPR are not completely understood. The etiology is not secondary to metabolic or respiratory acidosis.[130,131] Adenosine may act through A_1 receptors to increase DFT over time.[132] Aminophylline, an adenosine receptor antagonist, decreases DFTs.[134–136]

The presence of pacemakers and automatic internal cardiodefibrillators (AICDs) impact defibrillation management. Paddles should not be placed directly over pacemaker generators,[137] and these devices should be interrogated to reassess pacing thresholds after defibrillation. AICDs are not a contraindication to external defibrillation for VF/VT[138] and are shielded to withstand countershocks. AICD patches may increase transthoracic resistance.[139] Therefore, paddle orientation should be changed if initial countershocks fail. After defibrillation, the AICD unit should be tested.

Automated external defibrillators (AEDs) are increasingly common. AEDs analyze electrocardiographic patterns and sound an alarm and discharge when VF is detected. They require less training and are more rapid at administering countershocks.[78,140,141] AEDs have equivalent survival compared with manual defibrillators[142–144] and are endorsed by the AHA for out-of-hospital arrest.[145]

Current-controlled defibrillators may improve the success of defibrillation.[119,120,146] These devices enhance delivery of *appropriate* energy and reduce the risk of excessive energy delivery. Other developmental areas include delivery of biphasic (bidirectional) or multipulse, multipathway shocks.[122] These methods are in use for internal defibrillators, but their efficacy for external defibrillation has not been established.[147,148]

A precordial thump may achieve defibrillation and be used when a defibrillator is not immediately available. It may be successful in 11 to 25% during VT.[149,150] Unfortunately, precordial thumps may result in VF, asystole, or EMD,[150,151] and are less likely to convert VF.

Chest compressions must be temporarily discontinued to avoid electrical shock of those performing CPR. This "hands-off" interval is also used for rhythm analysis before defibrillation. Prolonging the hands-off period can significantly reduce the probability of successful cardioversion, and should be kept as short as possible.[151]

PHYSIOLOGY OF CARDIOPULMONARY RESUSCITATION

Mechanisms generating forward blood flow during CPR have been a subject of significant controversy. Kouwenhoven postulated that chest compressions translate directly to the heart.[152,153] This became known as the *cardiac pump*. Multiple laboratory and clinical investigations have verified this during closed-chest compression.[154–157] However, other mechanisms have been demonstrated.

At least two other mechanisms appear responsible for blood flow during CPR. The thoracic pump was discovered by observing that coughing during cardiac arrest generated forward flow. Chest compressions also cause a rise in thoracic pressures capable of forcing blood into the systemic circulation.[51] The heart in this circumstance merely functions as a conduit. Many studies have validated the thoracic pump mechanism during CPR.[48,158–160]

Another mechanism for blood flow generated during CPR is the abdominal pump. This emphasizes effects of abdominal compressions, which are now advocated for CPR.[161–164] The abdominal pump operates through arterial and venous components. The arterial component reflects compression of the abdominal aorta, forcing blood into the peripheral circulation. The aortic valve remains closed during abdominal compression and resists retrograde arterial flow. Simultaneously, the venous component fills the heart from venous pressure. Both contribute hemodynamic benefits during abdominal compressions in CPR.

Clearly, the cardiac, thoracic, and abdominal pump mechanisms are important concepts of CPR physiology. The technique(s) employed during CPR dictates which mechanism predominates. Other factors that can influence effectiveness of these pump mechanisms include: cycle rates, compression duration, body habitus, cardiac size, chest wall stiffness, and the presence of pulmonary disease, as well as the duration of the resuscitation effort. Understanding these mechanisms has led to improved CPR techniques and adjunctive devices.

CPR TECHNIQUES AND MECHANICAL ADJUNCTS

High mortality rates associated with cardiac arrest have led to investigators exploring several new techniques for performing CPR. Adjunctive devices to better facilitate performance of such new techniques have also been developed.

Active compression-decompression (ACD) is a promising means for improving CPR. Originating from successful resuscitation with a plunger, a device consisting of a handheld suction cup with a central piston and handle has been developed (Fig. 17-6). ACD-CPR can increase aortic pressures resulting in improved cerebral, coronary, and renal blood flow.[176] Ventricular filling and venous return are augmented by negative intrathoracic pressure during the active decompression phase.[177] Two initial studies reported increased ROSC and 24-hour survival with the ACD device. Survival to discharge was higher with ACD in both studies but did not reach statistical significance.[178,179] Data from 2866 patients using the ACD device were subsequently combined.[180] ACD improved 1-hour survival but long-term outcome was not significantly different from standard CPR. A randomized clinical trial demonstrated significantly improved 1-year survival following ACD compared to standard CPR.[181] Most recently, a prospective trial found that the ACD combined with controlled ventilation using an inspiratory impedance threshold device improved short-term survival when compared to standard CPR.[173]

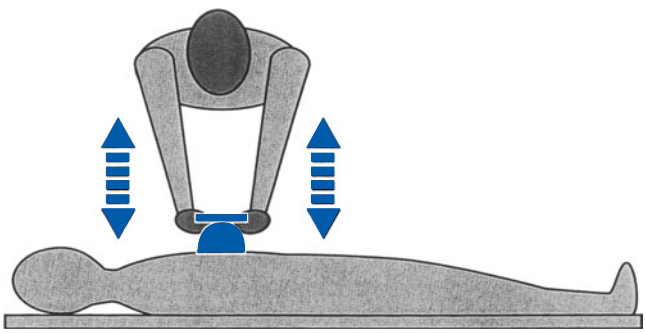

Figure 17-6. Active compression-decompression cardiopulmonary resuscitation (ACD-CPR) using a suction cup device attached to chest wall.

Combining chest and abdominal pumping techniques within the same compression cycle is another means for improving the effectiveness of CPR. The method has been termed *interposed abdominal compression* CPR (IAC-CPR). The technique employs chest compressions with abdominal compression during the relaxation phase of chest compression. The simplest application involves compressing the chest and abdomen at equal durations and is not associated with intra-abdominal injuries or aspiration. Initial clinical studies using IAC-CPR yielded encouraging results with significant improvement in outcome measures.[168] Return of spontaneous circulation and survival to discharge were both improved using IAC-CPR when examining inpatient cardiac arrests.[166,168,169] A hand-held device that allows IAC-CPR combined with compression-decompression mechanics has been developed for single-rescuer use (Fig. 17-7). The "Lifestick" was deemed safe and effective by the investigators.[172] Further studies will determine if this adjunct for manual CPR can favorably impact survival rates.

Noninvasive mechanical devices have been developed to enhance the effectiveness of CPR. These devices not only improve noninvasive CPR performance but also eliminate operator fatigue associated with the physical demands of performing CPR.

Fatigue becomes a particularly significant problem when attempting to perform ACD-CPR for extended periods of time. This has led to the development of an automatic chest compression device termed "LUCAS." Clinical applications using LUCAS have found it feasible for out-of-hospital CPR.[174] Preliminary trials indicate that the device may improve the 30-day survival of patients suffering witnessed cardiac arrest.[175]

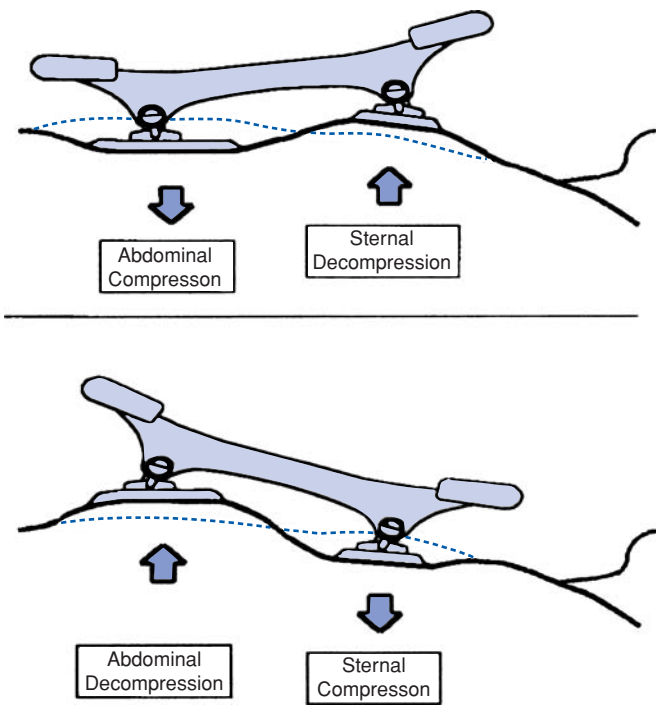

Figure 17-7. The Lifestick is designed to performed abdominal and sternal compression-decompression in a seesaw-like fashion. (*Reproduced with permission from Arntz HR et al: Phased chest and abdominal compression-decompression versus conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest. Circulation 2001; 104:768.*)

The pneumatic vest is another noninvasive mechanical device that alternates pressures around the thoracic cage (Vest-CPR). Vest-CPR utilizes a pneumatic bladder tailored to fit the chest wall. Air is forced into and out of the vest by a pneumatic drive. Clinical trials demonstrated improved outcomes with an increased rate of ROSC.[170] However, energy consumption and portability of the inflation system have made further clinical use impractical. An improved circumferential chest compression device has been developed that uses a pneumatically actuated constricting band.[171] Further trials are required to determine the feasibility of compression devices for clinical use.

Open chest cardiac massage (OCM) is an invasive resuscitative method which is more effective at returning blood flow during cardiac arrest. OCM was relatively common prior to 1960.[182] OCM is now only advocated for specific circumstances such as cardiac arrest from penetrating thoracic trauma. OCM should also be considered for cardiac arrest due to hypothermia, massive pulmonary embolism, pericardial tamponade, intrathoracic hemorrhage, and chest deformity precluding effective CPR. OCM is usually performed via a left lateral thoracotomy except following recent cardiac surgery, for which the prior sternotomy is re-entered. Thoracotomy is performed through the fifth intercostal space and the pericardium opened anterior to the phrenic nerve. The heart is compressed between both hands, or alternatively, with one hand while the other is used to occlude the thoracic aorta (Fig. 17-8).

Numerous studies have demonstrated superior hemodynamics during OCM compared to CCM.[56,183–187] Most notable are increased diastolic pressures and reduced central venous pressures,[56,185,188] which illustrate the favorable impact on coronary perfusion during OCM versus CCM. Cardiac output and cerebral blood flow are higher during OCM,[186,187] explaining successful ROSC when OCM follows failed resuscitative efforts with CCM. However, clinical outcomes are generally not improved when OCM follows prolonged CPR efforts.[189] Animal studies have suggested that OCM may improve results if applied early after a short period of ineffective CCM. A recent prospective, nonrandomized clinical trial illustrated the importance of instituting OCM earlier to improve outcome.[190] Patients receiving OCM had improved outcome which declined as the period of CCM prior to instituting OCM increased.

Early application of OCM may improve survival if downtimes prior to thoracotomy are minimized to reduce neurologic impairment. One setting in which OCM has been used routinely is in the postcardiotomy ICU. A recent review strongly confirmed the benefit of open chest massage in patients suffering cardiac arrest following open-heart surgery.[188] The study suggests that reopening the chest in this

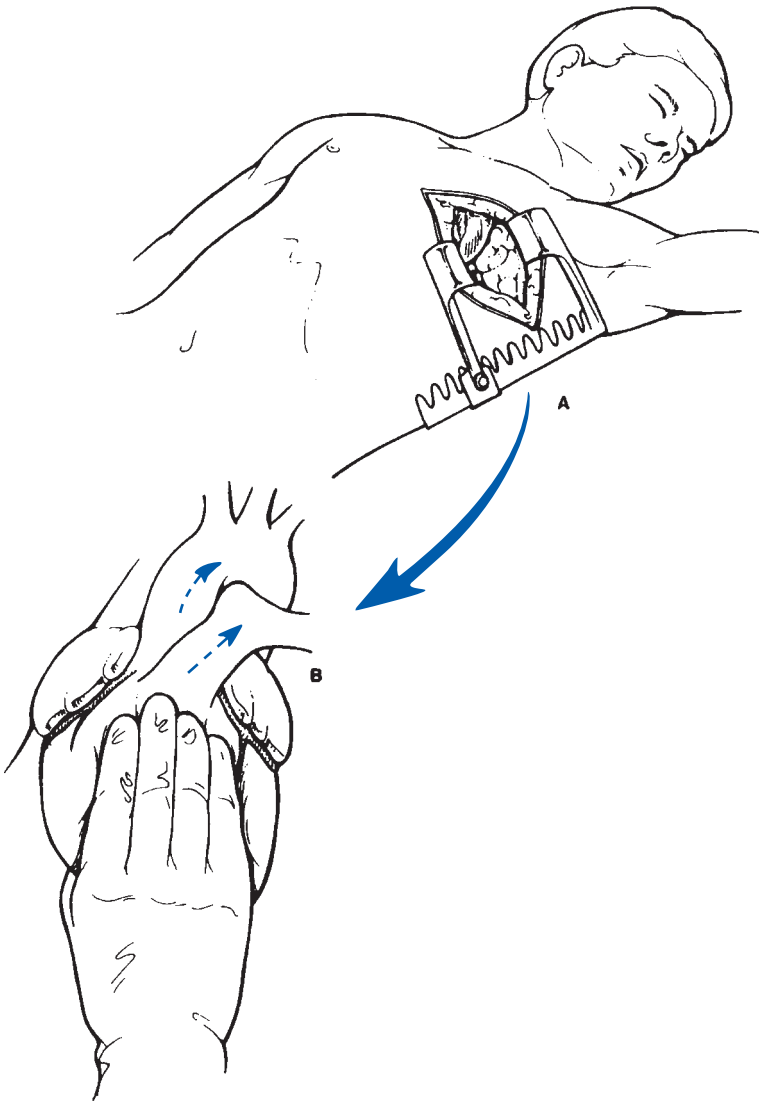

Figure 17-8. Technique of open chest cardiac massage. (*A*) The heart is exposed via an anterolateral thoracotomy through the fifth intercostal space. The pericardium is opened if there is evidence of pericardial tamponade; otherwise it is left intact. (*B*) The heart is massaged at a rate of 60 to 80 beats per minute.

setting has the greatest potential benefit in patients arresting within 24 hours of surgery and when performed within 10 minutes of cardiac arrest.

Potential complications of OCM include right ventricular perforation, hemorrhage, lung laceration, phrenic nerve injury, esophageal and aortic injury, cardiac lacerations, and empyema. Infection is surprisingly low (5%) given the nature of the procedure and related limitations on sterile technique.

The intra-aortic balloon pump improves hemodynamics during CPR; however, its value in this setting appears limited.

Cardiopulmonary bypass (CPB) can be used for treating cardiac arrest refractory to CPR. Hemodynamics, survival, and neurologic function improved in experimental models of cardiac arrest treated with CPB versus standard CCM. However, availability of emergency CPB is generally limited to tertiary care centers. A number of institutions have utilized CPB to bridge patients to transplantation following cardiac arrest.[192,193,196] Development of newer portable CPB systems has made the technology more attractive; CPB has been reported in a number of centers for treating cardiac arrest.[191–205] Cardiac arrest is a category for CPB in the registry for extracorporeal membrane oxygenation.[200] Multiple clinical series have demonstrated improved outcomes when CPB was utilized to treat refractory cardiac arrest (see Table 17-1). Survival was over 20% in most reported series. Identified prognostic factors include age, treatable conditions, and timely intervention. Generally, CPB should be instituted within 30 to 45 minutes of witnessed arrests, but survival after more extended periods of CCM has been documented.[193,195] Clearly, CPB can result in successful resuscitation following prolonged periods of CPR in pediatric cases[191,199] and hypothermic cardiac arrests.

Hypothermic cardiac arrest is a unique category in which survival can follow prolonged cardiac arrest. Here CPB is the method of choice because of its unique ability to rewarm the patient while providing resuscitative circulatory

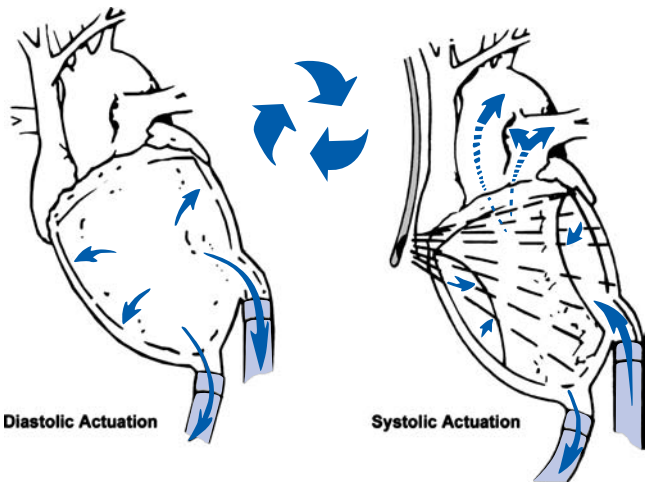

Figure 17-9. Direct mechanical ventricular actuation (DMVA). The ventricles are encompassed by a pneumatically driven device that is vacuum-attached to the arrested heart. Echocardiography allows assessment of device performance.

support.[165,167] The largest experience in adults treated for hypothermia was in Finland.[198] Findings demonstrated that age and arterial pH at the time of presentation had significant prognostic implications. The duration of CPR did not impact the likelihood of survival.

Direct mechanical ventricular actuation (DMVA) is a unique device that provides systolic and diastolic actuation of the ventricular myocardium without contact with the blood (Fig. 17-9). DMVA is pneumatically regulated with an atraumatic vacuum attachment. Rapid application is performed within minutes through a thoracotomy or sternotomy which results in physiologic, pulsatile blood flow.[206–210] Pulsatile reperfusion probably best explains the improved neurologic outcome following resuscitative circulatory support using DMVA versus CPB in animals.[222–224] Lack of blood contact also circumvents the need for anticoagulants and reduces thromboembolic complications. DMVA has been used successfully in humans for bridge to transplantation, postcardiotomy support, and recovery from severe myocarditis.[209,210] Further evaluations are currently aimed at supporting the acutely failing heart.[208] Recent improvements in drive control integrated with performance feedback from echo interrogation are anticipated to provide a more user-friendly device for resuscitative circulatory support.

PHARMACOLOGIC THERAPY DURING CPR

Peripheral venous access is preferred for speed, safety, and avoiding CPR interruption. Drugs take 1 to 2 minutes to reach the central circulation during CPR. Administration should be by bolus followed by flushes and extremity elevation. Peak drug concentrations are lower with peripheral versus central injection. Central access should be considered if responses to peripheral administration are absent. Internal jugular and supraclavicular sites are preferred to the femoral because return to the inferior vena cava is impaired during CPR. Long femoral lines overcome this problem. Routine fluid administration is not indicated without evidence of hypovolemia, as this may adversely affect coronary perfusion pressure by raising right atrial pressure.

When venous access is not possible, drugs may be administered via an endotracheal tube. Medications are given via a catheter passed beyond the tube's tip using twice the IV dose diluted in saline or water. Water provides better absorption but more adversely affects Pa_{O_2}. Rapid insufflations are given after each bolus for drug dispersion. Intracardiac injection is not recommended routinely during CPR. It may be used for epinephrine during OCM or if no other access is obtainable. Intracardiac injection results in high complication rates including cardiac injury, tamponade, and pneumothorax.

The principal agents recommended for ACLS are adrenergic agonists and antiarrhythmics. Alpha-adrenergic agonists have been the only drugs that definitively improved outcome in CPR. Their primary benefit is vasoconstriction. Increased peripheral resistance results in elevated aortic pressure, improving coronary perfusion. Epinephrine is given for this purpose.[129] Epinephrine's beta-adrenergic effect has not shown clear benefit in treating cardiac arrest. One milligram is recommended every 3 to 5 minutes during resuscitation attempts.[9] Epinephrine improves ROSC and survival in animal models of cardiac arrest. The minimum coronary perfusion pressure and blood flow needed for successful defibrillation are 15 mm Hg and 15 to 20 mL/min/100 g, respectively.[52,85] CPR rarely achieves these minimums without pressors. Reports using higher epinephrine doses generated enthusiasm. Subsequent clinical trials reported higher rates of ROSC, but no survival benefit.[211–212] One trial found that high-dose epinephrine had more adverse effects, which may be partly explained by increased oxygen demands.

Other nonadrenergic vasoconstrictive agents have been studied as alternatives to epinephrine. Vasopressin acts on unique receptors and may be beneficial for treating cardiac arrest refractory to epinephrine. Laboratory and clinical data indicate that vasopressin may be preferable to epinephrine.[213,214] A recent meta-analysis of five randomized clinical trials comparing vasopressin to epinephrine during cardiac arrest[216] found no evidence to support the use of one drug over the other. Though epinephrine is less expensive, vasopressin continues to be an acceptable alternative for treating cardiac arrest.

Vasopressin also mediates adrenocorticotropin release during CPR.[219] The hypothalamic-pituitary-adrenal axis is suppressed in cardiac arrest victims,[217–219] and low serum cortisol levels have been identified as a poor prognostic factor for ROSC.[217,218] Adrenal function in patients who have ROSC may also be insufficient for survival.[220] Further clinical trials are needed to determine if administration of

corticosteroids during CPR and/or following ROSC may benefit outcome.

The effectiveness of antiarrhythmics in sudden death has not been well substantiated. Recent randomized clinical trials have demonstrated amiodarone's effectiveness in treating cardiac arrest.[12,80,81,215] Amiodarone significantly improved survival to hospital admission compared to placebo for VF/VT.[215] In a more recent randomized clinical trial, amiodarone significantly increased survival to hospital admission compared to lidocaine when used to treat sudden death.[12] Improved survival to discharge with amiodarone did not reach statistical significance. Amiodarone is recommended for the treatment of persistent VT and/or VF. Lidocaine is an acceptable alternative.

Procainamide is recommended for recurrent VF/VT. Rapid infusion can cause hypotension. Procainamide is of little benefit *during* cardiac arrest and may worsen ventricular arrhythmias in the setting of hypokalemia and/or hypomagnesemia.

Magnesium sulfate should be administered for suspected hypomagnesemia or torsades de pointes. It is recommended for refractory VF/VT. Hypomagnesemia is associated with ventricular arrhythmias and sudden cardiac death and may hinder potassium replenishment in hypokalemic patients. Hypermagnesemia can cause flaccid paralysis and cardiorespiratory arrest.

Atropine enhances atrioventricular node conduction and sinus node automaticity. It is indicated for symptomatic bradycardia and asystolic arrest.[90,91,93] Asystole from prolonged ischemia is usually fatal. Atropine is unlikely to benefit, but is not harmful in such circumstances.[97] Adverse effects include tachycardia and anticholinergic effects.

Sodium bicarbonate is recommended for acidosis during cardiac arrest. Administration increases CO_2 which is eliminated by respiration. During CPR, CO_2 may accumulate rapidly, leading to a hypercarbic venous acidemia. Since CO_2 is diffusible across membranes, paradoxical intracellular acidosis may result and decrease the likelihood of successful resuscitation. Hypocarbic arterial alkalemia or the so-called venoarterial paradox may develop. Therefore, sodium bicarbonate may increase CO_2 levels, worsen the venoarterial paradox, and exacerbate intracellular acidosis. Other potential adverse effects include alkalemia with leftward shifts in the oxyhemoglobin desaturation curve, hyperosmolality, hypernatremia, and hypotension. Sodium bicarbonate has not been shown to improve results in cardiac arrest and is only recommended for acidosis, hyperkalemia, tricyclic antidepressant overdose, or prolonged CPR.[19]

CEREBRAL PROTECTION AND RESUSCITATION

The principal goal of CPR is to provide sufficient blood flow to prevent irreversible organ damage while awaiting definitive intervention. Unfortunately, *less than 10% of CPR* victims survive without neurologic damage.[221]

During cardiac arrest, consciousness is lost within seconds. High-energy phosphates and glycogen stores are depleted in minutes. Lactic acid accumulates which has direct cytotoxic effects. Limited cerebral flow may exacerbate intracellular acidosis by allowing anaerobic metabolism. Survival with normal neurologic function declines in minutes and ROSC after 5 minutes is associated with variable degrees of neurologic damage. Laboratory investigations using mechanical support have demonstrated that pulsatile flow is beneficial compared to nonpulsatile flow in the initial reperfusion period. Pulsatile reperfusion resulted in favorable flow to the gray matter[222] which correlated with increased postresuscitation cerebral high-energy phosphate content.[223] Cerebral function and histopathology significantly improved following pulsatile versus nonpulsatile reperfusion in a canine model of cardiac arrest.[224,225]

Mechanical circulatory support is advocated for resuscitation because CCM generates limited blood flow. During CPR, only venous valves can prevent transmission of high intrathoracic pressures to the jugular venous system. Cerebral blood flow is kept at 50 mL/min/100 g by autoregulation when cerebral perfusion pressures are in the normal physiologic range.[221] CPR results in low cerebral perfusion pressures, seldom exceeding 40 mm Hg.[18,52] Cerebral flow is only 10 to 15% of normal,[185] which may be more harmful than no flow at all.

Effects of cerebral reperfusion may be as important as ischemia itself because neurons function up to 60 minutes during ischemia. Reperfusion injury appears to be multifactorial. Calcium overload in mitochondria, free-radical injury, and the no-reflow phenomenon may all contribute to reperfusion injury.[221] The no-reflow phenomenon describes continued hypoperfusion that may last up to 3 hours. Platelet aggregation, altered calcium flux, vasoconstriction, and pericapillary edema are all presumed causative factors. Intracranial pressure may not be as important because it usually returns to normal soon after cardiac arrest. Cerebral blood flow remains depressed for 18 to 24 hours following a severe ischemic insult. Subsequent periods of hypoperfusion are believed to be secondary to calcium-induced precapillary vasoconstriction.

Abnormal cerebral blood flow following ischemic injury is more dependent on perfusion pressure. Moderate hypotension can lead to further cerebral ischemia and injury. Blood pressure should be normal to mildly elevated in the postresuscitation period. Moderate hyperoxia (P_{O_2} of 100 mm Hg) and mild hyperventilation (partial arterial pressure of carbon dioxide of 30 to 35 mm Hg) are desirable. Arterial pH is kept in the normal range. Anticonvulsants should be given as needed, as seizures occur in up to 30% of patients.

Mild hypothermia is proven effective for cerebral resuscitation. Animal experiments demonstrated improved neurologic function with active cooling following arrest. Clinical trials have subsequently shown cooling following ROSC improves neurologic outcome. More recent randomized

clinical trials found that mild therapeutic hypothermia improves neurologic outcome and survival in patients with ROSC.[226] And, patients who suffer coma following ROSC appear to benefit from therapeutic hypothermia.[227] These findings have led to new AHA recommendations for therapeutic hypothermia.[235]

Other considerations after ROSC include continuous hemodynamic monitoring, and use of supplemental oxygen. Antiarrhythmics are continued, as arrhythmias commonly occur due to increased circulating catecholamines. Beta-adrenergic blockade should be instituted unless bradycardia is a problem. Bradycardia requires that the airway and ventilation be carefully assessed. Atropine, epinephrine, and/or pacing are indicated if hypotension accompanies bradyarrhythmias.

Antiarrhythmics, pacemakers, and automatic internal cardiodefibrillators are also important considerations for patients surviving sudden death. Clinical studies have shown survival can be significantly improved with these interventions.[146,228,229] Amiodarone has also been shown to be effective in this regard.

Predicting which patients survive resuscitation efforts remains elusive. Patients presenting in VF/VT have a better prognosis compared with asystole or PEA.[10,232,233] Advanced age may not be a prognostic indicator when considering other comorbidities.[10,11,233,234] Location of the arrest (ICU versus non-ICU) also impacts outcome.[10,11] Comorbid conditions are associated with more than 95% of mortalities after cardiac arrest including renal failure, metastatic cancer, pneumonia, sepsis, hypotension, stroke, and home-bound lifestyle.[10] Survival is more likely for witnessed arrests, CPR initiated within 5 minutes, and CPR durations of 15 minutes or less. Mortality increases from 44% for CPR less than 15 minutes to 95% for CPR that is longer in duration.[10,234]

In contrast to inpatients, in whom comorbidities play a major role, delayed therapy outweighs all other prognostic factors for out-of-hospital arrests. Other key determinants for survival include the initial rhythm, witnessed arrest, downtime prior to CPR, and any delay in treatment. Survival rates are highly variable, ranging from 20 to 25% following relatively short down times. Early definitive care is also associated with improved outcome. As with in-hospital arrest, VF/VT has the best prognosis and bystander CPR has repeatedly been associated with improved survival rates.[235] In addition, several studies found less neurologic morbidity in cardiac arrest victims who received bystander CPR. The decrease in mortality from bystander CPR is primarily due to reduced postresuscitation anoxic encephalopathy. Return of consciousness within 24 to 48 hours of arrest is a favorable prognostic sign.[10]

Long-term survival in patients discharged after out-of-hospital arrest is reasonably good. The reported 1-year survival rate ranges from 75 to 85%, and approximately 50% are still alive at 4 years (Table 17-2). The majority of these patients ultimately die of cardiac causes.[16,236] Positive predictors for long-term survival are cardiac arrest associated with acute myocardial infarction; no prior history of myocardial infarction; and short time intervals between arrest, CPR, and definitive care.[237] Primary antiarrhythmic events, congestive heart failure, impaired left ventricular function, extensive CAD, and complex premature ventricular depolarizations are less likely to result in long-term survival after discharge.

Unfortunately, not all patients who survive sudden death have a subsequent good quality of life.[242] Depression is a common problem following discharge but usually resolves within a few months.[10] The rate of significant mental impairment in those who survive is variable. Significant neurologic impairment usually results in death prior to hospital discharge. While neurologic deficits are a significant problem,[238] many survivors of sudden death enjoy normal neurologic function (see Table 17-2).

ETHICAL CONSIDERATIONS

Resuscitation efforts should be discontinued when ACLS efforts do not result in ROSC. Discontinuation is based on clinical judgment. Although several studies show that CPR for longer than 30 minutes is unlikely to result in long-term survival, there are many anecdotal reports of neurologically intact survival following prolonged resuscitations.[10] Determination of medical futility is relevant when the patient has a significant underlying medical condition; metastatic cancer and sepsis are examples of such conditions.

CONCLUSION

Early defibrillation, effective BLS, and timely ACLS measures remain the mainstay for ROSC and survival following cardiac arrest. Unfortunately, survival rates remain dismally low. Use of adjunctive methods may improve reperfusion in select patients when initial ACLS efforts fail. Application of CPB for hypothermic cardiac arrest is an example of how devices can favorably impact select patients. Recommended use of CPB and other adjunctive devices for refractory cardiac arrest should be considered.

Combining rapid response, automatic defibrillators, optimal pharmacologic support, therapeutic hypothermia, and selected use of circulatory support devices can further strengthen the "chain of survival" promoted by the AHA.[19] Improvements in survival and neurologic outcome demonstrated by therapeutic hypothermia have led to new additions in AHA guidelines.[235] Integrating such therapy in appropriately selected patients deserves careful attention.

Timely implementation of any indicated therapy will be critical for improving outcomes in cardiopulmonary resuscitation. Identifying patients at risk for sudden death will provide additional opportunity for preventive measures (AICDs and antiarrhythmics). Well-designed clinical trials remain the best means to direct these treatment strategies.

Table 17–2.

Published Reports of Clinical Outcomes Following Cardiac Arrest

			Hospital discharge		Long-term survival (%)									CPC neurologic outcomes (%)					
Author	Rhythm	No. cases	No.	(%)	30 Days	3 Mos	6 Mos	8 Mos	1 Year	2 Years	3 Years	4 Years	5 Years	1) Intact	2) Moderate	3) Severe	4) Coma	5) Brain dead	Hospital setting
Abramson[239]	[a]ALL	NR	100	NR	33	29								36					In and out
Brindley[230]	ALL	247	55	22.4															In
Bunch[231]	VF	200	80	40									99	40					Out
Cobb[241]	VF	406	383	94					26	36									Out
Cohn[233]	ALL	105	22	21	21									73	20	7	0	0	In
Dorian[12]	VF	347	14	4															Out
Earnest[16]	NR	117	38	32							25			57		7			Out
Eisenberg[242]	ALL	1567	302	19			81		76	66	55	49							Out
Gudjonsson[237]	ALL	222	21	9										81					Out
Herlitz[82]	ALL	13,453	NR	NR	4														Out
Liberthson[236]	VF	301	42	14										60	28	12			In and Out
Lund[240]	ALL	1263	94	7				81		81					21				Out
Peberdy[232]	ALL	14,720	2502	17										86					In
Rockswold[238]	ALL	514	83	16					15	50				59	41				Out
Sandroni[234]	ALL	114	37	32			24	26							57		14		In
Snyder[244]	ALL	63	25	40										64	32	4			In
Wernberg[243]	ALL	1686	72	4											18	6			In and Out
Wik[49]	ALL	176	6	3										83	17				Out

[a]*ALL= cardiac arrest, PEA, VT/VF, respiratory arrest.*

CPC = Cerebral Performance Categories (1–5); NR= not reported; PEA, pulseless electrical activity; VT/VF = ventricular tachycardia/ventricular fibrillation.

Neurologic outcome expressed as percent patients with designated cerebral perfusion categories as defined in Cohn et al.[233]

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CHAPTER 18

Temporary Mechanical Circulatory Support

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A number of devices have been developed and approved for acute circulatory support. As opposed to the more long-term devices that are for prolonged use as a bridge to transplantation, this group of support devices is more applicable to the acute resuscitative phase. Patients in cardiogenic shock require early aggressive therapy. Despite inotropic drugs, intubation, and control of cardiac rhythm, some patients remain hemodynamically unstable, are refractory to medical therapy, and require some type of mechanical circulatory support.[1,2] The need for circulatory support in the postcardiotomy period is relatively low and has been estimated to be in the range of 0.2 to 0.6%.[3] In addition, cardiogenic shock occurs in 2.4 to 12% of patients with acute myocardial infarction (AMI)[4] with a mortality as high as 75%.[5]

The expansion of indications for circulatory support, development of better support devices, and improved results mandate that all surgeons acquire an understanding of the devices currently available and be familiar with one or two of these support systems. Studies show that even smaller facilities that do not have advanced heart failure programs or cardiac transplantation can have improved patient survival if a device can be implemented rapidly and the patient transferred to a tertiary-care facility with expanded capabilities.[6] In this chapter, we describe the devices currently available, indications for support, patient management, and the overall morbidity and mortality associated with temporary mechanical support. In addition, we describe some of the more promising devices that have just received approval or that are currently undergoing trial. The goal of all temporary assist devices is to achieve improved function of the native heart, allowing for removal of the device. If recovery is unlikely, then transition to heart transplantation (see Chap. 65) or a long-term device (see Chaps. 67 and 68) are the only solutions for achieving long-term survival.

COUNTERPULSATION

Historical Notes

The concept of increasing coronary blood flow by retarding the systolic pulse pressure was demonstrated by Kantrowitz and Kantrowitz in 1953 in a canine preparation and again by Kantrowitz and McKinnon in 1958 using an electrically stimulated muscle wrap around the descending thoracic aorta to increase diastolic aortic pressure.[7–9] In 1961, Clauss and colleagues used an external counterpulsation system synchronized to the heartbeat to withdraw blood from the femoral artery during systole and reinject it during diastole.[10] One year later, Moulopoulos, Topaz, and Kolff produced an inflatable latex balloon that was inserted into the descending thoracic aorta through the femoral artery and inflated with carbon dioxide.[11] Inflation and deflation were synchronized to the electrocardiogram to produce counterpulsation that reduced end-systolic arterial pressure and increased diastolic pressure. In 1968, Kantrowitz reported survival of one of three patients with postinfarction cardiogenic shock refractory to medical therapy using an intra-aortic balloon pump.[12] These pioneering studies introduced the concept of supporting the failing circulation by mechanical means. Currently, intra-aortic balloon counterpulsation is used in an estimated 70,000 patients annually.[8]

Physiology

The major physiologic effects of the intra-aortic balloon pump (IABP) are a concomitant reduction in left ventricular afterload along with an increase in coronary perfusion pressure secondary to an increase in aortic diastolic pressure.[13–15] Important related effects include reduction of left ventricular systolic wall tension and oxygen consumption, reduction of left ventricular end-systolic and end-diastolic volumes,

reduced preload, and an increase in coronary artery and collateral vessel blood flow.[16–19] Cardiac output increases because of improved myocardial contractility owing to increased coronary blood flow and the reduced afterload and preload, but the IABP does not directly move or significantly redistribute blood flow.[20,21] IABP counterpulsation reduces peak systolic wall stress (afterload) by 14 to 19% and left ventricular systolic pressure by approximately 15%.[16,20,22,23] Since peak systolic wall stress is related directly to myocardial oxygen consumption, myocardial oxygen requirements are reduced proportionately.[24–26] Coronary blood flow is subject to autoregulation, and in experimental animals, the IABP does not increase flow until hypotension reduces flow to less than 50 mL/100 g of ventricle per minute.[14] However, as measured by echocardiography and color-flow Doppler mapping, peak diastolic flow velocity increases by 117% and the coronary flow velocity integral increases by 87% with counterpulsation.[27] Experimentally, collateral blood flow to ischemic areas increases up to 21% at mean arterial pressures greater than 190 mm Hg.[28]

Several variables affect the physiologic performance of the IABP. The position of the balloon should be just downstream of the left subclavian artery (Fig. 18-1). Diastolic augmentation of coronary blood flow increases with proximity to the aortic valve.[29,30] The balloon should fit the aorta so that inflation nearly occludes the vessel. Experimental work indicates that for adults, balloon volumes of 30 or 40 mL significantly improve both left ventricular unloading and diastolic coronary perfusion pressure when compared with smaller volumes. Inflation should be timed to coincide with closure of the aortic valve, which for clinical purposes is the dicrotic notch of the aortic blood pressure trace (Fig. 18-2). Early inflation reduces stroke volume, increases ventricular end-systolic and end-diastolic volumes, and increases both afterload and preload. Diastolic counterpulsation is visualized easily as a pressure curve in the arterial waveform and indicates increased diastolic perfusion of the coronary vessels (and/or bypass grafts).[31,32] Deflation should occur as late as possible to maintain the duration of the augmented diastolic blood pressure but before the aortic valve opens and the ventricle ejects. For practical purposes, deflation is timed to occur with the onset of the electrocardiographic R wave. Active deflation of the balloon creates a suction effect that acts to decrease left ventricular afterload (and therefore myocardial oxygen consumption).

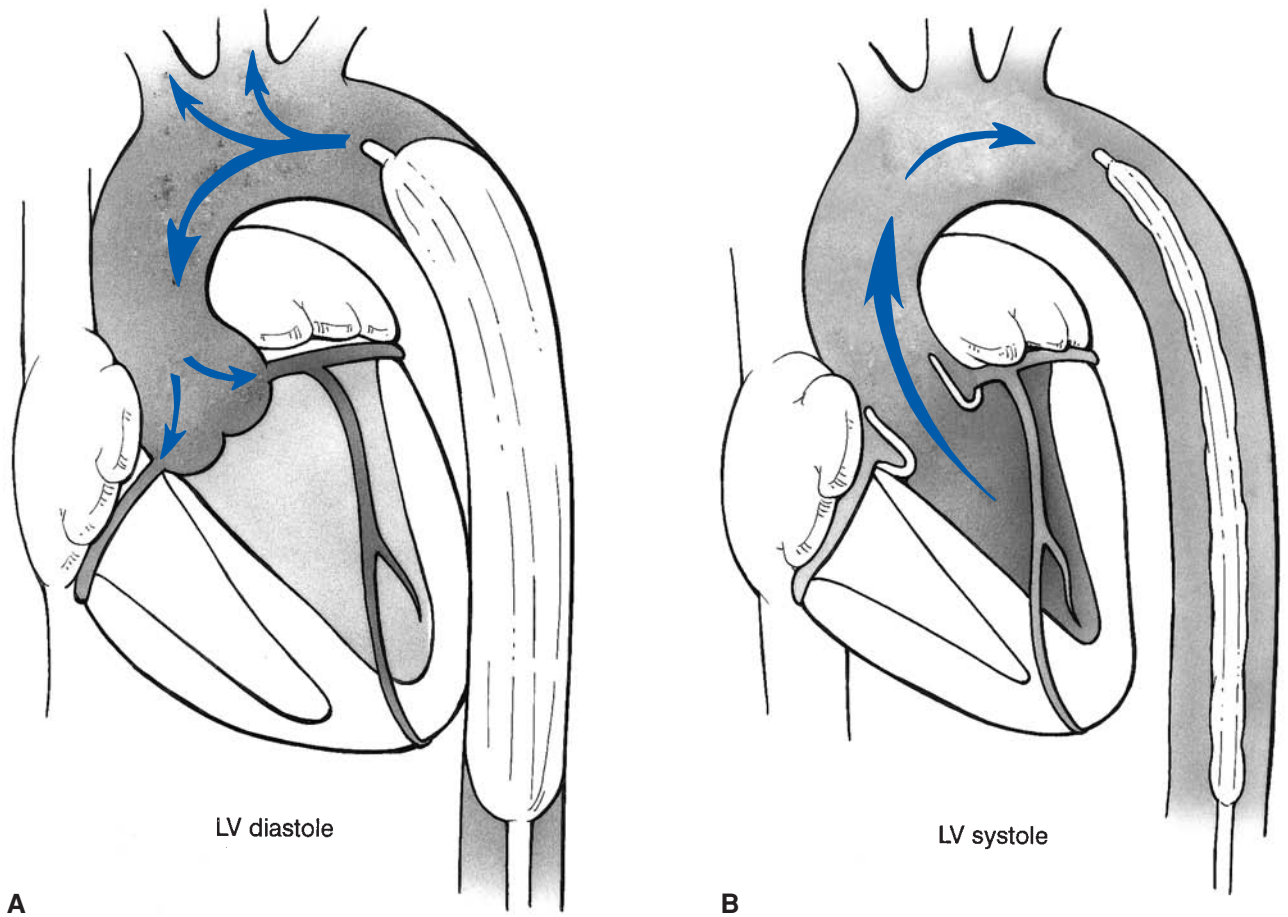

Figure 18-1. (**A**) Balloon inflation during left ventricular (LV) diastole occludes the descending thoracic aorta, closes the aortic valve, and increases proximal coronary and cerebral perfusion. (**B**) Balloon deflation during LV systole decreases LV afterload and myocardial oxygen demand.

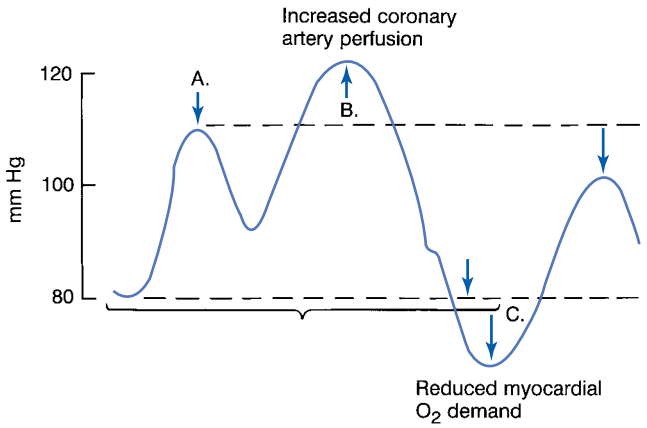

Figure 18-2. Illustration showing the effect of the intra-aortic balloon on aortic pressure. After ejection produces the pulse (*A*), inflation of the balloon increases aortic diastolic pressure (*B*). At end diastole, sudden deflation reduces aortic end-diastolic pressure (*C*) below that of an unassisted beat and reduces afterload and myocardial oxygen demand.

Biologic factors that influence the in situ hemodynamic performance of the IABP include heart rate and rhythm, mean arterial diastolic pressure, competence of the aortic valve, and compliance of the aortic wall. Severe aortic regurgitation is a contraindication to use of the IABP; very low mean aortic diastolic pressures reduce aortic root pressure augmentation and coronary blood flow. A calcified, noncompliant aorta increases diastolic pressure augmentation but risks injury to the aortic wall. On the other hand, young patients with a highly elastic, compliant aorta may manifest decreased diastolic pressure augmentation.

By far the most important biologic variables are heart rate and rhythm. Optimal performance requires a regular heart rate with an easily identified R wave or a good arterial pulse tracing with a discrete aortic dicrotic notch. Current balloon pumps trigger off the electrocardiographic R wave or the arterial pressure tracing. Both inflation and deflation are adjustable, and operators attempt to time inflation to coincide with closure of the aortic valve and descent of the R wave. During tachycardia, the IABP usually is timed to inflate every other beat; during chaotic rhythms, the device is timed to inflate in an asynchronous fixed mode that may or may not produce a mean decrease in afterload and an increase in preload. In unstable patients, every effort is made to establish a regular rhythm, including a paced rhythm, so that the IABP can be timed properly. The newer-generation IABP consoles come with algorithms that select the most appropriate trigger mode and time inflation and deflation automatically.

Indications

The traditional indications for insertion of the IABP are cardiogenic shock, uncontrolled myocardial ischemic pain, and postcardiotomy low cardiac output.[33–36] In recent years, indications for IABP have broadened to include patients with high-grade left main coronary artery stenosis, high-risk or failed percutaneous transluminal coronary angioplasty, atherectomy, or stents; patients with poorly controlled ventricular arrhythmias before or after operation; and patients with postinfarction ventricular septal defect (VSD) or acute mitral insufficiency after myocardial infarction (MI).[37–40] In addition, the IABP occasionally is used prophylactically in high-risk patients with poor left ventricular function (LVF) with either mitral regurgitation or preoperative low cardiac output owing to hibernating or stunned myocardium. These patients may benefit from temporary afterload reduction during weaning from cardiopulmonary bypass, particularly if myocardial contractility is not improved immediately by revascularization. In some institutions, a femoral artery catheter is inserted in anticipation of IABP use in patients undergoing complex procedures who have myocardial dysfunction.[41] In exceptional patients, IABP is used with extracorporeal membrane oxygenation (ECMO) to unload the left ventricle and generate pulsatility while providing circulatory assistance for postcardiotomy patients.[42–44] Some groups routinely insert an IABP prior to insertion of more long-term left ventricular assist sytems in order to optimize right ventricular function.

Nearly 90% of patients who receive IABP counterpulsation have various manifestations of ischemic heart disease with or without associated valvular heart disease.[45–47] A few patients have insertion of the balloon pump for end-stage cardiomyopathy, acute endocarditis, or before or after heart transplantation.[48]

The vast majority of patients who receive the IABP on the medical service have ischemic heart disease primarily manifested by cardiogenic shock or unstable, refractory angina. Of 231 patients who had IABP insertions at the Cleveland Clinic, Eltchaninoff reports that 83 (34.6%) were for complications of AMI. Forty-four (18.3%) were owing to failed angioplasty, 48 (20%) were for high-risk angioplasty, and 31 (12.9%) were for stabilization before cardiac surgery.[35] Only 13 (5.4%) were for end-stage cardiomyopathy.

The timing of IABP insertion varies widely between reports. The percentage of IABPs inserted before cardiac surgery varies between 18% at St. Louis University Medical Center and 57% in a group of community hospitals that do cardiac catheterization.[49,50] The overwhelming reason for intraoperative use of the IABP is failure to wean from cardiopulmonary bypass. Approximately 75% of intraoperative balloon insertions are for this reason. Preoperative low cardiac output and postinfarction angina are additional indications for intraoperative insertion of the IABP. Approximately one-half of patients who require intraoperative IABP have urgent or emergency operations.

Techniques of Insertion

The IABP usually is inserted into the common femoral artery either by the percutaneous technique or by surgical cutdown.[51] A cutdown is used most often during cardiopulmonary

bypass when the pulse is absent. The superficial femoral artery is avoided because of its smaller size and increased possibility of leg ischemia. For patients with small vessels, a 7.5F catheter without a sheath is recommended to lessen the possibility of leg ischemia. The iliac and axillary arteries and, very rarely, the abdominal aorta are infrequently used alternate sites.[52,53] Direct insertion into the ascending aorta is used intraoperatively in patients with severe aortoiliac or femoral occlusive disease that prevents passage of the balloon catheter.[54–56]

The percutaneous method uses a guidewire and is faster than a cutdown.[57] Approximately two-thirds to three-quarters of all femoral arterial insertions use the percutaneous method.[58] Although percutaneous insertion was associated with a higher incidence of leg ischemia in the past, this is no longer true.[57,59] In the catheterization laboratory, both the guidewire and balloon are monitored by fluoroscopy, but this is not essential if not readily available. The cutdown technique may be done with local anesthesia outside the operating room but preferably is done in the operating room with local or general anesthesia because the risk of contamination is less. After the femoral artery is exposed, a guidewire is introduced, followed by dilating catheters and the balloon. The catheter can be inserted without the sheath in some instances.[60] The balloon catheter usually fits snugly in the arterial wound, so a purse-string suture is not needed. If bleeding is present around the entrance site, sutures are used for control. The wound is closed completely. Whenever possible, the tip of the balloon is visualized by fluoroscopy or transesophageal echocardiography in order to ensure optimal position just distal to the left subclavian artery.[61]

The timing of inflation and deflation of the balloon must be monitored closely during counterpulsation. This usually is done easily by observing the continuously displayed arterial pressure tracing; a second systolic pulse should appear with every heartbeat and begin just after the smaller first pulse begins to decay. Timing the balloon for irregular rhythms is difficult, and the circulatory support provided by the balloon is compromised; in these patients, attempts are made to convert the patient to a sinus or paced rhythm or to slow (80 to 90 beats per minute) atrial fibrillation using appropriate drugs or cardioversion. For tachycardias over 110 to 120 beats per minute, the balloon is timed to provide inflation on alternate beats if the machine is not able to follow each beat reliably. Generally, patients are not given heparin for the IABP. The exit site of the catheter must be kept clean with antiseptics and covered in an effort to prevent local infection or septicemia.

A percutaneous IABP can be removed without exposing the femoral puncture site. The exit site is prepped, and securing sutures are cut. The balloon catheter is disconnected from the pump and completely deflated using a 50-mL syringe. Pressure is first maintained over the iliac artery. The balloon is removed, and backbleeding is allowed from the femoral artery, which theoretically flushes any distal clot into the wound. The femoral artery then is compressed, and prograde flushing then is allowed. Finally, steady nonocclusive pressure is held over the femoral puncture site. Pressure is maintained over the puncture site for 30 minutes to ensure that thrombus closes the hole. If the balloon is inserted via a cutdown, the balloon preferably is removed in the operating room. The puncture site is closed with sutures. If blood flow to the lower limb is impaired after removal, a local thromboembolectomy using Fogarty catheters and an angioplasty procedure with a vein patch are done to restore full flow to the limb.

If the percutaneous needle punctures the iliac artery above the inguinal ligament intentionally or inadvertently in obese individuals, removal should be done through a surgical incision in the operating room because the backward slope of the pelvis makes pressure difficult to maintain after withdrawal, and substantial occult retroperitoneal bleeding may occur.

If the common femoral or iliac arteries cannot be used because of occlusive disease or inability to advance the guidewire, the axillary artery usually is exposed below the middle third of the clavicle for insertion.[52,53] This vessel is smaller than the femoral artery but generally more compliant. Fluoroscopy or transesophageal (not transthoracic) echocardiography is recommended to ensure that the guidewire does not go down the ascending thoracic aorta into the heart.

Transaortic insertion is done only for postcardiotomy patients who have severe peripheral vascular or aortoiliac disease that precludes femoral insertion. The catheter may be inserted through an 8- or 10-mm woven Dacron or polyfluorotetraethylene graft that is beveled and sutured end to side to the ascending aorta using a side-biting clamp on the aorta.[56] The opposite end of the graft is passed through a stab incision in the chest wall below but near the xiphoid. The incision in the fascia and soft tissues must be large enough to accommodate the balloon catheter. The balloon is passed through this sleeve into the aorta and guided into the proximal descending thoracic aorta so that the balloon does not occlude the left subclavian orifice when inflated. The suture cuff of the balloon catheter is trimmed so that it can be inserted into the graft and tied tightly to achieve secure hemostasis. This connection is placed just beneath the skin so that none of the graft protrudes. The catheter is secured in place and managed in the same way as IABPs placed through other insertion sites.

A simpler method uses two aortic purse-string sutures to secure the aorta around the balloon catheter. No graft is used, yet bleeding complications are minimal.[54,55] Regardless of the technique of insertion, balloon catheters inserted through the ascending aorta are removed in the operating room to secure closure of the aorta.

Pulmonary arterial counterpulsation for right-sided heart failure has not achieved wide use.[62,63] Because of the short length of the pulmonary artery, a prosthetic graft (20 to 25 mm) is sewn end to side to the main pulmonary artery and tied around the balloon catheter placed inside. There are

little data regarding the amount of afterload reduction of the right ventricle.

Complications

Reported complication rates of the IABP vary between 12.9 and 29% and average approximately 20%.[36,58,64] Life-threatening complications are rare.[65] Leg ischemia is by far the most common complication (incidence 9 to 25%); other complications include balloon rupture, thrombosis within the balloon, septicemia, infection at the insertion site, bleeding, false aneurysm formation, lymph fistula, lymphocele, and femoral neuropathy.[66,67] There is no significant difference in limb ischemia in the five different types of IABPs clinically available.[64,68]

Balloon rupture occurs in approximately 1.7% of patients and usually is manifested by the appearance of blood within the balloon catheter and only occasionally by the pump alarm. Rupture may be slightly more common with transaortic insertion. Although helium usually is used to inflate the balloon, gas embolism has not been a problem. If rupture occurs, the balloon should be deflated forcibly to minimize thrombus formation within the balloon and should be promptly removed. If the patient is IABP-dependent, a guidewire is introduced through the ruptured balloon, the original balloon is removed, and a second balloon catheter is inserted over the wire. If the ruptured balloon is not removed easily, a second balloon is inserted via the opposite femoral or iliac artery or through the axillary artery to maintain circulatory support.[69]

Removal of a kinked or thrombosed ruptured balloon that cannot be withdrawn by firm traction requires operation. A thrombosed balloon can severely lacerate the femoral artery. The catheter should be withdrawn as far as possible with firm traction. The location of the tip should be determined by x-ray or ultrasound, and an incision should be planned to expose that segment of the vascular system. In the operating room, thrombolytic drugs may be considered if these drugs are not contraindicated by recent surgery.[70] The trapped balloon is removed through an arteriotomy after control of the vascular segment is obtained.

Although the incidence of clinically significant lower leg ischemia varies from 9 to 25% of patients, up to 47% have evidence of ischemia during the time the IABP is used.[66,67] Thus, the preinsertion status of the pedal pulses should be determined and recorded before the IABP is inserted in every patient. After insertion, the circulation of the foot is followed hourly by palpating pulses or by Doppler ultrasound. Foot color, mottling, temperature, and capillary refill are observed; the appearance of pain, decreased sensation, and compromised circulation indicates severe ischemia that requires restoration of the circulation to the extremity as soon as possible. There are three alternatives. If the patient is not balloon-dependent, the balloon removed immediately. In the majority of patients, this relieves the distal ischemia; a few patients require surgical exploration of the puncture site, removal of thrombus and/or emboli, and reconstruction of the femoral artery. If the patient is balloon-dependent, a second balloon catheter can be introduced into the opposite femoral or iliac artery and the first removed. If this alternative is not available or attractive, circulation to the ischemic extremity is restored using a cross-leg vascular graft or, less commonly, an axillofemoral graft.[70,71] Prompt revascularization preempts development of the compartment syndrome (incidence 1 to 3%) and the need for fasciotomy. Prompt and aggressive treatment of leg ischemia has reduced the incidence of amputation to 0.5 to 1.5%, but if amputation is necessary, the level often is above the knee. Several risk factors for development of leg ischemia have emerged. Female gender, peripheral vascular disease, diabetes, cigarette smoking, advanced age, obesity, and cardiogenic shock are reported to increase the risk of ischemic complications after IABP. Since the IABP is inserted for compelling indications, identification of risk factors does not influence management, except to encourage removal of the device as soon as the cardiac status of the patient allows. In some series, longer duration of IABP counterpulsation is associated with an increased risk of complications.[66]

Although most ischemic complications are the result of impairment of arterial inflow, severe atherosclerotic diseases of the descending thoracic aorta may produce trash embolization of atherosclerotic material that can cause the blue toe syndrome and eventually require amputation. Emboli also may reach the renal and visceral arteries to produce ischemia of these organs. The presence of aortic atherosclerosis can be determined by echocardiography, and if present, insertion through the axillary artery may be considered.[72] The ischemic rate of axillary insertions is not known because of the low number of cases reported.

Approximately 1% of patients develop false aneurysms at the femoral puncture site either in the hospital or shortly after discharge, and rare patients develop an arteriovenous fistula. Both conditions are confirmed readily by duplex scanning and require repair; neglected false aneurysms can rupture. The rare complication of lymphocele or lymph fistula preferably is treated surgically by local exploration and suture control.

Bleeding produces a local hematoma that is not evacuated unless skin necrosis is likely. If bleeding occurs in the wound, the wound is explored, bleeding is stopped, part of the hematoma is evacuated without extending the dissection, and the wound is reclosed. Bleeding from transaortic insertion is uncommon (3 to 4%). Retroperitoneal bleeding from an iliac artery puncture may not be obvious but may cause death.

Septicemia occurs in up to 1% of patients, but the risk increases with the duration of IABP residence. Most catheters are removed within 48 to 72 hours. Septicemia is an indication for IABP removal, but if the patient is balloon-dependent, a replacement balloon catheter is inserted in a new site. Suspected septicemia is treated aggressively, after blood cultures are obtained, with broad-spectrum

antibiotics that are switched to one or more specific antibiotics when the organism is known. Local infections occur in 2 to 3% of patients and usually are treated by drainage, packing, antibiotics, and secondary closure.

Acute aortic dissection from the catheter tip piercing the intima has been reported.[36] This problem is prevented preferably by not advancing the catheter against resistance and monitoring with fluoroscopy or transesophageal echocardiography. Occasional femoral neuropathies resolve over time but can be disabling. Transaortic IABP is associated with a 2 to 3% incidence of cerebral vascular accidents.[55]

Results

Very few complications of IABP cause death. Rare instances of bleeding (retroperitoneal or aortic), septicemia, central nervous system injury, or aortic dissection may cause or contribute to a patient's death. Mortality is higher in patients with ischemic leg complications than in those without.

Counterpulsation increases coronary arterial flow, reduces afterload and myocardial oxygen consumption, and experimentally reduces infarct size early after infarction.[73] Without revascularization, IABP produces a marginal increase in survival, but with revascularization, both short- and long-term survival and quality of life are improved substantially.[74–76]

However, mortality is high in patients who receive an IABP because of the cardiac problems that led to the need for the device. Overall hospital mortality ranges from 26 to 50%[77–79] (Fig. 18-3). Risk factors for hospital mortality include advanced age, female gender, high New York Heart Association (NYHA) class, preoperative nitroglycerin, operative or postoperative insertion, and transaortic insertion in one study and age and diabetes mellitus in another. A third study correlates hospital death with AMI, ejection fraction of less than 30%, NYHA class IV, and prolonged aortic cross-clamp and bypass times.[78] Time of insertion affects hospital mortality. Preoperative insertion is associated with a mortality of 18.8 to 19.6%.[48] Mortality for intraoperative insertion is 27.6 to 32.3%.[48] Postoperative insertion produces a mortality of 39 to 40.5%. Mortality is highest at 68% for patients with pump failure, is lowest at 34% for patients with coronary ischemia, and is 48% for patients who had a cardiac operation.[33] Risk factors available at the time of weaning from cardiopulmonary bypass associated with the likelihood of hospital death are heart block, advanced age, female gender, and elevated preoperative blood urea concentration.[72]

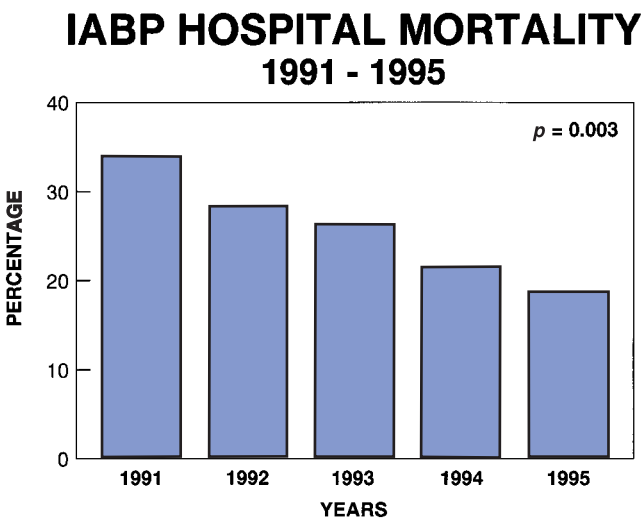

Figure 18-3. Hospital mortality for this 5-year period was 26%.

Long-term survival varies with the type of operation and is highest in patients who had cardiac transplantation or myocardial revascularization.[48] Patients who received an IABP and who required valve surgery with or without revascularization have a poorer prognosis. Creswell and colleagues found 58.8% of all patients alive at 1 year and 47.2% alive at 5 years. Naunheim and associates found that nearly all survivors were in NYHA class I or II.[45] Approximately 18% of hospital survivors have some symptoms of lower extremity ischemia.[79] Although the literature supports a significant complication rate and mortality with IABP use, the more recent data suggest a trend toward continued improvement of results. The report from the IABP registry from 1996 to 2000 reports the same trends in terms of IABP use: hemodynamic support during cardiac catheterization (20.6%), cardiogenic shock (18.8%), weaning from cardiopulmonary bypass (16.1%), preoperative use in high-risk patients (13%), and refractory unstable angina (12.3%).[80] Major complications (including major limb ischemia, severe bleeding, balloon leak, and death directly due to IABP insertion or failure) occurred in only 2.6% of patients, with an in-hospital mortality of 21.2%.[80]

Given the overall ease of IABP insertion, excellent physiologic augmentation of coronary blood flow and left ventricular unloading, this form of therapy should be considered as the first line of mechanical support in patients who do not have significant peripheral vascular disease. There is some suggestion that preoperative prophylactic IABP insertion in high-risk patients [e.g., left ventricular ejection fraction (LVEF) of less than 40%, unstable angina, left main stenosis of greater than 70%, or redo coronary artery bypass grafting (CABG)] can improve cardiac index, length of intensive-care unit (ICU) stay, and reduce mortality.[81,82] However, with meticulous myocardial protection and the judicious use of inotropes, such as epinephrine and milrinone, most groups experienced in dealing with such high-risk patients do not find routine IABP insertion helpful.

DIRECT CIRCULATORY SUPPORT

Background

The need for acute cardiac support beyond cardiopulmonary bypass was clear from the early days of cardiac surgery. Spencer and colleagues reported the first successful clinical use of a temporary device in 1965 after four patients were placed on

femoral-femoral cardiopulmonary bypass. Only one patient survived to discharge. Subsequently, in 1966, the first successful use of a left ventricular assist device was reported after a double-valve operation.[83] Debakey used an assist device that was implanted in an extracorporeal location between the left atrium and the axillary artery, marking the first use of an extracorporeal temporary device support system. The patient survived for 10 days on the pump and eventually was discharged home.

The excitement surrounding these events prompted the formation of the Artificial Heart Program in 1964 and propelled the National Heart Institute to support and encourage the development of mechanical circulatory support systems.[84] One of the objectives of this program was to promote the development of a support system that would be used in cases of acute hemodynamic collapse.

Ideal Device

Despite recent advances in biotechnology, recognition of many of the problems and complications associated with extracorporeal circulation has delineated the limitations of these devices. The components of an ideal device must overcome some of the existing problems.

An ideal device should be capable of supporting adequate flow, maximizing hemodynamics, and unloading the ventricle for patients of all sizes. Although the use of different cannulation approaches can address some of these issues (see below), even under ideal conditions, the currently available pumps are only able to support flows up to a maximum of 6 L/min. This limitation may be detrimental in large or obese patients.

At the other extreme is the need to support patients with small body surface areas. Current devices have addressed the problem associated with variations in patient size by being designed as extracorporeal systems. Therefore, by virtue of having small-diameter cannulas transversing the chest, the pumps can support patients with varying body surface area. The disadvantage of such a system is the potential for driveline and mediastinal infections. In addition, the length of the cannula between the heart and the device, particularly the inflow cannula, predisposes to areas of stasis and potential thrombus generation. Thromboembolic complications, despite adequate anticoagulation, are one of the leading causes of death in patients supported on devices.

All current pumps require anticoagulation, which increases the ever-present threat of early postoperative bleeding. In addition, requirements for transfusion of large amounts of coagulation factors and platelets enhance the inflammatory response that is induced by surgery and is further perpetuated by the circuit. Activation of the contact and complement systems and the release of cytokines by leukocytes, endothelial cells, and macrophages further increase the potential negative and detrimental effects of use of temporary assist devices.[85,86] The ensuing inflammatory cascade and volume overload can have detrimental effects on the pulmonary vascular resistance and lead to right ventricular overload, often necessitating the addition of a right ventricular assist device.

Current temporary assist devices all have the capability of biventricular support as needed, provided that the lungs can support oxygenation and ventilation. In cases of acute lung injury superimposed on circulatory failure, extracorporeal life support (ECLS, i.e., with ECMO) is the only device currently approved that can support an in-line oxygenator.

The multitude of clinical scenarios that often lead to the need for mechanical support all require that support be instituted in an expeditious manner. All current devices therefore must be easily implantable. In the postcardiotomy setting with access to the great vessels, the cannulas should allow the versatility of choosing any inflow or outflow site that is clinically indicated (see below). In an active resuscitative setting, such as cardiac arrest in the catheterization laboratory, in which time is critical and transport to the operating room often impractical, percutaneous cannulation must be an option.

Table 18-1 summarizes some of the components of an ideal temporary support device. At present, no single device is inclusive of all the components. Until the rapid innovations in this field lead to the development of an ideal device, the currently available technology must be tailored to the specific requirements of each patient, taking into consideration the duration of support needed.

Table 18–1.

Characteristics of an Ideal Temporary Support Device

1. Accommodates patients of all sizes, regardless of body surface area
2. Easy to insert
3. Maximizes hemodynamics while unloading the heart to allow for myocardial recovery
4. Is adaptable for patients who require biventricular support
5. Supports the use of an oxygenator as needed, particularly in the group of patients with acute lung injury
6. Requires minimal anticoagulation
7. Has a biocompatible surface that does not promote thrombus generation
8. Causes minimal destruction of blood or plasma components
9. Allows for ambulation and physical rehabilitation
10. Converts easily to a long-term implantable device

Indications for Support and Patient Selection

A wide range of indications exist for acute mechanical support, the primary goal of all being rapid restoration of the circulation and stabilization of hemodynamics. The routine use of transesophageal echocardiography (TEE) has helped greatly in assessing the etiology of cardiogenic shock by allowing evaluation of ventricular function, regional wall motion abnormalities, and valvular mechanics. In a patient with mechanical complications secondary to MI such as acute rupture with tamponade, acute papillary muscle rupture, or postinfarction VSD, emergent surgical correction may obviate the need for device support. Similarly, in the postcardiotomy setting with failure to separate from cardiopulmonary bypass, TEE may direct the surgeon to the need for additional revascularization and reparative valve surgery and successful weaning from bypass.

If echocardiography fails to reveal a surgically correctable cause for cardiogenic shock, most surgeons use hemodynamic data to consider the need for mechanical assistance. These criteria include a cardiac index of less than 2.2 L/min/m^2, systolic blood pressure of less than 90 mm Hg, mean pulmonary capillary wedge pressure or central venous pressure of greater than 20 mm Hg, and concomitant use of high doses of at least two inotropic agents.[87] These situations may be associated clinically with arrhythmias, pulmonary edema, and oliguria. In such circumstances, use of an IABP may be considered as the first step. In the postcardiotomy setting, the preceding hemodynamic criteria, in absence of mechanical support, are associated with a greater than 50% chance of mortality.[88] In this setting, some believe that earlier implantation of an assist device capable of supporting higher flows and allowing the heart to rest may improve results and allow for recovery of stunned myocardium.[89] Furthermore, new pharmacologic agents such as the phosphodiesterase inhibitor milrinone, nitric oxide, and vasopressin have helped to optimize hemodynamics during this critical initial period, reducing the need for concomitant right ventricular support.[90,91]

Once mechanical assistance has been instituted, the stabilized patient can undergo periodic evaluation to assess native heart recovery, end-organ function, and neurologic status. If appropriate, evaluation for cardiac transplantation ensues. Patients without malignancy, severe untreated infection, or neurologic deficit or who are at an advanced age are selected for cardiac transplantation if all other criteria are met, and there is no sign of cardiac recovery. In this subgroup, we generally transition to a chronic ventricular assist device until an organ becomes available. In patients with gradual improvement in myocardial pump function, the devices may be weaned and removed (see below).

DEVICES

Devices currently approved by the Food and Drug Administration (FDA) for temporary support include centrifugal pumps, roller pumps, venoarterial extracorporeal membrane oxygenation (ECMO), the ABIOMED devices, the Thoratec device, and the TandemHeart device. A number of other devices are undergoing investigation for short-term support.

Continuous-Flow Pumps

Two types of pumps are available commercially for extracorporeal circulation: roller pumps and centrifugal pumps. In adults, roller pumps are used rarely, if ever, for temporary circulatory support beyond routine cardiopulmonary bypass applications because of important disadvantages. Although inexpensive, roller pumps are insensitive to line pressure and require unobstructed inflow. Additionally, roller pumps may cause spallation of tubing particles and are subject to tubing failure at unpredictable times. These systems require constant vigilance and are difficult to operate for extended periods. Use of roller pumps beyond 4 to 5 hours is associated with hemolysis and, for this reason, is inappropriate for mechanical assistance that may involve several days to weeks of support.[92]

Centrifugal pumps

Centrifugal pumps are familiar assist systems because of their routine use in cardiopulmonary bypass. Although many different pump-head designs are available, they all work on the principle of generating a rotatory motion by virtue of moving blades, impellers, or concentric cones. These pumps generally can provide high flow rates with relatively modest increases in pressure. They require priming and deairing prior to use in the circuit, and the amount of flow generated is sensitive to outflow resistance and filling pressures. The differences in design of the various commercially available pump heads are in the numbers of impellers, the shape and angle of the blades, and the priming volume. The only exception is the Medtronic BioPump (Medtronic Bio-Medeicus, Inc., Eden Prairie, MN), which is based on two concentric cones generating the rotatory motion. The pump heads are disposable, relatively cheap to manufacture, and mounted on a magnetic motorized unit that generates the power. Despite design differences, in vitro and in vivo testing has shown no clear superiority of one pump over the other.[93–95] Although earlier designs caused mechanical trauma to the blood elements leading to excessive hemolysis, the newly engineered pumps are less traumatic and can be used for longer periods. Studies have documented that centrifugal pumps have a superior performance with regard to mechanical injury to red blood cells when compared with roller pumps.[96]

COMPLICATIONS: Complications with temporary mechanical assistance are high and very similar for patients on centrifugal pump support or ECLS (see below). The major complications reported by a voluntary registry for temporary circulatory assistance using primarily left ventricular, right ventricular, and biventricular assist devices (LVADs, RVADs, and BVADs) are bleeding, low cardiac output with BVADs, renal failure, infection, neurologic deficits, thrombosis and emboli, hemolysis, and technical problems (Table 18-2). The incidence of these complications in 1279 reported patients

Table 18–2.

Significance of Differences Between Prevalence of Complications among Circulatory Assist Devices

Complication	Centrifugal devices (%)	Pneumatic devices (%)	*p* Value
Bleeding/DIC	48.3	38.2	.002
BV failure/low CO	33.1	29.1	NS
Renal failure	30.7	37.2	.030
Infection	11.3	24.3	<.001
Neurologic	11.9	11.7	NS
Thrombus/emboli	9.6	12.9	NS
Hemolysis	5.1	10.4	< .001
Technical problems	3.6	7.4	.003

DIC = disseminated intravascular coagulopathy; BV = biventricular; CO = cardiac output; NS = no significance demonstrated.

differed significantly between continuous perfusion systems and pneumatically driven systems (see below) with respect to bleeding, renal failure, infection, and hemolysis. Neurologic deficits occurred in approximately 12% of patients, and in Golding's experience, noncerebral emboli occurred equally often.[97] Golding also found that 13% of patients also developed hepatic failure. An autopsy study found anatomic evidence of embolization in 63% of patients even though none had emboli detected clinically.[98]

Complications reported from the University of Missouri[99] in 91 patients who had undergone centrifugal mechanical support for postcardiotomy failure are also very similar, with 45% incidence of bleeding, 35% renal failure, 21% infection, and 4.4% thromboembolism. In addition, seal disruption between the pump head and the magnet is a common problem with prolonged support and will cause fluid accumulation in the magnet chamber. Therefore, inspection of the pumps every 12 hours is mandatory.

RESULTS: Although a meaningful comparison of results of centrifugal support from different institutions is not possible, in general, overall survival has been in the range of 21 to 41% (Table 18-3). The voluntary registry reported the experience with 604 LVADs, 168 RVADs, and 507 BVADs;

Table 18–3.

Review of Large Series in the Literature Reporting Outcomes of Centrifugal Mechanical Assistance in the Setting of Postcardiotomy Cardiac Failure

Reference	Patients (no.)	Biventricular (%)	Mean duration of support days (range)	Weaned (%)	Survived (%)
Noon[159]	141	16.3	3.8 (1–22)	54	22
Magovern[94]	77	46.8	2.2 (<1–7.7)	56	35
Joyce[101]	34	NR	NR	62	41
Curtis[99]	91	54.0	2.2 (<1–18)	46	21
Combined registry*	559	NR	NR	45	26

**Volunteer registry established by the American Society for Artificial Organs ISHLT.*
NR = not reported.

approximately 70% were with continuous-flow pumps and the remainder with pulsatile pumps.[1] There were no significant differences in the percentage of patients weaned from circulatory assistance or the percentage discharged from the hospital according to the type of perfusion circuitry. Overall, 45.7% of patients were weaned, and 25.3% were discharged from the hospital.[1] The registry also reports that long-term survival of patients weaned from circulatory support is 46% at 5 years.[1] Most of the mortality occurs in the hospital before discharge or within 5 months of discharge.

Golding reported an identical hospital survival rate for 91 patients in 1992 using only centrifugal pumps, and Noon reported that 21% of 129 patients were discharged.[97–100] Patients who received pulsatile circulatory assistance were supported significantly longer than those supported by centrifugal pumps, but there were no differences in the percentage of patients weaned or discharged.[1] Survivors were supported an average of 3.1 days using continuous-flow pumps. Patients supported for AMI did poorly; only 11.5% survived to be discharged.

Data from the University of Missouri Hospital are also very similar.[99] From the 91 patients with postcardiotomy heart failure, 46% were weaned from the device, and 21% survived to hospital discharge. Although weaning was more successful with RVAD support alone compared with LVAD or BVAD support (100% for RVAD versus 48.5% for LVAD versus 44.9% for BVAD), survivals were not significantly different (RVAD 22%, LVAD 24.3%, and BVAD 18.4%). Some reports have suggested improved results. Joyce reports that 42% of patients supported by Sarn impeller pumps eventually were discharged.[101] This is the highest reported survival and probably reflects the fact that some of these patients were transplanted.

Extracorporeal life support (ECLS/ECMO)

By the 1960s, it was clear that cardiopulmonary bypass was not suitable for patients requiring circulatory support for several days to weeks. The development of ECLS as a temporary assist device [also referred to as *extracorporeal membrane oxygenation* (ECMO)] is a direct extension of the principles of cardiopulmonary bypass and follows the pioneering efforts of Bartlett and colleagues in demonstrating the efficacy of this technology in neonatal respiratory distress syndrome.[102]

There are a number of key differences between cardiopulmonary bypass and ECLS. The most obvious difference is the duration of required support. Whereas cardiopulmonary bypass typically is employed for several hours during cardiac surgery, ECLS is designed for longer duration of support. With ECLS, lower doses of heparin are used, and reversal of heparin is not an issue. Moreover, because a continuous circuit is used, areas of stasis have been minimized (such as cardiotomy suction or venous reservoir). In addition, the membrane oxygenator used allows for longer duration of support. These differences are thought to reduce the inflammatory response and the more pronounced coagulopathy that can be seen with cardiopulmonary bypass.[86]

A typical ECLS circuit is demonstrated in Fig. 18-4. The system consists of the following:

1. *Hollow-fiber membrane oxygenator with an integrated heat-exchange system.* The microporous membrane provides the necessary gas-transfer capability via the micropores where there is direct blood-gas interface with minimal resistance to diffusion. By virtue of the membranes being close to each other, the diffusion distance has been reduced

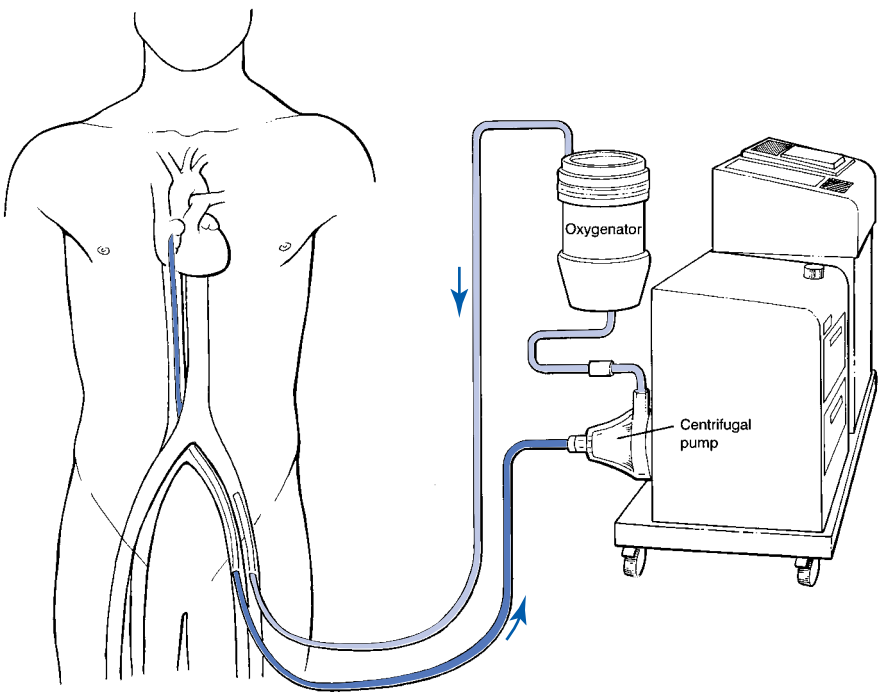

Figure 18-4. Percutaneous ECMO support is attained via femoral vessel access. Right atrial blood is drained via a catheter inserted into the femoral vein and advanced into the right atrium. Oxygenated blood is perfused retrograde via the femoral artery. Distal femoral artery perfusion is not illustrated.

without a significant pressure drop across the system.[104] Control of oxygenation and ventilation is relatively easy. Increasing the total gas flow rate increases CO_2 removal (increasing the "sweep") by reducing the gas-phase CO_2 partial pressure and promoting diffusion. Blood oxygenation is controlled simply by changing the fraction of O_2 in the gas supplied to the oxygenator.[103]

2. *Centrifugal pump.* These pumps are totally nonocclusive and afterload-dependent. An increase in downstream resistance, such as significant hypertension, will decrease forward flow to the body. Therefore, flow is not determined by rotational flow alone, and a flowmeter needs to be incorporated in the arterial outflow to quantitate the actual pump output. If the pump outflow should become occluded, the pump will not generate excessive pressure and will not rupture the arterial line. Similarly, the pump will not generate significant negative pressure if the inflow becomes occluded. This protects against cavitation and microembolus formation.
3. *Heat exchanger.* This allows for control of blood temperature as it passes through the extracorporeal circuit. Generally, the transfer of energy occurs by circulating nonsterile water in a countercurrent fashion against the circulating blood. Use of water as the heat-exchange medium provides an even temperature across the surface of the heat exchanger without localized hot spots.[103]
4. *Circuitry interfaced between the patient and the system.* The need for systemic anticoagulation on ECLS and the complications associated with massive coagulopathy and persistent bleeding during the postcardiotomy period lead to the development of biocompatible heparin-bonded bypass circuits. In 1991, the Carmeda Corporation in Stockholm, Sweden, released a heparin-coating process that could be used to produce an antithrombotic surface.[104] This process was applied to extracorporeal tubing and the hollow-fiber microporous oxygenator surface.[105] Initial experience suggested that the need for systemic anticoagulation had been eliminated. In addition, heparin coating has been associated with a decrease in the inflammatory response with reduced granulocyte[106] and complement activation.[107] Bindsler[108] and Mottaghy[109] reported excellent hemodynamic support with minimal postoperative blood loss in experimental animals for up to 5 days. Magovern and Aranki reported similar excellent results with clinical application.[110,111] Although these heparin-bonded circuits were thought initially to completely eliminate the need for heparinization, thrombus formation without anticoagulation remains a persistent problem. In a study of 30 adult patients with cardiogenic shock who underwent ECLS using the heparin-bonded circuits and no systemic anticoagulation, 20% of patients developed left ventricular thrombus by transesophageal echocardiography, and an additional 6% had visible clot in the pump head.[112] Protamine administration after starting ECLS can precipitate intracardiac clot. If the left ventricle does not eject and blood remains static within the ventricle, clot formation is more likely. Intracavity clot is more likely in patients with MI owing to expression of tissue factor by the injured cells. Protamine may bind to the heparinized coating of the new circuit and negate an anticoagulant effect.[113]

CANNULATION: A key difference between the centrifugal pump and ECLS is the presence of an in-line oxygenator. As a result, ECLS can be used for biventricular support by using central or peripheral cannulation. Intraoperatively, the most common application of ECLS has been for patients who cannot be weaned from cardiopulmonary bypass after heart surgery. In these cases, the existing right atrial and aortic cannulas can be used. An alternative strategy is to convert the system to peripheral cannulas, which potentially permits later decannulation without opening the chest.

The cannulation is done by surgical cutdown in the groin for exposure of the common femoral artery and vein. The entire vessel does not need to be mobilized, and exposure of the anterior surface of the vessels would suffice. A purse-string suture is placed over the anterior surface of the vessel. The largest cannula that the vessel can accommodate is selected. Typically, arterial cannulas are 16F to 20F and venous cannulas are 18F to 28F in size. The cannulation is performed under direct vision using Seldinger's technique. A stab incision is made in the skin with a no. 11 blade knife, a needle is inserted through the stab incision into the vessel, and a guidewire is advanced gently. Dilators then are passed sequentially to gently dilate the tract and the insertion point in the vessel. The cannulas then are inserted, the guidewire is removed, and a clamp is applied. For venous drainage, a long two-stage cannula (Fem-Flex II, Research Medical, Inc., Midvale, UT) is directed into the femoral vein to the level of the right atrium under transesophageal echocardiographic guidance.

To minimize limb complications from ischemia, one strategy is to place a 10F perfusion cannula in the superficial femoral artery distal to the primary arterial inflow cannula to perfuse the leg (Fig. 18-5). This cannula is connected to a tubing circuit that is spliced into the arterial circuit with a Y-connector.[114] The distal cannula directs continuous flow into the leg and significantly reduces problems with leg ischemia. An alternative strategy is to completely mobilize the common femoral artery and sew a 6 or 8 mm short Dacron graft to its anterior surface as a "chimney." The graft serves as the conduit for the arterial cannula, and no obstruction to distal flow exists. This strategy also allows for a more secure connection and avoids problems with inadvertent dislodgment of the cannulas because of loosening of the purse strings. In general,

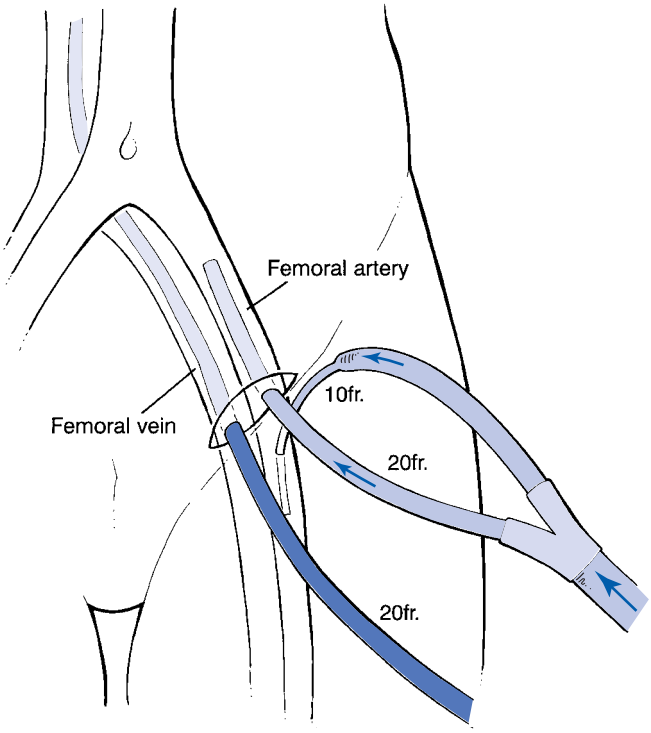

Figure 18-5. Surgical exposure of the femoral vessels facilitates cannulation for ECMO. A small 10F cannula is used to perfuse the distal femoral artery.

complete percutaneous placement of arterial cannulas is avoided to prevent iatrogenic injury during insertion and ensure proper positioning of the cannula. However, when venovenous bypass is the only mode of support needed, percutaneous cannulation is performed. Surgical exposure is not necessary, and bleeding is less with this technique. Although traditionally the perfusion circuit involves atrial drainage and femoral reinfusion (atriofemoral flow), a recent prospective study has shown the reverse circuit (femoroatrial flow) to provide higher maximal extracorporeal flow and higher pulmonary arterial mixed venous oxygenation.[115]

Central cannulation sometimes is indicated because of either severe peripheral vascular disease or the desire to deliver the highly oxygenated blood directly to the coronary arteries and the cerebral circulation. In patients with an open chest, aortic and right atrial cannulas are used. Reinforcing purse-string sutures are placed and tied over rubber chokers and buttons for later tying at decannulation. The catheters are brought through the chest wall through separate stab wounds, and after bleeding is secured, the chest is covered, but not closed, over mediastinal drainage tubes.[92]

An alternative central cannulation site is the axillary artery. Direct cannulation of this artery has been associated with progressive edema of the arm.[116] Therefore, the best strategy to maintain arm perfusion is to expose the axillary artery and sew a 6 or 8 mm graft to the vessel as a "chimney." The cannula then is place in the graft and tied securely with several circumferential umbilical tapes.

Once instituted, the system is simple enough to be monitored by trained ICU nurses and maintained by a perfusionist on a daily basis. Evidence of clots in the pump head requires a change. Leakage of plasma across the membrane from the blood phase to the gas phase continues to be a problem, gradually decreasing the efficiency of the oxygenator and increasing resistance to flow and necessitating oxygenator exchanges. Using this system, ECLS flows of 4 to 6 L/min are possible at pump speeds of 3000 to 3200 rpm. Higher pump speeds are avoided to minimize mechanical trauma to blood cells. Other means of improving flow include transfusion of blood, crystalloid, or other colloid solutions to increase the overall circulating volume. Physiologically, ECLS will unload the right ventricle but will not unload the ejecting left ventricle, even though left ventricular preload is reduced.[117] In normal hearts, the marked reduction in preload and small increase in afterload produced by the arterial inflow from the ECLS system reduces wall stress and produces smaller end-diastolic left ventricular volumes because the heart is able to eject the blood it receives. However, if the heart is dilated and poorly contracting, the marked increase in afterload provided by the ECLS system offsets any change in end-diastolic left ventricular volume produced by bypassing the heart. The heart remains dilated because the left ventricle cannot eject sufficient volume against the increased afterload to reduce either end-diastolic or end-systolic volume. ECLS, therefore, theoretically may increase left ventricular wall stress and myocardial oxygen consumption unless an IABP or other means is used to unload the left ventricle mechanically and reduce left ventricular wall stress.[119] We routinely use IABP in the majority of patients to decrease the increased afterload imposed by ECLS and add pulsatility to the continuous flow generated by the centrifugal pump. Kolobow has devised a spring-loaded catheter introduced through the femoral vein to render the pulmonary valve incompetent to decompress the left ventricle during ECLS, but this has not been used clinically.[118] Others use atrial septostomy to decompress the left ventricle if the pulmonary artery pressures remain elevated.[119]

As mentioned previously, the versatility of ECLS is that it allows rapid restoration of circulation by peripheral cannulation during active resuscitation in the setting of acute cardiac arrest, acute pulmonary embolism, or patients in cardiogenic shock who cannot be moved safely to the operating room. It is also used occasionally in the catheterization laboratory to support high-risk procedures. More recently, ECLS has been used to support some minimally invasive cardiac operations.

An isolated RVAD is rarely indicated in the postcardiotomy setting because, in general, these patients have global biventricular dysfunction. ECLS as an RVAD (with outflow to the pulmonary artery via the right ventricular outflow tract) may be used only in patients with good function of the left ventricle. Exclusive right ventricular dysfunction is rare but may occur if retrograde cardioplegia is used and fails to protect the right ventricle, in cases of pulmonary

thromboendarterectomy, or in patients with right ventricular infarction. Note that if significant pulmonary hypertension is present, this configuration may not load the left ventricle adequately.

COMPLICATIONS: The experience in adults with ECMO for postoperative cardiogenic shock is more limited because of nearly universal bleeding problems associated with the chest wound in combination with heparin anticoagulation with the ECMO circuit.[120] Pennington reported massive bleeding in six of six adults supported by ECMO following cardiac surgery. Even without the chest wound, bleeding was the major complication in a large study of long-term ECMO for acute respiratory insufficiency.[121] Muehrcke reported experience with ECMO using heparin-coated circuitry with no or minimal heparin.[122] The incidence of reexploration was 52% in the Cleveland Clinic experience; transfusions averaged 43 units of packed cells, 59 units of platelets, 51 units of cryoprecipitate, and 10 units of fresh-frozen plasma. Magovern reported somewhat less use of blood products but treated persistent bleeding by replacement therapy and did not observe evidence of intravascular clots; two patients developed stroke after perfusion stopped. Other important complications associated with ECMO using heparin-coated circuits included renal failure requiring dialysis (47%), bacteremia or mediastinitis (23%), stroke (10%), leg ischemia (70%), oxygenator failure requiring change (43%), and pump change (13%).[118] Nine of 21 patients with leg ischemia required thrombectomy and one amputation. Half the patients developed marked left ventricular dilatation, and six patients developed intracardiac clot detected by TEE.[90] Intracardiac thrombus may form within a poorly contracting, nonejecting left ventricle or atrium because little blood reaches the left atrium with good right atrial drainage.[40,82,89,108] We have observed intracardiac thrombus in heparinized patients and those perfused with pulsatile devices and a left atrial drainage cannula. The problem, therefore, is not unique to ECMO or the location of the left-sided drainage catheter but is related to LVF. In patients on ECMO with a left ventricular thrombus, we have removed the thrombus at the time a HeartMate LVAD was implanted for a bridge to transplantation.[122]

More recent reports demonstrate that the high incidence of complications using ECLS has continued to plague temporary support mechanisms based on continuous flow. Kasirajan reported an 18.9% incidence of intracranial hemorrhage, with female gender, heparin use, elevated creatinine, need for dialysis, and thrombocytopenia being important associated risk factors.[123] Smedira recently reported on 107 postcardiotomy patients supported on ECLS, with a 48% infection, 39% need for dialysis, 29% neurologic events, 5% pump thrombus formation, and 27% limb complications.[124]

RESULTS: Table 18-4 summarizes some of the reported results with ECLS for postcardiotomy circulatory support. Magovern reported improved results in 14 patients supported by a heparin-coated ECMO circuit after operations for myocardial revascularization.[117] Eleven of 14 patients (79%) with revascularization survived, but none of three patients with mitral valve surgery and none of four patients who underwent elective circulatory arrest survived. Overall, 52% of the whole group survived, but two patients developed post-perfusion strokes that probably were the result of thrombi produced during perfusion. Although the Cleveland Clinic experience with heparin-coated ECLS circuits produced a survival rate of 30%, the patient population was more diversified and represented only 0.38% of cardiac operations done during the same time period.[112] In a recent report on 82 adult patients supported with ECMO for a variety of indications, survival for postcardiotomy was 36%, whereas none of the patients who had acute cardiac resuscitation survived, and survival for cardiac allograft failure was 50%.[125]

More recently, the Cleveland Clinic reported their results looking at 202 adults with cardiac failure.[85] With an extended follow-up up to 7.5 years (mean 3.8 years), survival was reported to be 76% at 3 days, 38% at 30 days, and 24% at 5 years. Patients surviving 30 days had a 63% chance of being

Table 18–4.

Representative Clinical Trials Evaluating Extracorporeal Membrane Oxygenation for the Treatment of Postcardiotomy Cardiogenic Shock

Reference	Patients (no.)	Duration of support (range)	Weaned from device, no. (%)	Survived to hospital discharge, no. (%)
Magovern[117]	21	9–92 h	16 (76)	1 (52)
Wang[160]	18	7–456 h	10 (55)	6 (33)
Muehrcke[122]	23	0.5–144 h	9 (39)	7 (30)
Magovern[161]	55	8–137 h	36 (65)	20 (36)

alive at 5 years, demonstrating that the high early mortality remains the Achilles heal of this technology. Interestingly, patients who were weaned or bridged to transplantation had a higher overall survival (40 and 45%, respectively). Failure to wean or bridge was secondary to end-organ dysfunction and included renal and hepatic failure and occurrence of a neurologic event while on support.[85] Another report from the Cleveland Clinic looking at 19,985 patients undergoing cardiac operations found that 107 (0.5%) required ECLS for postcardiotomy failure. Younger age, number of reoperations, emergency operations, higher creatinine concentration, greater left ventricular dysfunction (LVD), and history of MI were significant predictors of the need for mechanical support.[124] Although overall survival was 35%, in the subgroup bridged to a chronic implantable device, system survival was 72% (see below for bridge-to-bridge experience).

Pulsatile Pumps

Abiomed BVS 5000/AB5000

The ABIOMED BVS 5000 blood pump is an extracorporeal device designed to provide pulsatile univentricular or biventricular support. In 1992, it became the first such device to receive FDA approval. It has been used in Europe and the United States for the purpose of postcardiotomy pump failure, with more than 2400 patients currently reported to the registry. The system is a simple, user-friendly extracorporeal pulsatile pump that is available in over 450 centers in the United States. The pump is configured as a dual-chamber device containing both an atrial chamber and a ventricular chamber that pumps the blood pneumatically to the outflow cannula (Fig. 18-6). The two chambers and the outflow tract are divided by trileaflet polyurethane valves that allow for unidirectional blood flow.

The pump chamber itself consists of a collapsible polyurethane bladder with a capacity of 100 mL. With the BVS 5000 and BVS 5000i consoles, filling of the atrial chamber depends on gravity (the height of the chamber relative to the patient's atrium), the central venous pressure (preload), and the central venous capacitance. The atrial bladder operates in a fill-to-empty mode and therefore can be affected by changes in the height of the pump relative to the patient or the volume status of the patient. The pump usually is set approximately 25 cm below the bed. The adequacy of filling can be assessed visually because the pump is transparent. The passive filling (absence of negative-pressure generation)

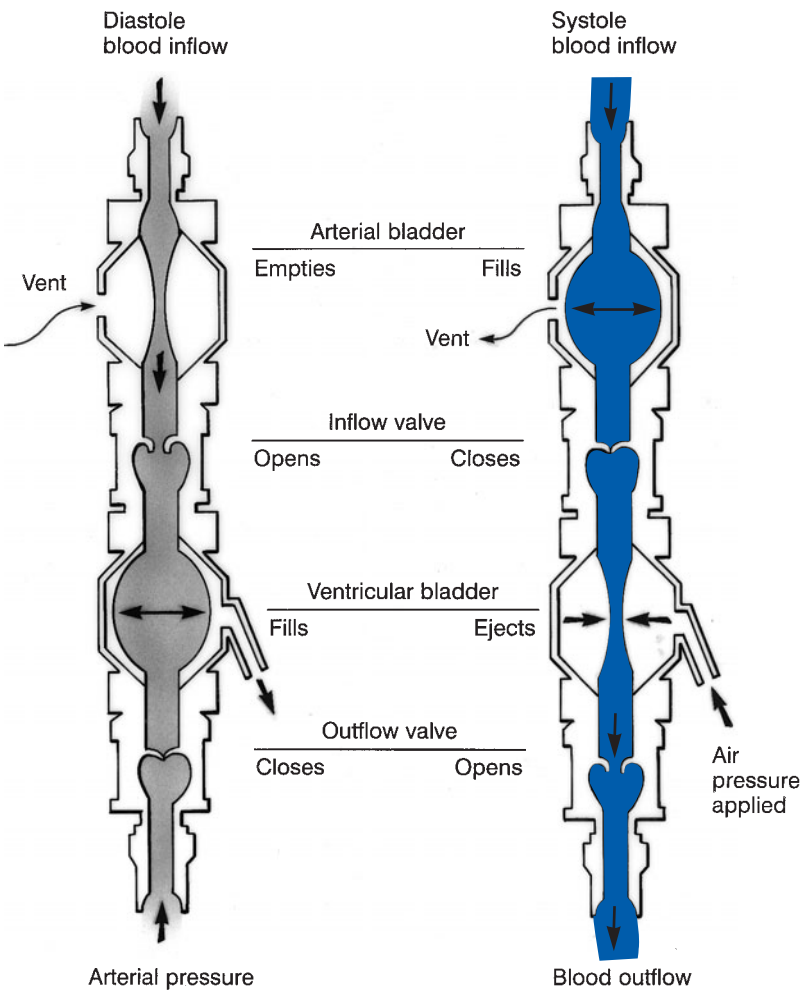

Figure 18-6. The ABIOMED BVS 5000. (*Left*) The atrial chamber empties through a one-way valve into the ventricular chamber (diastole). (*Right*) The pneumatically driven pump compresses the ventricular chamber, and blood flows through a one-way valve into the patient (systole). During pump systole, the atrial chamber fills by gravity.

is designed to prevent atrial collapse with each pump cycle as well as to prevent suctioning of air into the circuitry.

The ventricular chamber requires active pulsatile pumping by a pneumatic driveline. Compressed air is delivered to the chamber, causing bladder collapse and forcing blood out of the pump to the patient. During diastole, the air is vented to the atmosphere, allowing refilling of the chamber during the next cycle. The rate of pumping and the duration of pump systole and diastole are adjusted by the pump microprocessor that operates asynchronous to the native heart rate. The pump makes adjustments automatically to account for preload and afterload changes and delivers a constant stroke volume of approximately 80 mL. The maximum output is approximately 5 to 6 L/min with the BVS 5000i console. This design requires minimal input by personnel except during periods of weaning. Medical management should include optimizing the patient's hydration status and outflow resistance because the pump's performance depends on these parameters.

The main advantage of this device is the ability to provide independent univentricular or biventricular support as needed. The device has not demonstrated any significant hemolysis, and the pulsatile flow may have some degree of physiologic benefit. As opposed to the centrifugal pump and ECLS, patients can be extubated and can have limited mobility, such as transfer from bed to chair or dangling of the legs from the bed.

The AB5000 circulatory support system, introduced in 2004, consists of the pneumatically driven ABIOMED ventricle and an updated smaller console. The AB5000 console is easily portable and uses vacuum-assisted drainage and can drive both the standard blood pump, or "heart on a stick," and the newer ABIOMED ventricle. The ventricle is designed for short to intermediate (<3 months) support and incorporates many of the features of the ABIOCOR total artificial heart. It is driven pneumatically with valves that are constructed of Angioflex, ABIOMED's proprietary polyether-based polyurethane plastic. The AB5000 system uses the same cannulas as the BVS 5000 system. Inflow cannulas can be configured for atrial or ventricular placement. Perhaps the most attractive aspect of the upgraded system is that bedside conversion from the "heart on the stick" to the ventricle is made possible by quick-connect attachments. As such, patients implanted with a BVS 5000 system at an outlying hospital can be converted to the more long-term ventricle at the receiving institution without reopening the patient's chest or going on bypass. This makes for a very versatile and flexible system.

Another attractive option of the ABIOMED mechanical support system is the ease with which it can be placed without cardiopulmonary bypass. While off-pump placement of other ventricular assist systems has been described, they are cumbersome and are not used routinely. Off-pump insertion of the ABIOMED is facilitated by its small, flexible cannulas. The ability to avoid cardiopulmonary bypass is a distinct advantage in patients suffering cardiogenic shock. However, the combination of the high vacuum setting and smaller cannula size can lead to hemolysis.[125] Optimal cannula placement without chamber collapse or a high-velocity jet at the inflow cannula tip must be confirmed by transesophageal echocardiography prior to leaving the operating room. Anticoagulation to an activated clotting time (ACT) of 200 s should be started as soon as chest tube drainage is less than 50 mL/h for 4 hours.

CANNULATION: ABIOMED cannulas are constructed from polyvinyl chloride and have a velour body sleeve that is tunneled subcutaneously. Three sizes of wire-reinforced inflow cannulas are available commercially. These include malleable 32F, 36F, and 42F cannulas. Arterial cannulas have a precoated Dacron graft attached. They are available in two sizes and are sewn in an end-to-side fashion: a 10 mm graft for anastomosis to the smaller and lower-resistance pulmonary artery and a 12 mm graft for anastomosis to the ascending aorta.

Careful cannula insertion is important for optimal performance. Venous inflow must be unimpeded, and outflow grafts must not be kinked. In addition, careful consideration must be given to cannula position when bypass grafts cross the epicardial surface of the heart. Depending on the location of these grafts, these cannulas must be placed such that graft compression cannot occur. The three-dimensional layout of this geometry needs to be visualized and thought out in advance, particularly if chest closure is planned. Any graft compression will make recovery unlikely.

It is technically much easier to use cardiopulmonary bypass for placement of these cannulas, although off-pump insertion is possible and may be preferable in certain clinical situations, particularly for isolated right-sided support.[126] A side-biting clamp typically is used on the aorta to perform the outflow anastomosis. If the patient is on cardiopulmonary bypass, the pulmonary artery anastomosis can be done without the need of a partial cross-clamp. The length of the graft is measured from the anticipated skin exit site to the site of anastomosis, and the Dacron graft is cut to an appropriate length such that there is no excessive tension or any kinking. The cutaneous exit site is planned so that approximately 2 cm of the velour cuff extends from the skin and the remainder is in the subcutaneous tunnel. The cannula is not tunneled subcutaneously until after completion of the anastomosis. For the aortic anastomosis, incorporation of a Teflon or pericardial strip helps to control suture-line bleeding. (In addition, RVAD placement can be performed without the need for cardiopulmonary bypass. If this technique is used, the cannula must be externalized from the skin prior to insertion into the pulmonary artery.

For inflow cannulation, a double-pledgeted purse-string suture using 3-0 polypropylene is placed concentrically for cannula placement. Tourniquets must be secured firmly to prevent inadvertent loosening of the purse-string suture and bleeding from the insertion sites. In addition, the heart generally is volume loaded to prevent air embolism during insertion.

For right-sided support, the 42F cannula is used for drainage from the midatrial wall with the cannula directed to the inferior vena cava. For left-sided drainage, several options are available. The 36F malleable cannula is used because it provides the versatility to accommodate variations in anatomy and clinical conditions. Left atrial cannulation can be achieved via the interatrial groove, the dome of the left atrium, or the left atrial appendage. Alternatively, the body of the right ventricle or the left ventricular apex may be cannulated.[127] There is no need to excise a core of the ventricular apical muscle, as is common with other ventricular assist devices.[128] Ventricular cannulation offers the advantages of excellent ventricular decompression, which may improve ventricular recovery,[129] but bleeding from around the cannula also may become a problem, particularly in the setting of recent MI.

One of the advantages of the ABIOMED is that the perfusionist can prepare and de-air the circuit while the cannulas are being placed. Connecting the cannulas to the externalized circuit is easy and can be done expeditiously.

The consoles for both the BVS 5000i and AB5000 are simple to operate. The control system automatically adjusts the duration of pump diastole and systole primarily in response to changes in preload. Pump rate and flow are visible on the display monitor. With the AB5000, console vacuum is adjusted to the lowest possible setting that provides adequate flow. As further testament to the versatility of this system, the addition of an oxygenator to the RVAD has been described,[130] and this can be invaluable in the management of patients with concomitant lung failure after bypass.

COMPLICATIONS: As with all patients who require postcardiotomy mechanical support, complications are frequent. Guyton[131] reported 75% bleeding complications, 54% respiratory failure, 52% renal failure, and 26% permanent neurologic deficit. Infection occurred in 13 patients (28%) while on the device, but only three cases were considered device-related. Other complications included embolism in 13% and hemolysis in 17% and mechanical problems related to the atrial cannula site in 13% of patients.[124] No major changes in platelet count or blood chemistries occur during the period of circulatory support.

Jett and colleagues[127] reported on 55 patients supported on the ABIOMED for a variety of indications, including postcardiotomy failure (28), failed transplant allograft (8), AMI (2), and myocarditis (1). They reported a 40% incidence of bleeding, 50% respiratory complications, and 25% neurologic complications. Marelli[126] also reported a similar incidence of complications in 19 status I patients, with three developing renal failure, nine re-explored for bleeding, and three dying of sepsis and multisystem organ failure. As with all acute mechanical support systems, these relatively high complication rates are a reflection of the significant pre-existing hemodynamic insult that occurs necessitating implementation of mechanical support. Early device insertion should be considered and may improve overall outcome.[87]

RESULTS: The ABIOMED system is available in over 500 U.S centers, with over 6000 patients supported to date. Results from several reports have been summarized in Table 18-5. In a multicenter study, Guyton[131] reported that 55% of postcardiotomy patients were weaned from support and 29% were discharged from the hospital. However, 47% of patients who had not experienced cardiac arrest before being placed on circulatory support were discharged. Of 14 patients who had presupport cardiac arrest, only one (7%) was discharged. In another report of 500 patients treated with the BVS 5000 system that included 265 (53%) who could not be weaned from cardiopulmonary bypass, 27% of patients were discharged from the hospital.[132] Recent data using this device in a wide range of clinical situations, including postcardiotomy failure, have indicated successful wean of 83% and discharge to home of 45% of patients.[133] These excellent results are also reported by Marelli[126] in 14 of 19 patients who were weaned

Table 18–5.

Clinical Experience with ABIOMED Support for Postcardiotomy Cardiogenic Shock

Reference	Patients (no.)	Biventricular support (%)	Mean duration of support (days)	Weaned, no. (%)	Discharged, no. (%)
Guyton[131]	31	52	4.7	17 (55)	9 (29)
Minami[162]	26	31	NR	16 (62)	3 (50)
Körfer[133]	55	NR	5.7 ± 6.9	33 (60)	27 (49)
ABIOMED postmarket surveillance study registry*	876	50	5	NR	271 (31)

**Voluntary ABIOMED Registry.*
NR = not reported.
Source: ABIOMED postmarket surveillance study data courtesy of Diane Walsh, ABIOMED, Inc., Danvers, MA.

or transplanted with a 1-year survival of 79%. Korfer[133] also recently reported 50% hospital discharge in 50 postcardiotomy patients supported with the ABIOMED and 7 of 14 patients transplanted with a 1-year survival of 86%. The ABIOMED worldwide registry experience suggests that better results can be expected from experienced centers with heart transplant programs.[134] In fact, early transfer of patients from smaller facilities (the "spokes") to transplant centers (the "hub") has been shown to result in improved overall survival.[6]

Thoratec ventricular assist device

The Thoratec VAD (Thoratec Laboratories Corp., Berkeley, CA) was introduced clinically in 1976 under an investigational device exemption (IDE) and was approved as a bridge to heart transplantation in 1996. Although it was first used clinically for postcardiotomy support in 1982, it has been approved only recently for use as a temporary cardiac assist device. As such, it is the only device currently available that bridges the gap between short- and long-term devices. The advantage of this concept is that it allows the device to be implanted initially with the intent of myocardial recovery, particularly in the postcardiotomy heart failure setting. If myocardial recovery does not occur, then the device can be used long-term until a suitable heart becomes available for transplantation. Although this concept is desirable and offers the advantage of avoiding a second operation for transitioning from a temporary support device (bridge to bridge) to a more chronic device (see below), it comes at increased expense (because of the higher price of the pumps) and also can create ethical dilemmas if the patient recovers but ends up not being a transplant candidate.

The device is a pneumatically driven pulsatile pump that contains two seamless polyurethane bladders within a rigid housing.[135] The inlet and outlet ports contain monostrut tilting-disk valves to provide unidirectional flow. The effective stroke volume of each prosthetic ventricle is 65 mL. The pneumatic drive console applies alternating negative and positive pressures to fill and empty each prosthetic bladder. Driveline vacuum and positive pressures can be adjusted to improve filling and systemic arterial pressure. The pump eject time (equivalent of ventricular systole) also can be adjusted depending on preload and afterload conditions. One or both pumps may be used to provide univentricular (LVAD or RVAD) or biventricular support (BVAD).

The prosthetic ventricles are placed on the upper abdomen and are connected to the heart and great vessels by large-bore, wire-wrapped polyurethane cannulas that traverse the chest wall.[136,137] The cannulas are connected to a large console via pneumatic drivelines. The pumps can be operated in three control modes. The fixed-rate mode operates independently of the patient's heart, and the rate is set by the operator. In the external synchronous mode, the pump empties when triggered by the patient's R wave on the electrocardiogram. The usual mode for most patients is the fill-to-empty mode, in which ejection occurs when the device senses that the prosthetic ventricle is filled. In this volume mode, heart rate is determined by the rate of prosthetic ventricular filling.

Thoratec pumps reside on the upper abdominal wall and are connected to a large, wheeled console containing compressed-air tanks. A smaller, more portable TLCII driver is also available.

CANNULATION: Device implantation typically is performed on cardiopulmonary bypass. Recently, a method has been described for off-pump insertion as an RAVD.[138] As with the ABIOMED, it is important to select the cannula position and cutaneous exit sites carefully. The pump should be planned to rest on the anterior abdominal wall. Lateral placement may lead to excessive tension at the skin exit sites and prevent formation of a seal. Approximately 1.5 to 2 cm of the felt covering of the cannulas must extend beyond the skin exit site, with the remainder in the subcutaneous tunnel to promote ingrowth of tissue and create a seal. The length of the cannulas extending out must be adjusted based on the length of the atrial cannula (if one is used). The end of the atrial cannula widens out to connect to the inflow port of the device and therefore cannot be trimmed. On the other hand, ventricular or outflow cannulas can be trimmed to adjust the length. For optimal connection to the pump, the inflow and outflow cannula exit sites should be 4 cm apart.

The outflow cannula generally is attached first. The arterial cannulas are available with a 14 mm Dacron graft (for the pulmonary artery) or an 18 mm Dacron graft (for the aorta) and must be cut to length after the appropriate exit site has been selected. They come in two lengths, 15 and 18 cm, which again are selected based on the patient's anatomy and the planned exit site. The graft is generally sewn on the aorta or pulmonary artery after applying a partial-occluding clamp and sewn with 4-0 polypropylene suture with or without a strip of pericardium or Teflon felt for reinforcement. Inflow can be accomplished by cannulation of the atria or the ventricles.[139] All cannulations generally are reinforced with a double layer of pledgeted concentric purse-string sutures. For atrial cannulation, a 51F right-angled cannula is available in two lengths, 25 and 30 cm. For the left atrium, the cannula is inserted through the atrial appendage, the interatrial groove, or the superior dome of the left atrium. For right atrial cannulation, the cannula is inserted into the midright atrial wall and directed toward the inferior vena cava. If this cannula is inserted toward the tricuspid valve, the leaflets may interfere with proper inflow because they get sucked into the cannula during negative pressure. In addition, if the tip is not advanced to reside properly in the right atrium, negative pressure intermittently can cause the compliant right atrial wall to collapse around the cannula and interfere with proper filling of the pump.

An alternative approach can use the ventricles for inflow cannulation.[139] This provides better drainage,

higher flows, and perhaps improves the chance of myocardial recovery. This is achieved by placing a concentric layer of pledgeted horizontal mattress sutures at the apex of the left ventricle or the acute margin of the right ventricle (superior to the posterior descending artery). The cannulas used for this purpose can be either the blunt-tip 27 cm straight ventricular tube or the smooth-tipped, beveled 20 cm ventricular tube. The previously placed sutures are passed sequentially through the cuff, the apex of the heart is elevated, and the mean arterial pressure at the aorta is maintained at over 70 mm Hg to prevent air embolization during cannula insertion. Either a core of tissue is removed or a cruciate incision is made with care not to cut any of the mattress sutures. The cannula then is inserted and secured by tying the sutures. The free end can then be directed out through the previously planned cutaneous exit site, and a tubing clamp is placed on it.

INITIATION OF SUPPORT: Connecting the cannulas to the pump is difficult and must be done with care. The connections to the pump have a sharp, beveled edge that should be directed carefully under gentle pressure to fit the cannulas without damaging the inner surface of the tube. In addition, if this tip bends, it may provide a nidus for thrombus formation. The inflow cannula typically is connected first. Prior to connecting the outflow cannula, a purse-string suture is placed on the outflow Dacron graft, and a 5F to 7F vascular catheter with an aspiration port is introduced through it and directed into the pump chamber through the outflow valve. This maneuver is critical because de-airing can be difficult as a result of the way the pump sits on the abdomen. The outflow cannula then is connected. Prior to releasing the tubing clamps and flooding the chamber with blood, the air in the chamber is aspirated. Once all the air is evacuated, the de-airing catheter and the inflow tubing clamp are removed, allowing the chamber to fill with blood. Then gentle hand pumping can be performed to ensure complete air evacuation through the opening in the Dacron graft prior to removing the outflow tubing clamp.

Bypass flow is reduced before starting the pump. This ensures complete filling of the chambers to minimize the possibility of air being introduced into the circuit by the negative pressure of the pump. If a BVAD is in place, we start the LVAD first and then the RVAD. The pump is begun in the fixed-rate mode, and negative pressure is set low at –5 to –10 mm Hg. The inflow sites also should be covered with saline. Driveline pressure and systolic duration can be adjusted to optimize pump flows. Additional refinements can be made once the chest is closed.

COMPLICATIONS: The complications reported for patients bridged to transplantation are similar to those reported for postcardiotomy patients. In a multicenter trial, the most common complications were bleeding in 42%, renal failure in 36%, infection in 36%, neurologic events in 22%, and multisystem organ failure in 16% of patients.[135] Similar complications have been reported from other centers.[135,140,141]

RESULTS: Most temporary use of the Thoratec VAD is for postcardiotomy patients, but the device also has been used for patients after MI and during cardiac transplant rejection.[135,140,141] The Thoratec pump also has been used to support a patient with myocarditis who eventually recovered adequate native heart function.[142] After cardiotomy, results are similar to those obtained with continuous-flow devices and the ABIOMED BVS 5000. In a review of 145 patients with nonbridge use of the Thoratec device, 37% were weaned, and 21% were discharged.[71] More experienced centers have achieved hospital survival rates of over 40%.[140,141] Renal failure and MI are poor prognostic events for survival.[131]

The Thoratec premarket approval experience (Table 18-6) for the treatment of 53 patients with postcardiotomy heart failure had an in-hospital survival of 28%. The majority of these patients were supported with a BVAD. The Bad Oeynhausen group, however, has reported a 60% survival for postcardiotomy patients supported with the Thoratec device.[140] Clearly, the greatest advantage that the Thoratec device offers is that it can be applied for longer duration of support than any other temporary device mentioned previously. This feature may be uniquely advantageous, particularly because the duration of support necessary is usually unclear in advance. All other devices mentioned have an increasing complication rate with longer duration of support. Furthermore, the Thoratec device allows for physical rehabilitation and ambulation of the patients during the recovery period.

Newer devices

TANDEMHEART: The TandemHeart PTVA (percutaneous ventricular assist) System (CardiacAssist, Inc. Pittsburgh, PA) is a percutaneously deployed ventricular assist device that recently has received 510k FDA approval for short-term (<6 hours) support. The device is powered by a small hydrodynamic centrifugal pump that resides in a paracorporeal location. The rotor of the pump is suspended and lubricated by a fluid interface of heparinized saline. Cannulas are introduced from the femoral vessels by either percutaneous or direct insertion techniques. The inflow cannula is designed to be directed across the atrial septum to allow for left atrial decompression. The device can be introduced either in the catheterization laboratory using fluoroscopy or directly in the operating room using TEE guideance. Most of the experience with the device has been in the catheterization laboratory, where it has been used extensively to facilitate high-risk percutaneous interventions.[143] Flows of up to 4 L are reported. Patients with this device are bed-bound, given that the device is inserted through the femoral vessels. Patients also receive a moderate amount of heparin because the pump is hydrodynamic in design. It is

Table 18–6.

Premarket Approval Experience with Thoratec Support for the Management of Postcardiotomy Cardiogenic Shock

Variable	Primary cohort*	Posttransplant†	Delayed‡
Demographics:			
Patients (no.)	29	9	15
Men (%)	79	89	80
Age (years):			
Mean	52	49	51
Range	38–66	25–66	23–68
Configuration, no. (%)			
LVAD	14 (48)	0 (0)	3 (20)
RVAD	9 (0)	3 (33)	4 (27)
BVAD	15 (52)	6 (67)	8 (53)
Length of support (days):			
Mean	12	10.3	14.5
Range	0–80	2–26	0–42
Outcome, no. (%)			
Weaned and discharged	10/29 (35)	4 (44)	1 (7)
Alive with device	0 (0)	0 (0)	0 (0)
Dead	19 (65)	5 (56)	14 (93)

**Met all the study inclusion and exclusion criteria for weaning from bypass.*
†An additional group of transplant recipients who needed a ventricular assist device immediately after cardiopulmonary bypass.
‡Delayed use (patients left the operating room and came back later because of postcardiotomy cardiogenic shock; they did not meet the study criteria).
BVAD = biventricular assist device; LVAD = left ventricular assist device; RVAD = right ventricular assist device.
Source: Data courtesy of Nancy Olson, Thoratec, Inc.

a very versatile system that can be deployed and discontinued rapidly. One beneficial aspect for postcardiotomy support is that the entire device can be removed in the ICU without reopening the patient's chest.[144] RVAD configurations with the outflow cannulas directed into the main pulmonary artery also have been described.

LEVITRONIX CENTRIMAG: The Levitronix CentriMag pump is a magnetically levitated paracorporeal ventricular assist device that is designed for postcardiotomy support.[145] It is capable of providing over 9 L of support. It is available commercially in Europe, but at the time of this writing, its use in the United States is investigational only. Very little friction is generated by its impeller, which is suspended magnetically, and it requires only a very small priming volume. It can be configured for both right- and left-sided heart support with pre-existing cannulas inserted directly through the chest. Careful ambulation is possible.

CANCION: The Cancion pump (Orqis Medical) is another magnetically levitated rotary pump currently undergoing testing in the MOMENTUM trial for patients with decompensated heart failure. It is not intended as full support but rather to augment renal blood flow. Designed to be used on an intermittent basis, the goal of therapy is to break the neurohormonal cycle of heart failure. Inflow consists of a percutaneously placed cannula that is directed into the iliac artery. Pump outflow is directed into the descending aorta by another catheter inserted from the contralateral femoral artery. Studies have shown improvements both in hemodynamic parameters and in the neurohormonal axis of heart failure patients.[146]

IMPELLA: The Impella pump has been acquired recently by ABIOMED and is being marketed as the Impella Recover system.[146] The device is a microaxial pump, with both peripheral or central cannulation configurations available. In either case, the pump is directed across the aortic valve into the left ventricle. Flows of up to 6 L are reported. A right ventricular support device also has been developed. An FDA-approved clinical trial has been approved recently for the percutaneous pump capable of flows of 2.5 L.

BRIDGE-TO-BRIDGE/HEART TRANSPLANTATION

The *bridge-to-bridge strategy* refers to the use of one of the short-term support systems to potentially stabilize a moribund patient to allow for the institution of a more long-term support device should short-term stabilization occur and more meaningful recovery be anticipated.

ECMO has many advantages in the bridge-to-bridge arena. The system is simple, relatively cheap, easy to assemble rapidly, and very portable. Full cardiopulmonary support can be established rapidly by peripheral cannulation. As a result, ECLS can be used as a lifesaving option in patients with hemodynamic collapse who initially are not known to be candidates for cardiac transplantation and therefore are candidates for more chronic ventricular assist device support.[119,148] The clinical settings in which ECLS is used include patients who present with massive MI who remain in cardiogenic shock despite inotropic support and IABP counterpulsation, chronic heart failure patients with acute decompensation, and patients with cardiac arrest. Improved results with implantable ventricular assist devices have prompted implementation of strategies using ECLS as a means to rapidly establish circulatory support to maintain hemodynamics as transplant evaluation is initiated and neurologic status is determined. This strategy is aimed at maximizing patient survival and limiting the duration of support with temporary assist devices by early transition to a chronic ventricular assist device (bridge to bridge) that would allow patient rehabilitation and eventual transplantation. Furthermore, operative and perioperative costs of implanting the more permanent LVADs are avoided in patients who already may have suffered irreversible sequelae of multisystem organ failure.[149] Pagani recently reported the results of 33 patients with primary cardiac failure who were placed on ECLS.[148] The etiology was ischemic in 58%, nonischemic in 30%, and postcardiotomy in 12%. Overall, 73% of these patients were in cardiac arrest or had experienced a cardiac arrest within 15 to 30 minutes of initiation of ECLS. Ten patients who were transplant candidates and could not be weaned from ECLS were bridged to an LVAD. Six patients were transplanted and discharged, two were alive on the LVAD awaiting transplantation, and two died. Overall, ECLS was discontinued in 27% of patients because of absolute contraindications to transplantation, primarily because of neurologic injury. However, 80% of patients transitioned to an LVAD survived. This aggressive strategy and remarkable survival are secondary to selection of patients who are most likely to survive at the expense of more initial deaths on ECLS. If the entire group of patients in this study are considered, only 36% survived to discharge. Interestingly, the need for RVAD support in the group of patients with ECLS as a bridge strategy was 40%, significantly higher than the 10% reported for patients who receive an LVAD as the initial device. This may be secondary to the inflammatory response to ECLS and associated increase in pulmonary vascular resistance.[150,151] On the other hand, an increased frequency of multisystem organ failure may lead to a greater need for perioperative BVAD support.[152–154]

Similar improved results have been reported from the Cleveland Clinic in which 18 of 107 postcardiotomy patients who were appropriate transplant candidates were converted to an LVAD.[125] Of these, 72% survived to trasplantation and 92% were alive at 1 year. The successful use of LVADs for postcardiotomy support also has been reported by DeRose in a group of 12 patients.[155] LVAD support was converted to a HeartMate device at a mean of 3.5 days. Of these, eight were transplanted, and one was explanted with an overall survival of 75%.

Korfer and associates also reported on 68 patients supported with the ABIOMED BVS 5000 system.[137] The majority of these patients were postcardiotomy, with 32 being weaned and 13 transplanted. Overall survival was 47%. More recently, Korfer reported on 17 patients with postcardiotomy shock who received the Thoratec device. In this group, seven were transplanted and one was weaned successfully, for an overall survival of 47%.[145] With its availability in the catheterization laboratory and the ease with which it can be implanted, it is likely that TandemHeart will have an important role in this evolving field.

Device Selection

To date, insufficient data exist to recommend one device over another for patients who require temporary mechanical support. Use of a particular device often is based on availability rather than science. Currently, the majority of heart centers use the ABIOMED BVS 5000 as their primary means of short-term cardiac support.

For centers with multiple devices, patient presentation and cardiopulmonary status will determine the device selected. Patients undergoing cardiopulmonary resuscitation are best serviced by urgent femoral cannulation. This avoids the time delay of transportation and sternotomy. Patients with severe hypoxia and lung injury either from aspiration or pulmonary edema benefit from the oxygenation and lung rest provided with ECMO.

For postcardiotomy support, all devices have been used with similar success. Typically, patients are supported for 48 to 72 hours while transplant evaluation is completed. Then they are transitioned to a more long-term device if myocardial recovery has failed. This approach avoids a high-risk emergency heart transplantation and provides the time necessary for improved organ function.

The best device for AMIs or myocarditis remains uncertain. However, a recent multicenter report of outcomes of patients in cardiogenic shock after AMI demonstrated a 67% rate of recovery when patients were supported with the

AB5000 system.[156] For fulminant myocarditis, the device that is least traumatic to the heart is advisable because recovery is likely. For more indolent myocarditis or giant cell myocarditis, transplantation is more likely, and a long-term implantable system may be the best choice.

For patients sustaining arrest in the catheterization laboratory, the TandemHeart with percutaneous transseptal left atrial drainage is a very attractive option.

Patient Management

The ultimate goal is to maintain optimal perfusion of all end organs, to allow time for recovery from an acute hemodynamic insult, and to prevent further deterioration of organ function. Ideally, pump flow would achieve a mixed venous saturation of greater than 70%. Low-flow states can often be corrected by intravascular volume expansion. With centrifugal pumps and ECMO, pump speed can be adjusted to control flow and allow some degree of cardiac ejection to decrease the likelihood of stasis and intracardiac thrombus formation. Increasing flow rates by using excessive pump speeds also cause significant hemolysis. Fluid administration to expand intravascular volume is the best way to increase flow. However, right-sided heart failure also may manifest as a low-flow state in the presence of low pulmonary artery pressures. This condition usually requires the institution of right-sided circulatory support and is associated with a lower overall survival.

Ventilatory support

Peak inspiratory pressures are maintained below 35 cm H_2O. Inspired oxygen is set initially at 100% with a positive end-expiratory pressure of 5 cm H_2O. Fractional inspired oxygen then is decreased gradually to less than 50%, with partial pressure of oxygen maintained at between 85 and 100 mm Hg. These measures are instituted to diminish the deleterious effect of barotrauma and oxygen toxicity in the setting of lung injury.

Anticoagulation

Anticoagulation should be done judiciously to weigh the balance of excessive risk of bleeding against clot formation in the pump. Platelet counts decrease within the first 24 hours of support; therefore, counts are monitored every 8 hours, and we routinely transfuse platelets to maintain counts above 50,000/mm^3 during routine support and above 100,000/mm^3 if bleeding is present. Fresh-frozen plasma and cryoprecipitate are given to control coagulopathy and maintain the fibrinogen concentration at greater than 250 mg/dL and also replace other coagulation factors consumed by the circuit. Although other institutions have reported on the use of plasminogen inhibitors such as aminocaproic acid and aprotinin to decrease fibrinolysis,[157] we have not used these drugs routinely because of concern for thrombus formation. In most cases, heparin infusion is started soon after adequate hemostasis is present. Anticoagulation is achieved by systemic heparinization with a continuous infusion starting at 8 to 10 μg/kg per hour and titrated to maintain the partial thromboplastin time (PTT) at between 45 and 55 seconds. For ECMO, in most cases, heparin infusion is started within 24 hours if used in the postcardiotomy setting but sooner in patients without a sternotomy. With heparin-bonded circuits, we target an ACT of 200 s.

Fluid management

Patients are diuresed aggressively while on support to minimize third-space fluid accumulations. If response to diuretic therapy is suboptimal because of renal insufficiency, we use a hemofilter/dialyzer spliced into the arterial or venous limb of the circuit, if feasible. Otherwise, we use continuous venovenous hemodialysis (CVVHD). This system permits control over fluid balance by continuous ultrafiltration that can be adjusted for volume removal and also allows for dialysis as needed.

Neurologic monitoring

Patients are sedated with fentanyl or propofol infusion to maintain comfort. Muscle paralysis is used as needed to decrease the energy expenditure and to decrease chest wall stiffness to allow for optimal adjustment of the ventilation parameters. All patients are assessed periodically off sedation to establish neurologic function. Response to simple commands, ability to move all extremities, and spontaneous eye movements are used as gross indications of intact sensorium. A low threshold of obtaining computed tomographic (CT) scans of the head is exercised if any change is noted or index of suspicion is high.

Weaning

A weaning trial is usually attempted after 48 to 72 hours of support. It is critical not to rush weaning and to allow time for myocardial as well as end-organ recovery. The principle of weaning is common to all devices, and all have various controls available that allow reduction of flow, thereby enabling more work to be performed by the heart. Flow is reduced gradually at increments of 0.5 to 1 L/min. Adequate anticoagulation is critical during this low-flow phase to prevent pump thrombosis, and in general, it is not recommended to reduce flow to $<$2.0 L/min for a prolonged period. We add additional heparin during this period to maintain an ACT of more than 300 s. With optimal pharmacologic support and continuous TEE evaluation of ventricular function, flows are reduced while monitoring systemic blood pressure, cardiac index, pulmonary pressures, and ventricular size. Maintenance of cardiac index and low pulmonary pressures with preserved LVF by echocardiography suggests that weaning is likely. A failed attempt at weaning results in resumption of full flow. Absence of ventricular recovery after several weaning attempts is a poor prognostic

sign. Patients who are transplant candidates undergo a full evaluation and subsequently are staged to a long-term ventricular assist device as a bridge to cardiac transplantation. We and others have found that early conversion to chronic ventricular support is beneficial and improves the low survival that is associated with cardiogenic shock, particularly in the postcardiotomy setting.[120,125,137,155]

SUMMARY OF COMPLICATIONS AND RESULTS

Duration of Support

Complications tend to increase with increasing length of support. Therefore, in general, these devices are used for less than 2 weeks, but longer durations have been reported (Table 18-7). An exception to this general rule is the Thoratec device, which can be extended for a longer period until cardiac transplantation. The longest reported duration of support with this device is 365 days. Table 18-8 summarizes the indications for which temporary support has been implemented.

Table 18–8.

Indications that Temporary Device Support has been Used for Acute Cardiogenic Shock

Postcardiotomy pump failure
Acute myocardial infarction
Decompensated heart failure
Postcardiac transplantation allograft dysfunction
Acute myocarditis
Deterioration during cardiac cathetrization procedures
Right ventricular failure after LVAD placement
Cardiac arrest
Massive pulmonary embolism

Complications

All current devices are thrombogenic and require anticoagulation. The delicate balance between overanticoagulation resulting in bleeding versus inadequate anticoagulation and thromboembolism is a major determinant of morbidity.

Bleeding

During the acute phase, bleeding remains a significant problem, occurring at suture lines and cannulation sites and often a diffuse coagulopathy that becomes difficult to localize. The high incidence is partly because of the hemostatic disarray associated with the operation, the low-flow physiologic state that necessitates pump placement, and the need for anticoagulation early in the course of support. In general, this translates into a large transfusion requirement that can be detrimental in terms of problems with transfusion reactions, increases in pulmonary vascular resistance, and importantly, increased sensitization of patients who later may require transplantation. The need for rapid transfusion often prohibits the use of filters that generally slow the rate of infusion. Golding had reported severe bleeding in 87% of patients supported with centrifugal pumps, with a mean transfusion requirement of 53 units of blood.[95] More recently, the Cleveland Clinic reported a median transfusion requirement of 14 units (range 1 to 99 units) using ECMO.[85]

The use of heparin-coated circuits has failed to reduce the coagulopathy and bleeding associated with ECMO effectively. However, peripheral cannulation with ECMO for acute support often is associated with much less bleeding than transthoracic approaches in the postcardiotomy setting. Similarly, with the ABIOMED and Thoratec devices, the incidence of bleeding has been as high as 27%.[89,135]

Table 18–7.

Duration of Support with Temporary Assist Devices

Device	Median support (days)	Range (days)
Centrifugal pump	2.3	1–14
ECMO	2.5	1–9
ABIOMED	5.6	1–81
Thoratec	42.0	6–365

Thromboembolism

Despite the development of heparin-coated systems, the incidence of thromboembolism remains a constant threat. Thrombin deposition in centrifugal pumps with increasing duration of support is a well-known phenomenon. Golding reported thromboembolism in 12.7% of 91 patients supported with a centrifugal pump for postcardiotomy pump failure.[95] In 202 adult patients supported with ECMO, pump-head thrombus was noted in 5%, and neurologic complications occurred in 29%.[85] Both factors were found to have a profound negative impact on survival or the ability to be weaned from support. Similarly, thromboembolic incidences of 8 and 13% have been reported for the Thoratec and ABIOMED devices, respectively. These numbers may underestimate the actual number of thromboembolic episodes. Curtis and colleagues reported autopsy results in

eight patients who had no clinical evidence of thromboembolism. In this group, five patients (63%) were found to have evidence of acute thromboembolic infarction in the cerebral, pulmonary, and system territories.[158]

Weaning and Survival

There are currently no data to indicate that one device is superior over another in terms of weaning and survival. Published reports suggest that weaning can be accomplished in approximately 45 to 60% of patients; however, survival overall is less than 30%, with only 50% of weaned patients discharged alive from the hospital. Reports on long-term follow-up in this group are unavailable. The Cleveland Clinic recently demonstrated in a cohort of patients supported on ECMO that the high early attrition rate diminishes rapidly within 6 months of ECMO removal, and 65% of patients discharged are alive at 5 years.[85] Risk factors associated with increased mortality have included age greater than 60 years, emergency operations, reoperations, renal insufficiency, and pre-existing LVD. In all series, sepsis, multisystem organ failure, and neurologic complications stand out as the causes of death.

The overall survival rate in reported series over the last decade has undergone a significant improvement at transplant centers where appropriate candidates are bridged to transplantation after a period of support. In the Cleveland Clinic experience, ECMO support was converted to an implantable LVAD in 18 patients.[85] Of these, 72% survived to transplantation with 92% 1-year survival. DeRose and colleagues have described the successful use of an implantable LVAD for postcardiotomy support in a group of 12 patients after elective or emergency coronary artery grafting requiring IABP, centrifugal, or ABIOMED LVAD support.[155] All were converted to the HeartMate device at a mean of 3.5 days. Of these patients, eight were transplanted, one was explanted, and all were discharged for an overall survival of 75%. Similar results have been described by Korfer and colleagues.[133] In their experience with 68 patients supported with the ABIOMED BVS 5000, the majority with postcardiotomy failure, 32 patients were weaned and 13 were transplanted with an overall survival of 47%. The Thoratec device was used in another 17 patients at their institution for postcardiotomy support, with eight survivors (47%), seven patients transplanted, and one weaned successfully.

CONCLUSION

Currently, a number of options exist for temporary circulatory support, and with advances in technology, the number of devices will expand. Each device has advantages and disadvantages, and to date, none satisfies all the requirements of an ideal device. We have clearly learned many lessons that should direct the development of systems and strategies that maximize survival and reduce complications. In this arena, better understanding of the host inflammatory response, appreciation of the induced derangement in the coagulation cascade, and development of systems that do not require anticoagulation should improve overall outcomes. In addition, development of therapies that alter reperfusion injury and preserve organ function is important. Agents and approaches that affect the inflammatory response in general, such as steroids, aprotinin, and plasmapheresis, or more specific blockades, such as leukocyte depletion or direct cytokine inhibition, will need evaluation.

Risk analysis also has taught us that patients requiring postcardiotomy support generally fit into a particular profile. Specifically, these are patients who require emergency operations, have poor ventricular reserve, are older, and have extensive atherosclerotic coronary disease and pre-existing renal dysfunction. Preoperative awareness should prompt maximization of medical pharmacologic support and a readiness to implement mechanical devices early in the face of cardiac pump failure.

Mechanical support also necessitates that adequate left ventricular decompression be achieved. In the postcardiotomy setting, current systems that allow these options are the ABIOMED, TandemHeart, and Thoratec assist devices. Levitronix and Impella devices are currently under investigation. Use of the centrifugal pump gradually has fallen out of favor. ECMO support should be reserved for cases of acute hemodynamic collapse in the immediate postmyocardial infarction period, disasters in cardiac catheterization laboratories, sudden witnessed cardiac arrest, or any other condition that requires rapid restoration of circulatory support. The primary advantage of ECMO in these settings is the ability to cannulate peripherally.

Finally, with the knowledge that myocardial ischemia can lead to irreversible damage in the postcardiotomy setting, recent data suggest an early transition of temporary support to more chronic vetricular access device support and transplantation. This strategy has improved survival rates from the 25 to 30% range to 50 to 75%.

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CHAPTER 19

Late Complications of Cardiac Surgery

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The most significant progress in cardiothoracic surgery over the past 5 years has been the maturing of multiple large clinical databases and their subsequent analysis. This has begun to clarify the relationship between preoperative health, surgical procedure, and postoperative complications (Table 19-1). Conclusions from these studies have more substance than earlier studies because large numbers of patients are entered into these databases.

Because the largest numbers of patients have coronary artery bypass surgery (CABS), much of the discussion stems from these specific complications. For the first time, significant data are available on beating-heart surgery as compared with traditional CABS using cardiopulmonary bypass. The difference between these two techniques is discussed where relevant and where quality data exist.

The Society of Thoracic Surgeons has been collecting clinical cardiac surgery data since 1989. From this extensive database we have been able to identify many of the major perioperative complications, their association with patient characteristics, and attempts at modification by therapies. In a 2003 analysis of the data, the 30-day operative mortality was 3.05%, and the major complication rate was 13.04%. The major complications reported were renal failure, stroke, prolonged ventilation, reoperation, and sternal infection. Preoperative patient characteristics are important contributors to postoperative complications in all these areas. Postoperative complications may be due to preoperative patient illnesses, to unavoidable consequences of operative decisions, or to technical complications. By carefully recording these morbid events, we are able to provide a better-quality service for our patients.

CARDIAC COMPLICATIONS

Postoperative Myocardial Ischemia

Although coronary bypass surgery is performed to improve myocardial blood flow, multiple complications occur that can impair perfusion and cause postoperative myocardial ischemia (PMI), low cardiac output, and sudden death. Of 3982 patients having cardiac surgery, 29 patients (0.7%) had a sudden cardiac arrest.[1] Six of 29 patients (21%) died during the hospitalization, whereas 23 of the patients (79%) were discharged after both closed and open resuscitation. Fourteen patients (48%) had PMI as the underlying cause, eight patients (28%) had either tamponade or graft malfunction, and seven patients (24%) had no identifiable etiology.

The Society of Thoracic Surgeons has defined PMI as the occurrence of any one of the following three postoperative findings: electrocardiographic (ECG) changes, serum markers, and decreased ejection fraction (EF). The incidence of PMI in this database is 1% (see Table 19-1). However, the diagnosis of PMI is still debated because of trauma, reperfusion, and cardiac arrest elevating biochemical serum markers without ongoing ischemia. In the literature, the incidence of elevated markers varies from 8 to 35%.[2]

The current laboratory standard for measuring myocardial necrosis is either cardiac troponin I or cardiac troponin T.[3,4] However, the degree to which troponin must be elevated is uncertain.[5] In 100 cardiac surgical patients, 17 patients had either new wall motion abnormalities or new Q waves on ECG.[6] These patients had a cardiac troponin I level of greater than 40 ng/mL. If patients were divided into two groups of less than 40 ng/mL and greater than 60 ng/mL, the patients with greater than 60 ng/mL were in the intensive-care unit (ICU) longer and ventilated longer. (Cardiac troponins are measured in nanograms per milliliter or micrograms per liter; the number remains the same as the unit changes.)

Prior to the measurement of troponins, the diagnosis of a heart attack was based on any two of three criteria: ECG changes, angina, and elevation of the MB fraction of creatine kinase (CK-MB). Angina is not a good indicator in postoperative patients. Patients were identified as having PMI by ECG and CK-MB standards, and troponin I levels were measured at four postoperative intervals.[2] The criteria for PMI were

Table 19–1.

STS Complication Rates, Jan–June 2005 (69,880 cases)

Atrial fibrillation	20.1%
Prolonged vent.	8.3%
Renal failure	3.8%
Pneumonia	3.0%
Reop. for bleeding	2.2%
Reop. for noncardiac problem	2.1%
GI complication	2.1%
Cardiac arrest	1.6%
Permanent stroke	1.4%
Reop. for other cardiac problem	1.1%
Anticoagulant complication	1.1%
Preoperative MI	1.0%
Septicemia	1.0%
Heart block	0.9%
Multisystem failure	0.8%
Transient stroke	0.7%
Leg infection	0.6%
Deep sternal wound infection	0.4%
Coma	0.3%
Acute limb ischemia	0.3%
Reop. for graft occlusion	0.2%
Pulmonary embolism	0.2%
Tamponade	0.2%
UTI	0.0%

new Q waves with CK-MB myocardial band elevation of greater than 50 μg/L or CK-MB myocardial band greater than 100 μg/L. Six of 50 patients had PMI by these criteria. Forty-four patients did not meet these criteria, and their troponin I levels peaked in 7 hours at a mean of 20.97 μg/L (17.11 to 24.83 μg/L). Patients who met the criteria for PMI had a mean cardiac troponin I level of 46.85 μg/L (36.4 to 57.3 μg/L). The only preoperative risk factor for an elevated postoperative troponin was preoperative elevation of the cardiac troponin level. The level at which troponins become diagnostic of PMI is still debatable, with levels as low as 3.1 μg/L being considered significant.[7]

Because troponins and CK-MB may be elevated just from surgical trauma, and because chest pain is an inaccurate indicator of postoperative myocardial ischemia, graft occlusion is often hard to diagnose. ECG, biochemical markers, and predischarge angiography were performed in 103 patients having CABS. Twelve patients had at least one graft occluded. Peak CK-MB levels in these patients averaged 52.2 μg/L as compared with 24.7 μg/L. Peak troponin T levels were 3.7 μg/L as compared with 1 μg/L.[8] In a second study, 2078 patients were followed for cardiac troponin I levels greater than 20 ng/mL and acute changes in their ECG.[9] Fifty-five patients fulfilled these criteria and underwent repeat angiography, in addition to having myoglobin, creatine kinase (CK), and CK-MB isoenzyme determinations. Early graft failure was found in 35 patients, whereas 20 patients showed no failure. CK/CK-MB and ECG changes could not distinguish between those with and without graft failure. Cardiac troponin I levels of 21.5 ng/mL at 12 hours and 33.4 ng/dL at 24 hours were the best discriminator. A third study reviewed 3308 coronary artery bypass grafting (CABG) patients for PMI either caused by graft occlusion or with patent grafts.[10] Ninety-four patients had repeat emergency angiography, which was performed because of a troponin I level of greater than 20 ng/mL or significant ECG changes. Fifty-six of 94 patients had a PMI caused by graft occlusion and 38 did not.

Three groups of patients then were studied with cardiac troponin I, CK, and CK-MB determinations and ECGs: PMI and graft occlusion, PMI and patent grafts, and 95 patients with no PMI and patent grafts. The best discriminator between PMI and no PMI was a troponin I level of greater than 10 ng/mL. The best discriminator for graft occlusion was a troponin I level of greater than 35.5 ng/mL. CK-MB determinations were not useful, and troponin I levels peaked at 12 hours after removal of the cross-clamp.

Biochemical markers are also predictors of postoperative left ventricular (LV) dysfunction and increased mortality.[11] In one study, 800 patients were followed for 30 days for severe LV dysfunction or death. The median peak CK-MB level was 29 ng/mL, with more than one-half of the patients having levels five times greater than the upper limit of 5 ng/mL. The strongest predictor of LV dysfunction or death was a level greater than 100 ng/mL. In a second study, a level of 40 ng/mL was associated with increased risk of mortality.[12] However, this risk was gone at 1 year. Thirty-day mortality is increased by perioperative infarctions, and long-term quality of life is reduced.[13]

Serial troponin I determinations were followed in 60 patients randomly assigned to on-pump or off-pump coronary bypass procedures.[14] Off-pump patients had significantly less release of troponin I. Troponin levels often stay within the reference ranges after off-pump bypass surgery.[3]

Postoperative Atrial Fibrillation

From June to January 2005, the incidence of postoperative atrial fibrillation in the Society of Thoracic Surgeons'

National Adult Cardiac Surgery Database was 20% (see Table 19-1). The New York State Registry had 163 of 2111 (7.7%) readmissions owing to arrhythmias, which are the fourth most common reason for readmission with a median time from surgery of 8 days. Three-hundred and two patients were monitored continuously during hospitalization and for 2 weeks after discharge.[15] One-hundred and twenty-seven of 302 patients had atrial fibrillation, with 41 having it after discharge and 10 of these for the first time. The mean occurrence was 2.9 days from surgery, but the range was day 0 to 21 days. Sixty-nine percent of patients had no symptoms. Predictors of atrial fibrillation while hospitalized were greater than 65 years of age, history of intermittent atrial fibrillation, and atrial pacing. Predictors of atrial fibrillation after discharge were atrial fibrillation during hospitalization, valve surgery, and pulmonary hypertension. Four important issues are controlling the ventricular response to atrial fibrillation, preventing thromboembolism and anticoagulation management, chemical and electrical cardioversion, and preoperative prophylaxis.[16]

The Department of Veterans Affairs entered 3855 patients from 14 centers into a study and examined the incidence, risk factors, morbidity, and mortality from postoperative atrial fibrillation.[17] A total of 29.6% of patients had postoperative atrial fibrillation. Length of stay in the ICU and hospital stay were higher in the atrial fibrillation patients. ICU readmission, perioperative myocardial infarction (MI), congestive heart failure (CHF), reintubation, and stroke were increased. Hospital mortality was 5.95% for the atrial fibrillation patients and 2.95% for those without atrial fibrillation; six-month mortality was 9.36% as compared with 4.17%. In addition, postoperative atrial fibrillation was associated with a long-term decrease in survival, which also may be related to the treatment of atrial fibrillation with anticoagulants and antiarrhythmics.[18]

Risk factors for atrial fibrillation were studied in a multicenter trial that entered 4657 patients.[19] Of these patients, 32.3% had postoperative atrial fibrillation. Risk factors were advanced age, history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), valve surgery, and postoperative withdrawal of a beta blocker or angiotensin-converting enzyme (ACE) inhibitor. Reduced risk was related to postoperative use of a beta blocker, ACE inhibitor, supplemental potassium, or nonsteroidal anti-inflammatory drug (NSAID). Recurrent atrial fibrillation occurred in 43% with risk factors of advanced age, history of CHF and LV hypertrophy, and withdrawal of beta blockers and ACE inhibitors. Patients with recurrent atrial fibrillation had more complications than those with a single episode.

The incidence of stroke is increased in patients with postoperative atrial fibrillation.[20] Fifty-two patients had a postoperative stroke in a study population of 2630 patients, and 36.5% of the stroke patients had atrial fibrillation prior to the stroke. The stroke occurred a mean of 21.3 hours after atrial fibrillation and a mean of 6 days after surgery. Postoperative atrial fibrillation also may be associated with a decrease in neurocognitive function.[21]

One-hundred and sixty patients were followed prospectively after off-pump coronary bypass surgery.[22] Atrial fibrillation occurred in 33 patients (20.6%). Older age, grafting of the ramus intermedius, and repeat bypass were the risk factors identified. A review of the literature documents postoperative atrial fibrillation at 19% for the off-pump patients and 24% for the on-pump patients.[23] The conclusion of these authors is that neither method now can claim to result in less postoperative atrial fibrillation.

Chest Re-exploration

In the Society of Thoracic Surgeons' database, reoperation for bleeding was 2.2%, reoperation for tamponade was 0.2%, and reoperation for graft occlusion was 0.2%. Three-hundred and five patients (3.6%) of a cohort of 8586 patients were re-explored for bleeding in this study from Dartmouth.[24] In-hospital mortality for patients re-explored was 9.5% compared with the control group of 3.3%. Average length of stay after surgery was 14.5 days versus 8.6 days. Risk factors for re-exploration were long cardiopulmonary bypass times, the need for an intra-aortic balloon pump (IABP), older age, smaller body surface area, and more distal anastomoses. In a second study, 2898 patients were reviewed.[25] Eighty-nine patients (3.1%) were re-explored, and they had risk factors of smaller size, emergency surgery, increased age, and greater than five distal anastomoses. Aspirin and heparin, when used preoperatively, did cause higher bleeding in patients placed on cardiopulmonary bypass. Mortality rates were similar in propensity-matched groups, but patients requiring re-exploration had more use of inotropic drugs and longer admissions to the ICU and hospital. Patients who waited longer than 12 hours for re-exploration after admission to the ICU had more complications.

Chest re-exploration for tamponade is only 0.2%, and the echocardiographic diagnosis may be difficult.[26] One-hundred and forty-eight patients were diagnosed with tamponade, and this was divided into two groups: less than 72 hours after surgery and longer than 72 hours. In the early patients, transthoracic echocardiography had difficulty documenting the effusion, and, thus, diagnosis required transesophageal echocardiography (TEE). In general, the effusions were small and localized and often had no echocardiographic evidence of classic tamponade. Effusions present after 72 hours, which also were hemodynamically significant, were larger, global, and had classic echocardiographic findings.

Re-exploration may occur for sudden cardiac arrest. Seventy-nine patients were studied after cardiac arrest after open-heart surgery, and 20 of 79 (25%) survived to discharge.[27] Determinants of success were arrest within 24 hours of surgery, arrest in the ICU, and opening the chest within 10 minutes. After reopening the chest, cardiopulmonary bypass may need to be restarted.[28] Fifty-five patients were in the study group, having an incidence of 0.8%. The three major causes were cardiac arrest, bleeding, and hypotension. Twenty died in the operating room, 12 died before discharge, and the overall survival to discharge was

42%. Patients with an identifiable etiology for the problem were more likely to survive.

The incidence of uncomplicated pericardial effusion after open-heart surgery is high.[29] One-thousand two-hundred and seventy-seven patients had postoperative transthoracic echocardiograms at 20 and 30 days. At day 20, 22% of patients had effusions, and at day 30, 4% had evidence of late tamponade. Late tamponade was higher in valve patients and in those on anticoagulants.

PULMONARY COMPLICATIONS

Early extubation has been the most significant advance in the ventilatory care of post–open-heart surgery patients. This has allowed us to identify the preoperative, intraoperative, and postoperative risk factors of prolonged intubation. Preoperative routine spirometry does not predict length of postoperative intubation.[30] In this study, patients with 20% of predicted forced expiratory volume in 1 second (FEV_1) were extubated as quickly as those with better pulmonary function. Smoking does increase postoperative pulmonary complications.[31] Smokers had longer ICU stays but not necessarily longer intubation times. Full benefit from cessation of smoking takes about 6 weeks, with some benefit seen after 10 to 14 days. Both surgery- and patient-specific factors are related to pulmonary complications.

Early extubation may result in shorter ICU stays and earlier discharge.[32] Early extubation is not associated with higher complications but may be beneficial only in low-risk patients. Extubation for less than 6 hours as compared with between 6 and 24 hours showed no difference in ICU or hospital stay.[33] Early extubation is possible by modification of sedation and anesthesia, early reversal of paralysis, and established protocols with experienced nurses.

Prolonged mechanical ventilation can occur in almost 50% of open-heart surgical patients.[34] In this study, 167 of 400 patients were not extubated at 8 hours. The mean and median duration of ventilation were 21.6 and 8 hours. Failure to extubate at 8 hours occurred in 42.1%, and prolonged ventilation at 24 and 48 hours was seen in 6.8 and 5.3%. The most common cause of mechanical ventilation at 8 hours was a depressed level of consciousness (34.7%), followed by hypoxemia (25.1%). Most patients with hypoxemia have it for unknown reasons, although many were on nitroprusside. An additional 10.2% of patients were not extubated at 8 hours owing to concern about excessive bleeding. Hemodynamic instability was not a common reason for failure to extubate early. At 24 hours, 93% of all patients were extubated, and the primary reason for continuing intubation thereafter was hypoxemia. The causes were acute respiratory distress syndrome (ARDS), cardiogenic pulmonary edema, and unknown.

Respiratory failure is the most common reason for readmission to the ICU in patients undergoing CABS.[35] Seventy-five of 2117 patients (3.6%) were readmitted to the ICU. Respiratory failure caused 47% of the ICU readmissions. The readmitted patients had a mortality rate of 17% versus an overall mortality rate of 2.8%. These ICU readmitted patients had a median length of stay of 23 days; patients not readmitted to the ICU had a median stay of 6 days. Two independent risk factors were identified: preoperative renal failure and initial postoperative mechanical ventilation greater than 24 hours.

Prolonged (>72 hours) postoperative respiratory failure was studied by a review of 8802 patients having CABS.[36] In this cohort, 5.6% required postoperative ventilation for more than 72 hours. The duration of ventilation was calculated by the summation of all episodes of mechanical ventilation during the postoperative time. On multivariate analysis, the most significant risk factors were preoperative insertion of an IABP, documented COPD, and advanced age. The noted intraoperative risk factor was the duration of cardiopulmonary bypass, which may be associated with the presence of concomitant defects. Postoperative risks of prolonged ventilation were sepsis, endocarditis, gastrointestinal bleeding, new stroke, renal failure, deep sternal wound infection, and reoperation for bleeding. The 30-day survival for patients with respiratory failure was 75.7 versus 90% in patients with one or more complications other than respiratory failure.

Improvements in respiratory function may be achieved by maintaining an intact pleura, particularly during harvesting of the internal mammary arteries (IMA), and by off-pump coronary surgery. In one series, patients were divided into three groups, with one group having the IMA skeletonized with intact pleura, the second with open pleura and pedicled IMAs, and the third with skeletonized IMAs and open pleura.[37] The incidences of prolonged mechanical ventilation, pleural effusion, the need for thoracentesis, and clinically important atelectasis were highest in the pedicled group with open pleura. Off-pump coronary artery surgery may improve postoperative pulmonary function, as demonstrated in a review of 200 patients who were randomized to either on-pump or off-pump coronary revascularization.[38] This comparison reveals that 73 of 100 off-pump patients versus 50 of 97 on-pump patients were extubated at 4 hours after surgery. There was no difference in mortality or hospital readmissions.

Two groups of 19 patients were divided between on- and off-pump surgery.[39] No differences were found in postoperative pulmonary course in either of the two groups.

NEUROLOGIC COMPLICATIONS

Stroke

Neurologic complications are divided into three categories: stroke, cognitive dysfunction, and delirium. However, these divisions may be arbitrary. Concerns about neurologic injury from cardiopulmonary bypass have encouraged the development and possible acceptance of strategies of less complete revascularization techniques as well as the popularization of beating-heart surgery.

A paper was published in 1996 that focused on neurologic complications of CABS using cardiopulmonary bypass; and 6.1% of patients had a neurologic complication, with 3.1% having a stroke and 3% having deterioration of "intellectual function."[40] Mortality was highest in stroke patients at 21%, followed by the second group at 10%, and the unaffected patients at 2%. Patients with stroke had longer hospitalizations at 25 days, deterioration of function at 21 days, and the normal group was discharged at 10 days. The more significant the neurologic impairment, the higher was the probability of admission to rehabilitation or long-term care facilities. Risk factors for stroke were ascending aortic disease, a history of stroke, and age greater than 70 years. Risk factors for deterioration of cognitive function were age, systolic hypertension on admission, pulmonary disease, and excessive alcohol use.

Strokes are caused by several mechanisms. One study attempted to identify these etiologies in coronary bypass patients, and 388 patients with strokes from five medical centers were studied for an 8-year period.[41] Embolic events caused 62.1% of the strokes, and multiple etiologies were responsible for 10.1%, cerebral hypoperfusion for 8.8%, lacunar infarcts for 3.1%, thrombotic events for 1%, and hemorrhagic events for 1%. The remaining 13.9% had no etiology identified. Most strokes were noted on the first postoperative day. Cerebral emboli are thought to be related to manipulation of the aorta.

Risk factors for strokes may depend more on preoperative conditions than on intraoperative occurrences.[42] A series of patients having CABS were studied for stroke risk factors. When these factors were identified, a validation group of 1298 patients was studied to confirm the results. The authors noted that 5.7% had strokes. Five factors were associated with perioperative strokes: previous stroke, presence of carotid bruit, history of hypertension, increasing age, history of diabetes, and prolonged cardiopulmonary bypass time.

Perioperative strokes increase morbidity, mortality, and cost.[43] In 10,860 patients who had CABS, 244 patients had strokes at a frequency of 2.2%. Univariate analysis showed age, female gender, hypertension, diabetes, prior stroke, prior transient ischemic attack (TIA), and carotid bruits as preoperative risk factors. Multivariate analysis identified age, previous TIA, and carotid bruit as risk factors. One-year survival in stroke patients was 64 versus 94% in nonstroke patients. Five-year survivals were 44 and 81%, respectively. The patients with perioperative strokes had a 23% mortality before hospital discharge.

Other evidence exists that places the most emphasis on the intraoperative and postoperative course.[44] A large series of 11,825 patients undergoing CABS were followed prospectively from 1996 to 2001. Strokes occurred in 1.5% of the study group, with 75% of the strokes occurring in what were designated as preoperative low- and medium-risk groups. The intraoperative and postoperative risk factors were intra- or postoperative IABP, prolonged length of cardiopulmonary bypass, the need for reinitiation of cardiopulmonary bypass, low-cardiac-output syndrome, prolonged inotrope use, and preoperative atrial fibrillation.

The complexity of surgical procedure also was noted to increase the incidence of stroke in 783 patients who were divided into four groups: coronary artery bypass surgery, isolated valve surgery, combined CABS, and valve surgery, and multivalve surgery.[45] The stroke rate was 1.7% for patients undergoing coronary artery bypass grafting (CABG) only, 3.6% for those with isolated valve procedures, 3.3% for those with combined CABG and valve operations, and 6.7% for those with multivalve procedures.

The etiology of perioperative stroke is multifactorial. Reduction in its incidence will occur as a result of research on multiple fronts. This research includes identification and mitigation of preoperative risk factors, understanding of the significance of carotid artery disease, decreased manipulation of the aorta and intraoperative use of epiaortic ultrasound, improvement in cardiopulmonary bypass filters, air emboli control, and postoperative treatment of hemodynamic alleviation and arrhythmias, particularly atrial fibrillation.

Neurocognitive Dysfunction

Neurocognitive dysfunction relates to the decrease in performance of patients on standardized tests of mental function after open-heart surgery. The severity of the problem depends on the extent and completeness of testing. In a review of published studies, 22.5% of patients had neurocognitive deficits after open-heart surgery at 2 months.[46] This effect may be apparent even at 5 years, although the brain has significant ability to recover.[47] In a third study, 104 patients undergoing CABG with cardiopulmonary bypass were matched with nonsurgical controls.[48] Repeat measurements were made at 7 days, 4 months, and 3 years. Cognitive measures in surgical patients were worse at all postoperative intervals compared with controls.

The causes of cognitive dysfunction are multifactorial. Cardiopulmonary bypass is thought to be the most significant of these. Three-hundred and eight consecutive coronary artery bypass patients were tested for cognitive dysfunction by cognitive P300 auditory evoked potentials.[49] Standard psychometric testing did not document this subclinical cognitive impairment. Cardiopulmonary bypass was the only predictor of impairment. Valve operations cause greater impairment than just CABG.[50] Off-pump CABG may cause fewer declines than on-pump CABG.[51]

However, control populations have not been studied adequately to justify suggesting that all cognitive dysfunction is related to cardiopulmonary bypass.[52] One-hundred and twelve healthy volunteers were repeatedly administered neuropsychological tests to study result variability, which documented a range of results as each volunteer repeated the test.[53] Neurophyschological tests of CABG patients then were reanalyzed, adjusting for this variability. The result was that 7.7% of patients had evidence of neurocognitive decline at 3 months as opposed to 14 to 28%. In a second

study, four groups of patients were followed simultaneously.[54] The groups were CABG patients, off-pump patients, patients with coronary artery disease (CAD) but not having surgery, and heart-healthy patients. At baseline, all patients with CAD performed worse than the heart-healthy patients, and at 1 year, all patients with CAD performed the same. A third study compared cognitive dysfunction in CABG patients and patients with CAD but not having surgery.[55] At 1 year, there were no differences between the two groups.

Twenty-five patients having off-pump bypass surgery were matched with 50 on-pump patients.[56] Both groups had early decline of cognitive function with recovery, and cardiopulmonary bypass by itself is not the etiology. However, cerebral microemboli are reduced in patients who are not placed on cardiopulmonary bypass.[57]

Peripheral Nerve Injuries

Significant peripheral nerve injuries in open-heart surgery are brachial plexus injuries, ulnar nerve injury, and phrenic nerve injury. Of 421 patients having CABG, 55 patients (13%) had the following injuries: brachial radiculopathy, 23 patients; saphenous mononeuropathy, 13 patients; common peroneal mononeuropathy, 8 patients; and ulnar mononeuropathy, 5 patients.[58] In addition, unilateral vocal cord paralysis was found in 5 patients. In the patients with brachial injuries, 21 of 23 injuries affected the lower or medial cord fibers. In a second study, 13 of 201 patients (6.5%) who had a median sternotomy had a brachial plexus injury.[59] These injuries were not thought to be associated with arm placement, jugular vein cannulation, duration of operation, bypass time, sex, or type of operation. Instead, the authors felt that the width of opening of the sternal wound and height of elevation of the left IMA exposure contributed to the injuries. The rate of injury is higher in patients having the IMA harvested.[60] In this study, patients not having the IMA harvested had a 1% incidence of injury, whereas those with harvesting had a 10.6% incidence. Lesions were seen most frequently in the roots of C8–T1, with symptoms being continuous pain and motor and sensory deficits. Symptoms in eight patients lasted over 3 months. Somatosensory evoked potential (SSEP) monitoring documents subclinical transient losses during surgery in many patients.[61,62]

Subclinical ulnar neuropathies also may be frequent.[63] Fifty-three patients having CABG were studied prospectively.[64] Twenty patients (37.7%) had findings of ulnar neuropathy, with five being related to the brachial plexus. The average duration of symptoms was 2.3 months, but some patients had prolonged findings.

Phrenic nerve injury after open-heart surgery may cause significant morbidity.[65] The diagnosis depends on clinical evidence of shortness of breath, chest radiographs, and nerve conduction studies. In one study, 78 of 92 patients had abnormal postoperative chest radiographs, but only 42 of 78 had abnormal diaphragmatic motion and 24 of the 42 had phrenic neuropathy.[66] The etiology of phrenic nerve injury has been related to cold injury owing to topical ice and to harvesting of the IMA.[67,68] Skeletonization of the IMA may reduce the incidence.[69] The right IMA is closer to the right phrenic nerve than it is to the left. Phrenic nerve injury has been reported to be as high as 4% in this location.[70]

RENAL COMPLICATIONS

Patients who develop acute renal failure after CABS surgery have a higher mortality than those who do not.[71–73] The Veterans Administration reviewed 42,773 patients who had open-heart surgery at 43 locations.[71] Acute renal failure developed in 1.1% of patients, with a mortality of 63.7%. Those who did not require dialysis had a mortality of 4.3%. This study defined acute renal failure as the new need for the institution of dialysis within 30 days of surgery. This increase in mortality is independent of other preoperative and postoperative comorbidities. The etiology of preoperative dialysis-dependent renal failure is divided into two groups based on preoperative renal function.[74] Patients with normal preoperative renal function may require postoperative dialysis if the surgical procedure is performed emergently or if technical complications of the surgical procedure occur. Patients with decreased preoperative renal function may require dialysis with an otherwise nonemergent and uncomplicated course.

The development of renal insufficiency after open-heart surgery is associated with higher mortality than in patients with a normal serum creatinine concentration.[73] Of 2843 patients studied over a 2-year span, renal failure was divided into two groups: those with a serum creatinine rise of 1 mg/dL over baseline (group A) and those with acute renal failure requiring dialysis (group B). In the coronary artery bypass patients, 7.9% developed renal failure without dialysis, and 0.7% required dialysis. The baseline mortality was 1%, with group A having a 14% mortality and group B having a 28% mortality. Preoperative and intraoperative characteristics related to group A were increased age, elevated preoperative serum creatinine concentration, longer duration of cardiopulmonary bypass, diabetes, decreased EF, and increased body weight; in group B, the risk factors included increased preoperative serum creatinine concentration, duration of cardiopulmonary bypass, and presence of diabetes.

Patients with preoperative renal insufficiency have higher short- and long-term complications.[75,76] Overall length of stay and ICU days were increased. Thirty-day and 1-year mortalities are increased.[76] In patients with a preoperative creatinine concentration of 1.5 mg/dL, the in-hospital mortality rate was 14%, with 5% requiring dialysis. Additional preoperative risk factors for preoperative dialysis-dependent renal failure at discharge were female gender and emergency procedures.[77]

The duration of cardiopulmonary bypass has been identified as a risk factor for the development of acute renal failure. Postoperative renal function was compared in two groups in which cardiopulmonary bypass time was less than 70 minutes or greater than 90 minutes. Creatinine clearance, fractional excretion of sodium, and urine concentrations of *N*-acetyl-β-D-glucosaminidase, alpha$_1$-microglobulin, glutathione transferase-π, and glutathione transferase-α were measured.[78] Kidney-specific proteins were elevated postoperatively in both groups, but they were higher and occurred for a longer postoperative time in patients with cardiopulmonary bypass exceeding 90 minutes in duration. Multiple factors contribute to the renal damage, including nonpulsatile flow, embolization, and activation of known inflammatory pathways. Manipulation of bypass parameters may ameliorate this damage. On bypass, hematocrits of 21 to 25% may offer the greatest protection.[79]

Off-pump (beating-heart) surgery provides an additional insight into the renal effects of cardiopulmonary bypass.[80,81] A prospective study of 9631 patients from 1996 to 2001 found a combined dialysis-dependent renal failure of 4.1%, with off-pump surgery at 1.8% and cardiopulmonary bypass at 4.3%. However, off-pump surgery may not add any further renoprotective effects in patients with normal kidney function.[82]

In low-risk patients, little difference has been found in both postoperative renal dysfunction and postoperative markers of renal injury in comparisons of on-pump versus off-pump procedures.[82] A study of unselected patients who had creatinine clearances of less than 60 mL/min showed no difference in postoperative renal dysfunction than in those having either on-pump or off-pump procedures.[83]

GASTROINTESTINAL COMPLICATIONS

In the Society of Thoracic Surgeons' data, the incidence of gastrointestinal (GI) complications was 2.1%. The significance of this complication is its high mortality rate. GI complications can be divided into two groups: mesenteric ischemia and all other. Forty-six patients required surgical consultation of 8709 patients undergoing open-heart surgery, for an incidence of 0.53%.[84] Thirty-one of 46 patients (67%) had mesenteric ischemia, with 22 of 31 patients being explored and 14 of those explored died within 2 days of surgery. Seven of nine patients with mesenteric ischemia not explored died within 3 days of open-heart surgery. The remaining GI complications in decreasing order were diverticulitis, pancreatitis, peptic ulcer disease, and cholecystitis. The mortality in this group was 40%, with death occurring at a much later date after surgery. Preoperative risk factors were prior cerebrovascular accident (CVA), COPD, type II heparin-induced thrombocytopenia, atrial fibrillation, previous heart attack, renal insufficiency, and use of an IABP. In patients with mesenteric ischemia, the diagnosis is difficult.[85] Twenty-six laparotomies were performed for suspected mesenteric ischemia in 3024 open-heart patients. Seventeen of 26 had mesenteric ischemia, and 13 of 17 died. The four survivors had the ischemia limited to one segment of bowel.

WOUND COMPLICATIONS

Mediastinitis

Mediastinal wound complications are a significant source of postoperative mortality and increased cost.[86] Wound infections may be classified as superficial or deep (i.e., bone and retrosternal space). The sternum may dehisce with an infection or without. The incidence of deep sternal wound infection varies from 0.4 to 5%. *Staphylococcus aureus* and *Streptococcus epidermidis* are cultured from 70 to 80% of the wounds. Deep and organ-related surgical infections result in increased length of stay, costs of care, and mortality.[87] Long-term survival is decreased in these patients.[88] In one series, sternal infections developed in 40 of 3760 patients (1.1%). Early mortality was the same in the control group, but at 5 years, patients without sternal infections had a survival rate of 73% compared with 51% in patients with infections.[88]

Clinical predictors of sternal infections are diabetes, obesity, preoperative hemodynamic instability, preoperative renal failure on dialysis, use of bilateral internal mammary arteries, sepsis, and transfusions of more than four units of packed red blood cells after surgery.[88,89] Preoperative patient management may lessen the impact of these risk factors. Both accurate timing of preoperative antibiotics and tight control of perioperative blood sugar concentration in diabetic patients have been suggested as means to decrease these infections.[90]

The Society of Thoracic Surgeons studied a temporal chart with 331,429 patients in its database for major surgical-site infections (i.e., mediastinitis, saphenous vein harvest sites, and septicemia) and for the risk factors.[91] Major infections occurred in 3.51%, with one-quarter of these due to mediastinitis. The risk factors most strongly associated with major infections were a body mass index of 30 to 40 kg/m^2, diabetes mellitus, previous MI, urgent operative status, and hypertension. Risk factors that were present in a smaller number of patients but that also were predictors of infections were cardiogenic shock, dialysis-dependent renal failure, cardiopulmonary bypass time greater than 200 minutes, and perioperative immunosuppressive therapy. High-risk patients for major infections may be identifiable prior to surgery, and the risk factors may be modifiable.

Technical modification of IMA harvesting may decrease the incidence of sternal dehiscence.[92] Of 1146 patients who had bilateral IMA harvests, 304 were pedicled grafts and 842 were skeletonized in one series.[93] Sternal complications were more frequent in the pedicled group (4.5% versus 1.7%). The overall sternal wound-healing complications in the diabetic patients were higher in the pedicled group (10%) than in the skeletonized group (2.2%). Surgical mortality and graft patency were similar in both groups.

Prevention of infection begins prior to surgery with identification of patient-related risk factors, careful antibiotic prophylaxis, and preoperative hair removal. Intraoperative considerations include surgical technique, with judicious use of electrocautery, and foreign bodies, including bone wax.

Once mediastinitis is diagnosed, treatment options vary from débridement and closure to sternectomy and muscle flaps. In one study, débridement, rewiring, and delayed skin closure resulted in shorter healing time.[94] In a series of 5337 patients, 62 patients developed deep sternal infections (1.1%). Thirty-two were treated with débridement, rewiring, and delayed primary closure. This treatment failed in six initially and ultimately in two, with a median length of stay of 32 days and a median time to healing of 85 days. Twenty-five patients had muscle flap closure without sternal reapproximation, with a median length of stay of 31 days and a median time to healing of 161 days. Vacuum-assisted closure devices may be an important adjunct in many cases of sternal wound treatment.[95]

Radial Artery Harvest-Site Complications

The radial artery is currently harvested more frequently, with a patency rate of between 87.5 and 96.5% at 4 years.[96] The radial artery was harvested in 3977 patients, with a total of 4172 anastomoses.[97] There were no acute ischemic events of the hand. Late infection was 0.4%, and numbness and paresthesias occurred in 6.5 and 3% at 3 months. The Allen test has been used to judge the safety of harvesting the radial artery, and 11.6% of patients had a unilateral positive Allen test.[98] Additional testing may be warranted because the Allen test may lack sensitivity and specificity.[99] Doppler ultrasound and digital plethysmography were used on 187 patients.[100] Three-hundred and forty-six arms were studied, and 94 (27.1%) were excluded. Perfusion abnormalities such as nonreversal of flow, abnormal digital pressure, and inappropriate increase in ulnar velocity eliminated 54% of the arms, and anatomic abnormalities such as size less than 2 mm, congenital anomalies, and radial artery occlusion eliminated 46% of the arms. Many of the patients with complaints of hand pain or numbness improve over 12 months.[101] Two-hundred and eighty-eight patients having radial artery conduits were compared with a control group of 174 patients undergoing only CABG.[102] The only difference in the groups was an incidence of radial sensory neuropathy of 9.9% versus 5.2% in the control group.

HEMATOLOGIC COMPLICATIONS

Deep Venous Thrombosis and Pulmonary Emobilization

In a New York State Registry study, deep vein thrombosis (DVT) and pulmonary embolus (PE) were the fifth most common reason for readmission, accounting for 6.3% of readmissions.[103] This is in contrast to data published 15 years ago, when DVT and PE were thought to be infrequent complications with no indication for postoperative prophylaxis.[104]

Predischarge venous ultrasonography was performed in 330 patients after CABG.[105] Sixty-seven of 330 patients (20%) had DVT documented. The clots were found equally in the vein harvest leg and the nonoperative leg; 84% were in the calf and 16% in a proximal thigh vein. One patient had a massive PE, and one patient a symptomatic proximal DVT. In a second study, 66,180 patients were reviewed for symptomatic venous thromboembolism within 90 days of CABG.[106] Seven-hundred thirty-six of 66,180 patients developed either a symptomatic DVT or a PE. Two-thirds of the patients had been discharged at the time of diagnosis.

The most common postoperative treatments to prevent DVT are pneumatic compression stockings and anticoagulation with heparin or low-molecular-weight heparin (LMWH). Two-thousand five-hundred and fifty-one patients were assigned randomly to either receive subcutaneous heparin alone or subcutaneous heparin and pneumatic compression devices.[107] Sixty-nine of 2551 patients had a PE diagnosed, with 48 of the 69 patients being inpatients receiving only subcutaneous heparin. The heparin-only group had twice the number of PEs. The incidence of DVT diagnosed at discharge and on admission to an extended-care unit is decreased by using subcutaneous heparin or LMWH until hospital discharge.[108] DVT was found in 17.4% of patients on admission to the facility, with two PEs and one death from PE. Unilateral compression devices were not as protective as bilateral devices because either leg can be involved. Risk factors for DVT and PE were age, female gender, and postoperative complications.

Heparin-Induced Thrombocytopenia

Unfractionated heparin used during cardiopulmonary bypass can cause heparin-dependent platelet antibodies in 25 to 50% of open-heart patients in the immediate postoperative period.[109,110] This antibody-mediated thrombocytopenia is important because of its relationship to hypercoagulability in the form of venous and arterial thrombosis.[111] Heparin-induced thrombocytopenia (HIT) is diagnosed when two criteria are met: antibody seroconversion with either thrombocytopenia or clinical findings such as fevers and skin lesions. The risk of developing this clinical syndrome may be as high as 1 to 2% of cardiac surgical patients.[109]

The incidence of heparin-platelet factor 4 (PF4) antibody formation to either bovine or porcine heparin was studied in 207 patients.[112] Forty-four of 99 patients who received bovine heparin converted (44.4%), as did 33 of 108 patients who had received porcine heparin (30.6%). Ninety percent of the patients converted by the second postoperative day.

Patients who have had an episode of HIT preoperatively still can undergo cardiac surgery. In 4850 patients reviewed over 2 years, 10 had HIT prior to surgery.[113] Four

patients were anticoagulated with danaparoid sodium and six with heparin sodium after pretreatment with epoprostenol sodium. Platelet counts were not affected, and bleeding was not an issue.

Patients who have a history of HIT but are antibody-negative may have cardiac surgery using heparin.[111] Patients with HIT but no thrombosis should have an alternative regimen using lepirudin, argatroban, bivalirudin, or danaparoid.

HOSPITAL READMISSIONS

Hospital readmissions were 12.9% at 30 days after surgery in a study by the New York State Cardiac Surgery Reporting System.[103] In 1999, 16,325 patients had CABS, with 2111 being readmitted within 30 days. Postoperative infection and heart failure were the two most common reasons for readmission. The patient characteristics that were related to readmission were older age, female sex, African-American race, greater body surface area, and MI within 1 week. In a second study, patients older than 75 years of age had a readmission rate twice as high as younger patients (<64 years of age).[114] The three most common reasons were atrial fibrillation, chest pain, and CHF. However, in this study, 75% of patients older than 75 years of age recovered uneventfully. Readmission rates for women when matched carefully for disease severity may be the same as for men.[115]

Predicting readmissions is difficult because many are related to inadequate home care.[116] In one study, 44% of patients who were readmitted after CABG entered a community hospital.[117] Early discharge is not related to readmissions.[118,119] The reasons for readmission 2 years after CABG are recurrent angina pectoris and CHF.[120] Forty-four percent of the patients discharged after bypass surgery were readmitted at 2 years.

QUALITY OF LIFE

Indications for CABS include treatment of symptoms, prevention of heart attacks, and prolongation of life. However, these are related to the basic end point of returning our patients to an activity level that makes life enjoyable and worth living. Revascularization trials, including angioplasty and surgery, have documented improvement in quality of life as compared with medical therapy.[121,122] Cardiovascular mortality has decreased over the past three decades, and this may be due to the availability of revascularization interventions as compared with medical therapy.[122]

Two-hundred and fifteen consecutive open-heart patients were followed preoperatively and postoperatively with questionnaires to assess changes in quality of life.[123] Eighty percent of patients documented improvement. Patients had less improvement in energy if they were older than 70 years of age and in New York Heart Association (NYHA) functional class III or IV; patients had less improvement in sleep if they were older than 70 years of age; patients had less improvement in physical mobility if they were in NYHA functional class of III or IV. Other areas studied were social isolation and postoperative pain. Postoperative complications versus an uncomplicated recovery and valve versus bypass surgery had the same improvement.

Patients were studied 10 years after CABG for identification of factors that decreased quality of life.[124] Two thousand patients were entered, with 663 patients dying in the 10 years. Diabetes and COPD predicted decreased quality of life in all three tests that were used. Older age, female gender, and hypertension were predictors in two of the three tests. Predictors in a single test were preoperative duration of angina, preoperative functional class, cerebrovascular disease, obesity, duration of respiratory treatment, and postoperative use of inotropic drugs.

Preoperative patient characteristics play an important role in postoperative improvement.[125] Five-hundred and twenty-nine patients were followed at 6 months after elective bypass surgery for physical and mental health improvement. Of these, 73.2% had improvement in physical health and 41.6% in mental health. Patients with a body mass index over 35 kg/m^2, diabetes, COPD, peripheral vascular disease, and poor baseline physical function did not improve as much.

Gender and age have been shown to have an impact on quality of life after bypass surgery. Five-hundred and eight bypass patients were divided into three age groups: younger than 64 years of age, 65 to 74 years of age, and older than 75 years of age. The groups were studied at 1 year for physical, mental, and general health. Patients over age 75 did not have significant improvement in scores postoperatively.[126] However, other papers show that elderly patients can benefit. One-hundred and twenty-seven patients older than 80 years of age were followed after open-heart surgery,[127] with a mortality of 7.9% at 30 days and actuarial survival at 1 year of 83% and 2 years of 80%. Of those living, 83.7% were living at home, and 74.8% felt that they were in good health. Female gender has been reported to be a risk factor for decreased quality of life.[128] When women are matched to men, female gender is not associated with increased mortality or morbidity.[129]

In patients who undergo emergency bypass surgery or who are extremely ill after surgery, functional results appear good in the survivors.[130] Patients who survived to discharge had as good a functional recovery as historical controls that were not in cardiogenic shock. In addition, patients who suffer a cardiac arrest after surgery, if they survive, have a good functional recovery.[131] However, functional recovery in patients who have prolonged ICU stays (>5 days) is poor.[132]

CONCLUSION

As databases mature, expected outcomes are established. These expected outcomes will be used to measure existing clinical programs against a national standard. As an example of how this information may be applied, the Society of Thoracic Surgeons has released data about process measures and outcome

measures on participating programs to insurance companies.[133] The federal government through Medicare is trying to institute "pay for performance " initiatives whose intentions are to link reimbursement with expected results. Thus, the data collected on postoperative complications will become increasingly scrutinized and addressed with national standards.

At no time in the history of modern medicine have physicians and the health care system been more able to define and accurately report data related to procedural complications. The best strategies for prevention of complications derives from a full understanding of the periprocedure risk factors. The practice of quality surgery no longer can be limited to perioperative judgment and technical skill but should embrace the broadest aspects of medical care. This must include ongoing analysis of personal and cohort research and selected refinement to improve judgment and skill.

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PART

III

Ischemic Heart Disease

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CHAPTER 20

Indications for Revascularization

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Coronary artery disease (CAD) remains the most common pathology with which cardiologists and cardiac surgeons are faced. Accordingly, the practicing cardiac surgeon is confronted with no clinical question more often than "Is coronary bypass indicated in this patient?" It is our aim here to provide a practical overview of the current indications for myocardial revascularization with sufficient reference to the relevant studies on which they are based to afford the reader an appreciation of the strengths and limitations of their conclusions.

CLINICAL AND LABORATORY ASSESSMENT OF CORONARY ARTERY DISEASE

A surgeon's first introduction to a patient with CAD is frequently an angiogram. In addition to the coronary anatomy, the clinical presentation and results of noninvasive studies of myocardial perfusion and function are necessary to characterize the pathophysiologic implications of the angiographic disease and its impact on prognosis. Nonetheless, in the technological era in which we practice, the pivotal importance of the clinical history bears emphasis—particularly in an aging population. Since one of the objectives of surgery is to improve symptoms and quality of life, a thorough appreciation of the patient's functional status is a prerequisite to selecting the optimal therapeutic strategy.

The system proposed by the Canadian Cardiovascular Society (CCS) for grading the clinical severity of angina pectoris is accepted widely[1] (Table 20-1). Unfortunately, angina is a highly subjective phenomenon for both patient and physician, and prospective evaluation of the assessment of functional classification by the CCS criteria has demonstrated a reproducibility of only 73%.[2] Furthermore, there may be a strikingly poor correlation between the severity of symptoms and the magnitude of ischemia, as is notoriously the case among diabetic patients with asymptomatic "silent ischemia."

Electrocardiography, if abnormal, is helpful in assessing ischemic burden. Unfortunately, it demonstrates no pathognomonic signs in half of patients with chronic stable angina.[3] Conversely, a normal electrocardiogram (ECG) is a strong indicator of normal left ventricular (LV) function.[4] The monitoring of an ECG under stress conditions is simple and inexpensive and therefore is useful as a screening examination. Among patients with anatomically defined disease, stress ECG provides additional information about the severity of ischemia and the prognosis of the disease.[5–7] The sensitivity of the test increases with patient age, with the severity of the patient's disease, and with the magnitude of observed ST-segment shift.[5] If ST-segment depression is greater than 1 mm, stress ECG has a predictive value of 90%, whereas a 2-mm shift with accompanying angina is virtually diagnostic.[8] Early onset of ST-segment depression and prolonged depression after discontinuation of exercise are strongly associated with significant multivessel disease. Unfortunately, many patients cannot achieve their target heart rates owing to beta blockade or a limitation to their exercise tolerance as a result of coexisting disease, decreasing the usefulness of this test in these often high-risk patients. Resting abnormalities in the ECG also may limit the predictive accuracy of the test.

Perfusion imaging with thallium-201- or a technetium-99m-based tracer may be particularly useful in patients with abnormalities on their baseline ECG. Reversible defects demonstrated by comparison of images obtained after injection of the tracer at peak stress with rest images is indicative of ischemia and hence viability. An irreversible defect indicates nonviable scarring.[9,10] The results obtained with both tracers are similar, with the average sensitivity around 90% and specificity of approximately 75%.[5] For patients unable to exercise, pharmacologic vasodilators such as adenosine or dipyridamole may be used with similar sensitivity.[11–15]

Echocardiographic imaging during exercise or pharmacologic stress has gained increasing popularity among

Table 20–1.

Canadian Cardiovascular Society Angina Classification

0 = no angina
1 = angina only with strenuous or prolonged exertion
2 = angina with walking at a rapid pace on the level, on a grade, or up stairs (slight limitation of normal activities)
3 = angina with walking at a normal pace less than two blocks or one flight of stairs (marked limitation)
4 = angina with even mild activity

cardiologists. Comparative studies have demonstrated accuracy similar to that of nuclear studies,[4,16,17] with sensitivity and specificity both around 85%.[5] Patients unable to exercise may be stressed with high-dose dipyridamole[18,19] or, more commonly, dobutamine at doses from 5 to 40 μg/kg per minute.[5,18,19] An initial augmentation of contractility followed by loss or "dropout" is diagnostic of ischemia (and, accordingly, viability), whereas failure to augment contractility at low dose suggests scar.[10,20,21] Additionally, information regarding concomitant valvular disease may be obtained during the examination.

GUIDELINES FOR REVASCULARIZATION

The guidelines for surgical revascularization established by the American College of Cardiology (ACC) and American Heart Association (AHA) are shown in Table 20-2.[22] The basis for these guidelines reside in the large body of literature comparing medical therapy with surgical revascularization and, more recently, percutaneous coronary interventions (PCIs).

Before reviewing the results of the seminal trials of coronary artery bypass grafting (CABG) versus medical therapy performed in the 1970s and those of newer prospective, randomized trials comparing the results of surgery with PCI and medical therapy, some limitations of these trials must be recognized. First, in retrospective or registry studies, it is difficult to ensure comparable patient populations by virtue of the extraordinary anatomic and physiologic complexity of CAD, as well as the heterogeneity of the patient substrate. Differences in ventricular function and comorbidities such as age, diabetes, peripheral vascular disease, and pulmonary disease may have a profound impact on outcomes such as survival and quality of life. This becomes particularly relevant among the elderly "sick" patient population, which in many centers may comprise the majority referred for CABG. For example, caution must be exercised in interpreting the results of nonrandomized and registry reports of PCI versus surgery because the patients subjected to the former more often have single- or double-vessel disease,[23–25] whereas the latter commonly have triple-vessel or left-main disease.[23,25] Attempts to correct for selection bias with statistical techniques such as propensity matching, are only as valid as the parameters entered into the model. Data less tangible than gender or chronologic age, such as socioeconomic status or "physiologic age," are not accounted for easily in such analyses and yet may be a critical determinant of outcomes. Despite this limitation, retrospective and registry data provide a better glimpse of the real world of CAD. Most prospective, randomized trials include only a fraction of the total population undergoing revascularization by virtue of strict entry criteria. For example, the Bypass Angioplasty Revascularization Investigators (BARI) trial[26] entered only 5% of total patients screened. Therefore, although the prospective, randomized studies do provide objective data directly applicable to the specific patient subset represented in the study, extrapolation of the results to the more heterogeneous populations seen clinically can only be made if the implicit caveats are clearly understood. We must be mindful of the inescapable tradeoff between selection bias in registry studies and entry bias in randomized studies.

A second limitation of these studies is a consequence of the over-representation of patients at lowest risk of death in randomized trials; most are statistically underpowered with respect to survival analysis. For example, given current survival statistics, we would need approximately 2000 patients in each arm of a study to detect a 30% difference in mortality. The problem is compounded by the exclusion of the very patients for whom one would anticipate a survival advantage with adequate revascularization, such as those with depressed ventricular function. Randomized studies frequently employ softer endpoints such as angina or quality of life or create composites of qualitatively different endpoints, such as death, stroke, and myocardial infarction (MI). Meaningful analysis is further complicated by relatively short-term follow-up in most studies. Events, such as the need for subsequent revascularization and recurrence of angina, characteristically occur at different time intervals after these therapies (restenosis after PCI versus graft occlusion after CABG), and an 8- to 10-year follow-up period is needed to compare long-term results adequately. Patients themselves also generally are interested in outcomes measured in years, not months.

A third limitation is that significant improvements in each of these treatment strategies are occurring constantly. Examples include the use of antiplatelet agents,[27] angiotensin-converting enzyme (ACE) inhibitors,[28] lipid-lowering therapy,[29] internal thoracic aortic (ITA) grafts, and intravascular stents[30] and the development of drug-eluting stents.[31] These advances, along with aggressive secondary prevention after revascularization, have reduced the morbidity and mortality of CAD steadily in all patients, making

Table 20–2.

AHA/ACC Guidelines for CABG*

Asymptomatic/mild angina

Class I

1. Left main stenosis
2. Left main equivalent (proximal LAD and proximal circumflex)
3. Triple-vessel disease

Class lla

1. Proximal LAD stenosis and one- or two-vessel disease

Class IIb

1. One- or two-vessel disease not involving proximal LAD

If a large territory at risk on noninvasive studies or LVEF < 50%, IIa and IIb become class I indications

Stable angina

Class I

1. Left main stenosis
2. Left main equivalent (proximal LAD and proximal circumflex)
3. Triple-vessel disease
4. Two-vessel disease with proximal LAD stenosis and EF < 50% or demonstrable ischemia
5. One- or two-vessel disease without proximal LAD stenosis but with a large territory at risk and high risk criteria on noninvasive testing
6. Disabling angina refractory to medical therapy

Class IIa

1. proximal LAD stenosis with one vessel disease
2. One- or two-vessel disease without proximal LAD stenosis, but with a moderate territory at risk and demonstrable ischemia

If a large territory at risk on noninvasive studies and meets high risk criteria on noninvasive testing becomes a class I indication

Unstable angina/non-ST-segment elevation MI (NSTEMI)

Class I

1. Left main
2. Left main equivalent
3. Ongoing ischemia not responsive to maximal nonsurgical therapy

Class IIa

1. proximal LAD stenosis with one- or two-vessel disease

Class IIb

1. One- or two-vessel disease without proximal LAD stenosis when PCI not possible (becomes class I if high risk criteria on noninvasive testing)

ST-segment Elevation (Q-wave) MI

Class I

1. Failed PCI with persistent pain or hemodynamic instability and anatomically feasible
2. Persistent or recurrent ischemia refractory to medical treatment with acceptable anatomy who have a significant territory at risk and not a candidate for PCI
3. Requires surgical repair of postinfarction ventricular septal rupture or mitral valve insufficiency
4. Cardiogenic shock in patients less than 75 years of age who have ST-segment elevation, LBBB, or a posterior MI within 18 hours of onset
5. Life-threatening ventricular arrhythmias in the presence of ≥ 50% left main stenosis or triple-vessel disease

Class IIa

1. Primary reperfusion in patients who have failed fibrinolytics or PCI and are in the early stages (6–12 hours) of an evolving STEMI
2. Mortality with CABG is elevated the first 3–7 days after STEMI/NSTEMI. After 7 days, criteria for revascularization in previous sections apply

(continued)

Table 20–2.

AHA/ACC Guidelines for CABG* *(continued)*

Poor LV function
Class I
1. Left main stenosis
2. Left main equivalent
3. Proximal LAD stenosis and two- to three-vessel disease
Class IIa
1. Significant viable territory and noncontractile myocardium
Life-threatening ventricular arrhythmias
Class I
1. Left main disease
2. Three-vessel disease
Class IIa
1. Bypassable one- or two-vessel disease
2. Proximal LAD disease and one- or two-vessel disease
These become class I indications if arrhythmia is resuscitated cardiac death or sustained ventricular tachycardia
Failed PCI
Class I
1. Ongoing ischemia with significant territory at risk
2. Hemodynamic instability
Class IIa
1. Foreign body in critical position
2. Hemodynamic instability with coagulopathy and no previous sternotomy
Class IIb
1. Hemodynamic instability with coagulopathy and previous sternotomy
Previous CABG
Class I
1. Disabling angina refractory to medical therapy
2. Nonpatent previous bypass grafts, but with class I indications for native CAD
Class IIa
1. Large territory at risk
2. Vein grafts supplying LAD or large territory are greater than 50% stenosed

**Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or efficacy of a procedure. Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb: Usefulness/efficacy is less well established by evidence/opinion. Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.*

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass grafting; EF = ejection fraction; LAD = left anterior descending; LITA = left internal thoracic artery; LVEF = left ventricular ejection fraction; PCI = percutaneous transluminal coronary angioplasty.

differences in the hard endpoint of survival difficult to demonstrate for any therapy.[32] This trend likely will increase as the beneficial impact of the "quiet revolution" of secondary prevention becomes more widely appreciated.

COMPARATIVE TRIALS OF REVASCULARIZATION VS. MEDICAL THERAPY IN STABLE ANGINA

Medical Therapy

In the decades since CABG was popularized[33] and coronary angioplasty was introduced,[34] an enormous volume of data on the results of invasive revascularization has been collected. Remarkably, almost from the outset, many of these studies have been prospectively randomized. Yet, in the current era, there is a dearth of data concerning pharmacologic therapies for chronic CAD despite remarkable progress in recent years. For example, although nitrates are unquestionably effective in relieving symptoms, the impact of long-acting nitrates on clinical outcomes has never been tested rigorously. Furthermore, there has been only one trial of beta-blocker therapy in the treatment of angina, the Atenolol Silent Ischemia Trial (ASIST), which demonstrated benefit for patients with mild effort-induced angina or silent ischemia.[35] A handful of studies of combination therapy with beta blockers and calcium channel blockers also has demonstrated antianginal benefit.[36–38] Most recently, randomized trials of

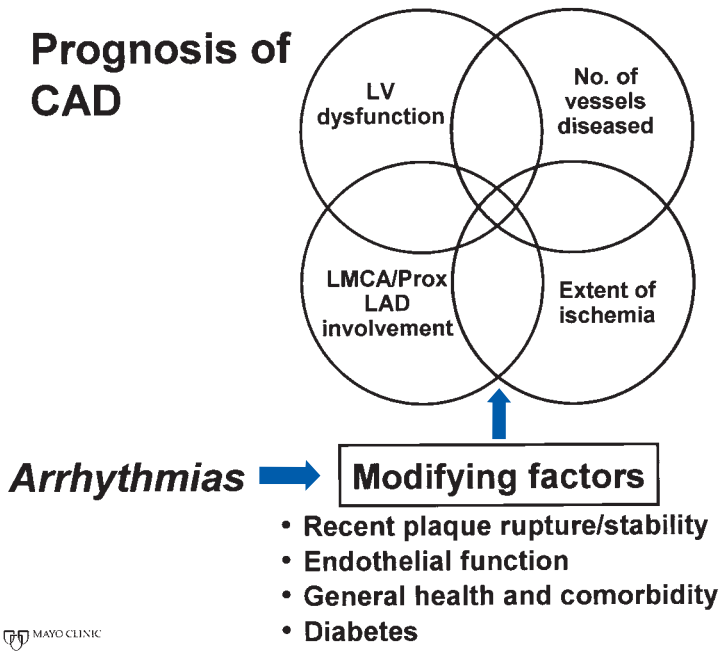

Figure 20-1. The decision regarding mode of therapy for coronary artery disease depends on the individual patient's prognosis as determined by both cardiac and noncardiac conditions.

two new drugs, nicorandil and ranolazine, have been reported.[39,40] However, beyond these few studies, there is little published on the impact of medical therapy alone on survival.

Surgical versus Medical Therapy

Three major randomized studies, the Coronary Artery Surgery Study (CASS),[41] the Veterans Administration Cooperative Study Group (VA),[42,43] and the European Coronary Surgery Study (ECSS),[44,45] as well as several other smaller randomized trials[46–48] conducted between 1972 and 1984, provide the foundation for comparing the outcomes of medical and surgical therapy. Despite the limitations noted earlier, these studies are remarkably consistent in their major findings, and the qualitative conclusions drawn from them continue to be generalizable to current practice.

The central message from all these studies is that the relative benefits of bypass surgery over medical therapy on survival are greatest in the patients at highest risk, as defined by the severity of angina and/or ischemia, the number of diseased vessels, and the presence of left ventricular (LV) dysfunction[42,49] (Fig. 20-1). For example, thus far, no study has shown survival benefit for CABG over medical therapy for patients with single-vessel disease.[50–52] It should be emphasized, however, that these trials involved primarily patients with moderate chronic stable angina. These conclusions therefore may not necessarily apply to patients with unstable angina or to patients with more severe degrees of chronic stable angina.

A meta-analysis[49] of the seven randomized trials cited earlier demonstrated a statistically enhanced survival at 5, 7, and 10 years for surgically treated patients at highest risk (4.8% annual mortality) and moderate risk (2.5% annual mortality) but no evidence of a survival benefit for the patients at lowest risk.[49] The overall survival benefit at 12 years for the three large and four smaller randomized studies is shown in Fig. 20-2. Nonrandomized studies also have demonstrated a beneficial effect of surgery on survival of patients with multivessel disease and severe ischemia regardless of LV function.[53–56]

There have been three recent randomized, controlled trials of invasive revascularization by PCI or CABG versus medical therapy. Their results make an even stronger case for revascularization. In the Asymptomatic Cardiac Ischemia Pilot (ACIP) trial, patients with anatomy amenable to CABG were randomized to angina-directed anti-ischemic therapy, drug therapy guided by noninvasive measures of ischemia, or revascularization by CABG or PCI.[57] At 2 years, mortality

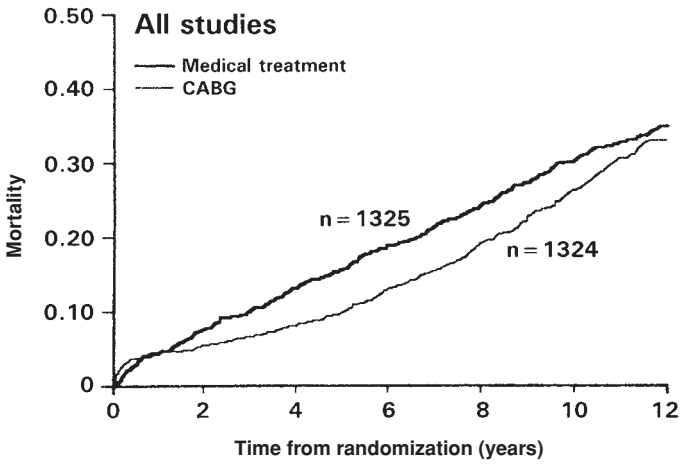

Figure 20-2. Survival (mortality) curves for all medically and surgically treated patients with chronic stable angina enrolled in seven prospective, randomized, controlled trials. *(Reproduced with permission from Yusuf S, Zucker D, Peduzzi P, et al: Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomized trials by the Coronary Artery Bypass Graft Surgery Trialist Collaboration. Lancet 1994; 344:563.)*

was 6.6% in the angina-guided group, 4.4% in the ischemia-guided group, and 1.1% in the revascularization group. The rates of death or MI were 12.1, 8.8, and 4.7%, respectively. By pairwise testing, the differences between revascularization and angina-guided therapy were statistically significant. The Medicine, Angioplasty, or Surgery Study (MASS-II) randomized patients with multivessel disease among medical therapy, PCI, and CABG. While survival at 1 year was equivalent, freedom from additional intervention was 99.5% for surgical patients and 93.7% for medically treated patients. Reintervention, incidentally, was even higher in the PCI group than in the medical group, with 86.7% free of additional intervention. Angina relief was superior in the CABG group (88%) than in the PCI group (79%) or the medical therapy group (46%).[58]

In the Trial of Invasive versus Medical Therapy in Elderly Patients with Chronic Symptomatic Coronary Artery Disease (TIME), elderly patients with chronic angina were studied. This trial failed to demonstrate a difference between optimized medical therapy and an invasive revascularization strategy (PCI or CABG) in terms of symptoms, quality of life, and death or nonfatal MI (20 versus 17%; $p = .71$). However, medically treated patients were at higher risk owing to major clinical events (64 versus 26% for invasive; $p < .001$), which mainly were attributable to rehospitalization and revascularization.[59] In this trial of severely symptomatic elderly patients, it was encouraging that the price of an initially conservative strategy, followed by crossover to revascularization in approximately 50% of patients, was not paid for in terms of death or MI.[59]

Early concern over a prohibitive operative mortality among patients with impaired ventricular function has been superseded by recognition that the survival of these patients on medical therapy was much worse than their survival with revascularization. This, coupled with ever-improving surgical techniques, such as advances in myocardial preservation and perioperative support, has made this specific subgroup the one in which the relative survival benefit of surgical therapy is the greatest. Accordingly, LV dysfunction in patients with documented ischemia is now considered an important indication—rather than a contraindication—for surgical revascularization.[41,49,53,60,61] Recent evidence that ischemic, viable, hypokinetic myocardium (hibernating or stunned) regains stronger contractile function following effective revascularization has prompted expansion of the indications for surgical revascularization among patients with severe LV dysfunction to include patients who otherwise would be considered candidates for cardiac transplantation. This subject is discussed in more detail below.

In summary, with regard to chronic stable angina, a survival advantage is demonstrable for surgical revascularization over medical therapy in patients with left main disease,[62] triple-vessel disease and LV dysfunction,[63,64] two-vessel disease and proximal left anterior descending (LAD) disease,[65] and severe ischemia and multivessel disease[66,67] (Fig. 20-3). These survival advantages have not been demonstrable among patients with single-vessel disease.[68–70]

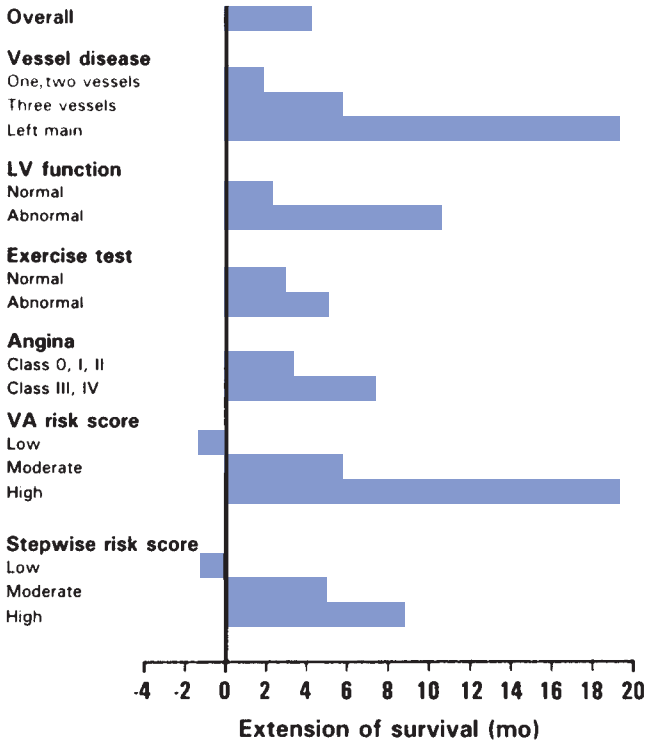

Figure 20-3. Extension of survival in months for various subgroups of patients with chronic stable angina treated by surgery as compared with those treated by medicine in seven prospective, randomized, controlled trials. *(Reproduced with permission from Yusuf S, Zucker D, Peduzzi P, et al: Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomized trials by the Coronary Artery Bypass Graft Surgery Trialist Collaboration. Lancet 1994; 344:563.)*

Apart from affording a survival benefit, CABG is indicated for the relief of angina pectoris and improvement in the quality of life. Between 80 and 90% of patients who are symptomatic on medical therapy become symptom-free following CABG. This benefit extends to low-risk patients for whom survival benefit from surgery is not likely.[49] Relief of symptoms appears to relate to both the completeness of revascularization and the maintenance of graft patency, with the benefit of CABG diminishing with time. Recurrence of angina following CABG occurs at rates of 3 to 20% per year. Although enhanced survival is reported when an ITA graft is used to the LAD artery, there is no significant difference in postoperative freedom from angina.[70] This may be due to vein graft occlusion or progression of native disease in grafted or ungrafted vessels.[42]

Unfortunately, few patients experience an advantage in work rehabilitation with surgery compared with medical management. Generally, employment declines in both groups and is determined nearly as much by socioeconomic factors such as age, preoperative unemployment, and type of job as by type of therapy or clinical factors such as postoperative angina. Notably, surgical revascularization has not been shown to reduce the incidence of nonfatal events such

as MI, although this may be due to perioperative infarctions that offset the lower incidence of infarction in each study follow-up.[54,71]

PCI versus Medical Therapy

Despite the increasing application of catheter-based technology to multivessel disease, most interventions historically have been in single-vessel disease.[25] Accordingly, most of the data comparing angioplasty with medical therapy are derived from studies consisting principally or exclusively of patients with a limited extent of obstructive disease, although most people with angiographically detectable stenosis in one vessel have more extensive atherosclerotic changes throughout other coronary vessels. Many of these trials also antedate the use of glycoprotein IIb/IIIa inhibitors, clopidogrel, and stents. Although angiographic success rates of 85 to 90% are commonplace, no study to date has ever shown a benefit in survival or subsequent MI for PCI over medical therapy in patients with stable angina pectoris. The results of several recent studies, however, have demonstrated improvement in symptoms and exercise tolerance.

In the ACME-I (A Comparison of Angioplasty with Medical Therapy) study, 212 patients with documented ischemia and a single coronary artery stenosis greater than 70% were assigned randomly to medical therapy or angioplasty.[72] After 6 months, there was no mortality difference in either treatment group, but PCI provided more complete angina relief with fewer medications and better quality-of-life scores, as well as longer exercise duration on stress testing, than medical therapy.[72] This benefit came at some cost, however; among the 100 angioplasty patients, 19 underwent repeat PCI, and 7 underwent CABG during the first 6 months, compared with 11 angioplasty procedures and no CABG in the patients randomized to medical therapy.[72] Moreover, nearly half of all patients assigned to initial medical therapy were asymptomatic at 6 months. Because this modest symptomatic benefit was achieved at such a large procedural and financial cost, patients who are either asymptomatic or have mild symptoms should have objective evidence of ischemia prior to PCI.[73] In a follow-up study by the same investigators, 101 patients with stable angina and two-vessel disease were randomized to PCI or medical therapy.[74] At 6 months, both groups had similar improvement in exercise duration, freedom from angina, and overall quality of life. These studies together suggest that in many patients an initial trial of medical therapy is appropriate.

Several recent studies have included patients with multivessel disease. In the Randomized Intervention Treatment of Angina-2 (RITA-2) study of 1018 patients with stable angina randomized to medicine or PCI, one-third had two-vessel disease, and 7% had three-vessel disease.[75] Perhaps surprisingly, at a median follow-up of 2.7 years, the primary endpoints of death or MI had occurred twice as often in the PCI group (6.3 versus 3.3%; $p < .02$). Surgical revascularization was required during the follow-up interval in 7.9% of the PCI group, and repeat angioplasty was required in 11%. In the medical group, 23% of patients required revascularization. Angina relief and exercise tolerance were improved to a greater degree in the angioplasty group early, but this difference disappeared by 3 years.[75] These results are echoed in the MASS-II trial, in which angina relief was superior with PCI, but rates of intervention/reintervention were higher in the PCI group.[58] Again, this supports an initial strategy of medical therapy.

A comparison of PCI versus medicine as initial strategy among patients with hyperlipidemia was done in the Atorvastatin versus Revascularization Trial (AVERT).[76] Among 341 patients with single- or double-vessel disease, ischemic events were less common in the medical therapy group than in the PCI group (13 versus 21%; $p < .05$). Although criticized for employing outdated angioplasty technology and other issues, the results of this study are consonant with the recent demonstration that lipid-lowering agents may have a powerful impact on ischemic events.[77–79] In some respects, the lower use of aggressive lipid-lowering agents in the PCI arm biased the results in favor of medical therapy.

A meta-analysis of percutaneous interventions versus medical management was published in 2005.[80] In patients with stable CAD, no benefit was found for invasive therapy in terms of death, MI, or need for subsequent revascularization. This provides compelling evidence that, thanks to substantial improvements in medical management, all patients should have a trial of optimized medical therapy prior to invasive intervention.[80]

PCI versus CABG

Randomized studies

A number of studies comparing an initial strategy of angioplasty versus early surgery have been carried out, all with similar results. It is important to recognize that these studies are comparisons of treatment strategies and not head-to-head comparisons of revascularization techniques. Accordingly, crossover is permitted, and endpoints are selected to determine adverse consequences of the algorithm.

A single-center Swiss study of 134 patients with isolated LAD artery disease was reported in 1994.[52] At 2.5 years of follow-up, there was no significant difference in combined outcomes of MI and cardiac death between treatment groups. There was, however, a greater need for surgical revascularization in the initial PCI treatment group, with 25% requiring a second revascularization procedure compared with only 4.4% in the initial CABG group. Although the PCI patients were taking significantly more antianginal medication, clinical impairment level, stress-test performance, and quality-of-life indices did not differ at 2 years. These findings held up at 5 years,[81] with no difference between groups with respect to mortality or functional outcome despite repeat procedures in the PCI group.

The Medicine, Angioplasty, or Surgery Study (MASS) from Brazil compared medical therapy, PCI, and CABG using an ITA bypass graft at a single center in 214 patients with stable angina, normal LV function, and proximal stenosis of the

LAD coronary artery.[51] In this relatively small but nonetheless important randomized trial, the combined endpoint of cardiac death, MI, or refractory angina requiring revascularization was statistically significantly less in surgically treated patients. Moreover, there was no significant difference between patients treated medically or with PCI. In comparison with medical therapy, however, both PCI and CABG surgery were shown to provide improved relief of severe symptoms of angina pectoris and a lower frequency of inducible ischemia on treadmill exercise testing. There was no difference among the three strategies with respect to mortality or late MI at 1 year. Similar findings were obtained at 5-year follow-up.[82]

The results of the MASS-II trial, which enrolled 611 patients with multivessel disease, have reported 1-year outcomes as noted earlier.[58] Although technology is a moving target, this trial has the advantage that approximately 70% of PCI patients had stents placed. Despite this, the results were remarkably similar to those of the first MASS trial, with a lower incidence of adverse events in the medical group than in the PCI group. Surgical therapy provided the best angina relief and lowest incidence of adverse events. All therapies had similar survival rates.

A number of larger prospective, randomized studies comparing PCI with CABG have been reported in recent years. All share the limitation that, in general, only a very small minority of patients undergoing revascularization at any center were entered into these trials.[83,84] Accordingly, the populations included in the trials may not be reflective generally of clinical practice. For instance, few patients in these studies had significant LV dysfunction, and most randomized patients had only one- or two-vessel disease. In the RITA trial, approximately one-third of patients had single-vessel disease.[85] Among clinically eligible patients in the BARI[68] trial and the Emory Angioplasty versus Surgery Trial (EAST),[69] approximately two-thirds of patients were excluded on angiographic grounds that included chronic total occlusion, left main coronary artery stenosis, diffuse disease, or other anatomic factors making PCI potentially dangerous.[68,69] Consequently, these randomized trials contain only a portion of the spectrum of patients with CAD encountered clinically.

Entry bias has a significant impact on the likelihood of observing an outcome difference between therapies. Since a high proportion of the randomized patients are in the low-risk group, in whom no survival advantage could be demonstrated when CABG was compared with medical therapy in the earlier CAST, ECSS, and VA randomized trials,[41–43] it is possible that any potential survival benefit of CABG over PCI in high- and moderate-risk groups may be masked.[84]

A second consideration in evaluating these studies is that the success of revascularization procedures depends not only on the criteria employed to define success but also on the interpretation of those criteria by both patient and physician. In the 1985–1986 National Heart, Lung, and Blood Institute PCI Registry, 99% of patients were discharged alive from hospital, and 92% did not sustain a MI or require CABG.[34] In the most recent BARI trial, 99% of patients survived hospitalization, and 88.6% of PCI-treated patients did not have an MI or require repeat revascularization by angioplasty or surgery during the initial hospitalization.[68] Employing event-free criteria (i.e., death, MI, or CABG) for the initial hospitalization, PCI can be judged successful. However, if a repeat revascularization procedure within 5 years is regarded as a negative outcome, then only 45.5% of PCI-treated patients are treated successfully.[68] Regardless, the lack of differences in mortality or MI rates permits individuals to select one or the other procedure as initial therapy without the likelihood that they will pay a serious price.

In the BARI, EAST, CABRI, GABI, and RITA multivessel PCI versus CABG trials,[68,69,85,86,177] mortality was similar between 1 and 5 years of follow-up in both the PCI and CABG treatment groups. Mortality ranged from 3% in the CABRI trial at 1-year follow-up[177] and 3.4% in the RITA trial at 2.5 years[85] to 13% in the BARI trial at 5 years.[68] A slightly higher incidence of MI was noted in some of these trials.

The incidence of repeat revascularization is higher among patients treated with angioplasty than in those treated with surgery in all trials carried out to date. The incidence of repeat revascularization in the PCI-treated patients ranged from 36.5% in the CABRI trial at 1-year follow-up to 62% in the EAST trial at 3 years. The repeat revascularization rate in the EAST trial for angioplasty-treated patients was much higher than that noted in the BARI, CABRI, and RITA trials. There was a concentration of repeat revascularization procedures in trials that required stress thallium and angiography studies at 1 year; thus, some of these procedures may have occurred in the EAST trial as a consequence of protocol-mandated tests rather than clinical indications.[17] In contrast to PCI, repeat revascularization is less common after CABG in these same studies. The incidence of repeat revascularization procedures in multivessel patients randomized to CABG ranged from 3.5% in the CABRI trial to 13.5% in the EAST trial.[69,177] Generally, repeat revascularization procedures were required five to eight times more often in patients with multivessel disease treated initially with angioplasty than in those randomized to initial CABG. The incidence of angina at follow-up also generally was greater in the PCI-treated patients than in those randomized to CABG.

In the BARI trial at 5 years, 54.5% of patients assigned initially to PCI had undergone a repeat revascularization procedure.[68] Of these, 23.2% had repeat PCI, 20.5% underwent CABG, and 10.8% had both PCI and CABG.[68] Sixty-nine percent of PCI-treated patients who were angina-free at 5 years had not required CABG. Among angina-free patients at 5 years, only 48% of the angioplasty-treated patients compared with 94% of the CABG patients had not had an additional revascularization procedure after the initial procedure.[68] An important subgroup analysis of the BARI trial demonstrated a marked survival benefit with surgery for patients with insulin-dependent diabetes receiving an ITA graft.[87]

Several more recent studies of PCI versus surgery have confirmed these findings. The Argentine Randomized Trial of Coronary Angioplasty versus Bypass Surgery in Multivessel Disease (ERACI) trial conducted between 1998 and 1990

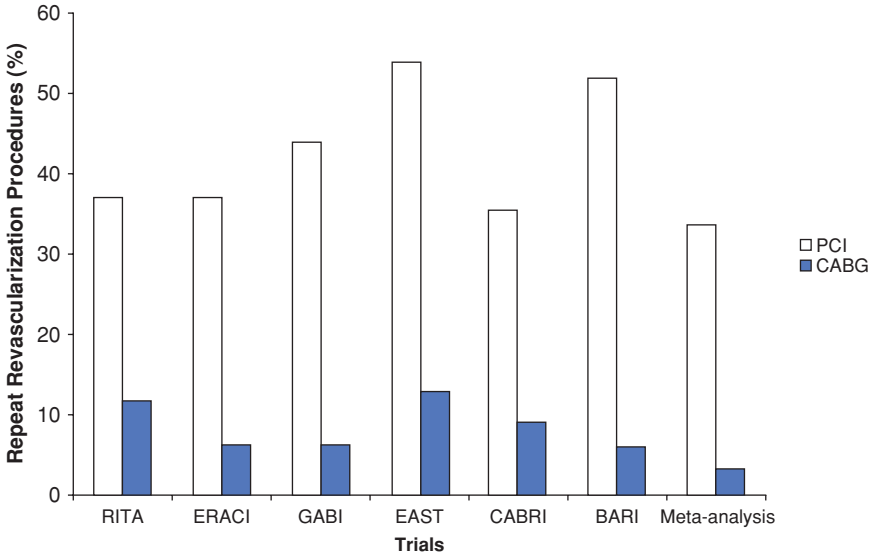

Figure 20-4. Risk of repeat revascularization in six randomized trials of PCI versus CABG and a meta-analysis.[83] See refs. 68, 69, 85, 86, 88, 177 for explanation of acronyms.

demonstrated no difference in death or MI but superior event-free survival in the CABG group at 1 and 3 years.[88,89] In the French Monocentric Study, 152 patients with multivessel disease underwent PCI or CABG.[90] Again, superior event-free survival was seen in the surgical group, driven predominantly by a lesser need for subsequent revascularization.

The impact of stent technology on the comparative results of PCI and CABG has been investigated recently. In the Arterial Revascularization Therapy Study (ARTS), 1205 patients with multivessel disease underwent CABG or PCI with bare-metal stents.[91] No significant differences in the primary endpoint of freedom from death, stroke, or MI at 1 year were observed, although the need for revascularization remained higher in the angioplasty group than in the surgery group. A similar study was performed by the second Argentine Randomized Trial of Coronary Angioplasty versus Bypass Surgery in Multivessel Disease (ERACI-2) study group.[92] Again, even with the use of stents, repeat revascularization was more common in the PCI group, particularly among diabetics, in whom repeat revascularization was reported as 22.3 versus 3.1% in the CABG group.[93] Of note, in this study, the 30-day mortality was higher in the CABG group than in the PCI group, as was the incidence of Q-wave MI. The relatively high operative mortality rate (5.7%) in the surgery group as compared with the angioplasty group has raised many questions. Despite this, at 5 years, there was no difference in survival, and again, CABG patients had a lower incidence of revascularization. The findings of the Surgery or Stent (SOS) study, which compared outcomes in almost 1000 patients with multivessel disease, demonstrated similar all-cause mortality among surgical compared with angioplasty patients and confirmed higher rates of repeat revascularization after angioplasty and lower freedom from angina pectoris in both patients with and without a recent acute coronary syndrome.[94] Of interest in this study, the reintervention rate, while still higher than after surgery, was far below that reported previously for angioplasty at only 17%.

A meta-analysis by Mercado and colleagues combined results from the ARTS, ERATS-II, MASS-II, and SOS trials. One-year outcomes demonstrated similar rates of death, MI, and stroke. Revascularization rates, however, remain higher with PCI.[95]

Recent progress in stent technology, particularly the introduction of drug-eluting devices, promises to further reduce the incidence of restenosis, likely narrowing the gap in late outcome between PCI and CABG. The use of stents certainly has reduced adverse remodeling,[96] and stent eluting medications such as sirolimus and paclitaxel are having a profound effect on the patterns of interventions for CAD. When compared with bare-metal stents, drug-eluting stents (DESs) have not been shown to convey any advantage in terms of MI or mortality but do demonstrate decreased rates of angiographic restenosis and major cardiac events in a meta-analysis of 11 randomized trials.[31] Despite a lack of long-term data, DESs are being implanted with increasing frequency. Interestingly, with the reduction in restenosis rates, evidence suggests that clinical outcomes after stenting may be limited by disease progression in native coronary arteries.[97] Therefore, it is not yet clear what the final impact will be of these burgeoning technologies.

In conclusion, the randomized trials of PCI versus CABG are useful, but only if results are interpreted in a context of patients entering or eligible to enter these trials.[83,84] PCI is a reasonable alternative to CABG, and for many patients, it is the preferred initial approach, provided that the patient understands that there may be a higher incidence of recurrent angina and need for repeat revascularization procedures. This applies to patients with multivessel disease and preserved LV function in the main. For most patients similar to those included in these published trials, it is reassuring that a nonsurgical revascularization procedure does not place them at increased risk of MI or death in comparison with the outcomes of surgical therapy. To extrapolate these results to patients who are not eligible for entry, however, it is intellectually flawed and potentially misleading.

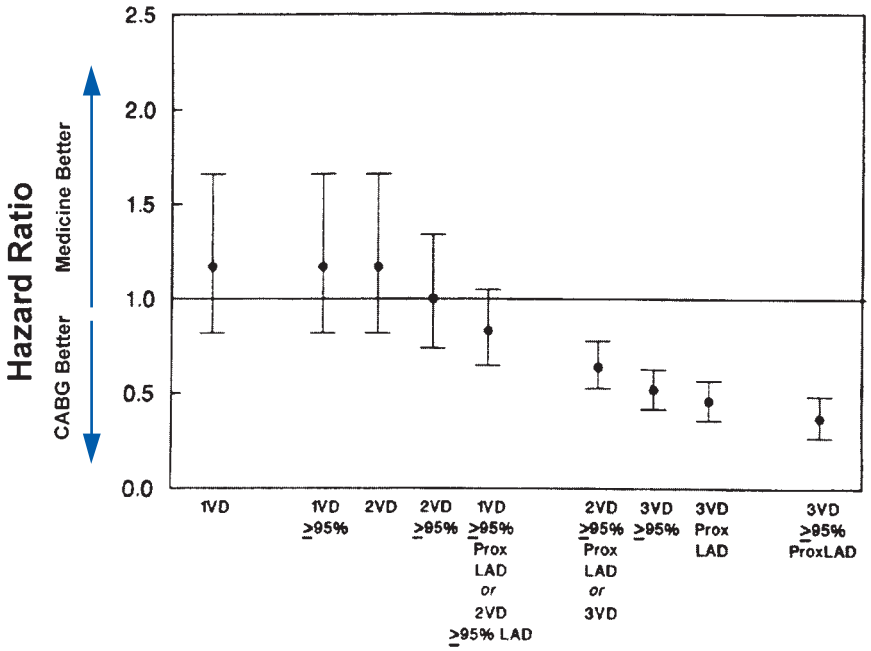

Figure 20-5. Hazard (mortality) ratios for CABG versus medicine calculated from the Cox regression model to evaluate relative survival differences. Points indicate hazard ratios for each level of a weighted (0 to 100), hierarchical, prognostic coronary artery disease index. Bars indicate 99% confidence intervals. Horizontal line at 1.0 indicates point of prognostic equivalence between treatments. Hazard ratios below this line favor CABG; those above the line favor medicine. VD, vessel disease; Prox LAD, proximal left anterior descending coronary artery. *(Reproduced with permission from Mark DB, Nelson CL, Califf RM, et al: Continuing evolution of therapy for coronary artery disease: Initial results from the era of coronary angioplasty. Circulation 1994; 89:2015.)*

Nonrandomized database comparisons

The information provided by randomized studies is completed by information gleaned from large, prospectively managed, nonrandomized database studies. In the Duke Cardiovascular Disease Databank, 9263 patients undergoing clinically indicated coronary angiography between 1984 and 1990 were followed for a mean of 5 years after nonrandomized treatment by CABG, PCI, or medical therapy.[25] Patients with valvular disease, prior revascularization, significant (>75%) left main disease, and congenital and nonischemic cardiomyopathy were excluded. Overall, 39% of the patients had single-vessel disease, 31% had two-vessel disease, and 30% had three-vessel disease. Initial therapy was medical in 3053 patients, PCI in 2788 patients, and CABG in 3422 patients. To correct for baseline differences among treatment groups, a standard covariate adjustment was performed that included all identified prognostic factors in a multivariate survival model. Complete follow-up was obtained in 97% of patients. The 5-year survival was 91%, remarkably similar to that reported from Emory, which showed an overall adjusted 5-year survival rate of 93% in both groups.[61] The mortality hazard ratios derived from the Cox regression model to evaluate relative survival differences in this database study are shown for medicine versus CABG in Fig. 20-5, PCI versus medicine in Fig. 20-6, and PCI versus CABG in Fig. 20-7.[25]

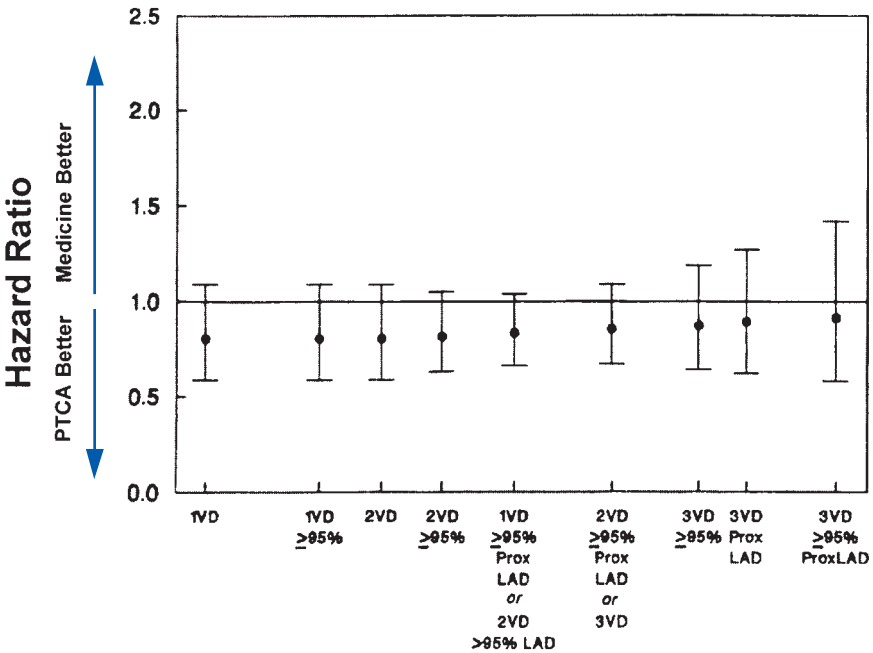

Figure 20-6. Hazard ratios for PCI versus medicine. See Fig. 20-4 for explanation. Points below the horizontal line favor PCI. *(Reproduced with permission from Mark DB, Nelson CL, Califf RM, et al: Continuing evolution of therapy for coronary artery disease: Initial results from the era of coronary angioplasty. Circulation 1994; 89:2015.)*

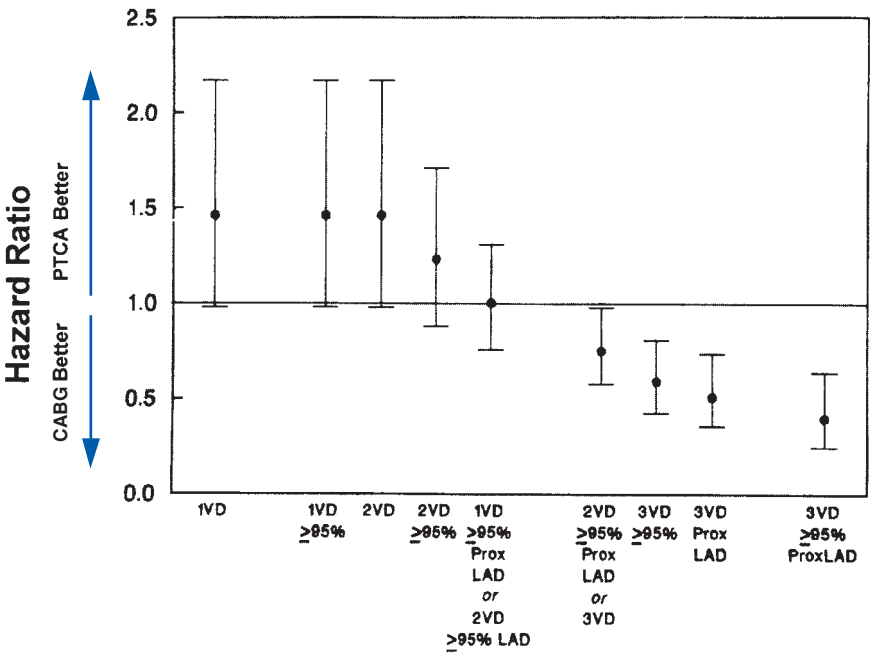

Figure 20-7. Hazard ratios for CABG versus PCI. See Fig. 20-4 for explanation. Points below the horizontal line favor CABG (not PCI as mislabeled). *(Reproduced with permission from Mark DB, Nelson CL, Califf RM, et al: Continuing evolution of therapy for coronary artery disease: Initial results from the era of coronary angioplasty. Circulation 1994; 89: 2015.)*

From a practical standpoint, in this database study and in the randomized trials, the effect of revascularization on survival depended largely on the extent of the CAD and is an example of the concept of benefit in relationship to a "gradient of risk." For the least severe (one-vessel) disease, there were no survival advantages of revascularization over medical therapy in up to 5 years of follow-up.[25] For intermediate levels of CAD severity (i.e., two-vessel disease), there was a higher 5-year survival rate for patients undergoing revascularization than for those treated medically. For patients with the most severe CAD (i.e., three-vessel disease), CABG provided a significant and consistent survival advantage over medical therapy. PCI appeared prognostically equivalent to medical therapy in these patients, but only a small number of patients in this subgroup underwent angioplasty. In comparing PCI with CABG, PCI demonstrated a small survival advantage over CABG for patients with less severe two-vessel disease, whereas CABG was superior for more severe two-vessel disease (i.e., proximal LAD artery involvement).[25]

These important findings have been confirmed in the current era of PCI with stent implantation using the New York State Database. Hannan and colleagues published results in 1999 using cases from 1993 to 1995.[98] In this study, a survival benefit was observed with angioplasty at 3 years for patients with single-vessel disease not involving the LAD, whereas those with LAD or three-vessel disease had superior outcomes with surgery. In the more recent study of patients with multivessel disease who received PCI, survival was higher among the 37,212 patients who underwent CABG than among the 22,102 patients who underwent stent placement after adjustment for known risk factors. The adjusted hazard ratio for the long-term risk of death after CABG relative to stents was 0.64 (95% CI 0.56 to 0.74) for triple-vessel disease and proximal LAD disease. This hazard ratio increased to 0.76 (95% CI 0.60 to 0.96) for patients with two-vessel disease and LAD involvement[99] (Fig. 20-8). This study has limitations of being a nonrandomized study and subject to bias; however, the surprising finding of a survival advantage apparent as early as 3 years postprocedure suggests that improvements in cardiac surgical anesthetic care, myocardial protection, and intensive-care management at least have matched, if not surpassed, advances in percutaneous technology. It is important to note that PCI targets the culprit lesion. In contrast, CABG targets both the culprit lesion and potential future culprit lesions by bypassing the diseased vessel. This may explain in part the apparent mortality benefit derived with CABG[100] (Fig. 20-9).

SPECIAL CIRCUMSTANCES

Acute Coronary Syndromes

The acute coronary syndromes (ACSs) cover a wide spectrum from ST-segment elevation MI with underlying coronary obstruction to Prinzmetal or variant angina in patients with coronary vasospasm in the absence of significant underlying obstruction. The term *non-ST-segment-elevation ACS* encompasses the entities of unstable angina, non-Q-wave MI, and postinfarction angina. They denote acute, symptomatic imbalances of the myocardial oxygen supply: demand ratio over a short time span. Prinzmetal angina, or coronary vasospasm, is diagnosed definitively by ECGs obtained during the episode of pain and is treated medically. Unstable angina is not a uniform clinical entity but consists of the spectrum of myocardial ischemia between chronic stable angina and MI. Unstable angina is defined as a recent change in the severity, character, or trigger threshold of

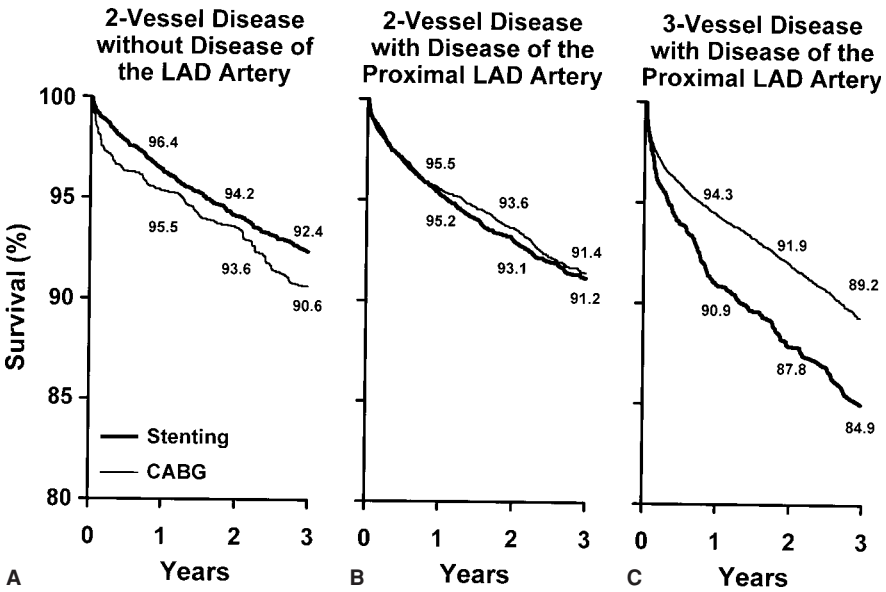

Figure 20-8. Unadjusted Kaplein-Meier survival curves in patients with two-vessel disease without involvement of the LAD artery (A); patients with two-vessel disease with involvement of the proximal LAD artery (B); and patients with three-vessel disease with involvement of the proximal LAD artery (C). *(Reproduced with permission from Hannan E, Racz M, Walford G, et al: Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med 2003;352:2174.)*

chronic stable angina or new-onset angina. Approximately 5.6 million Americans have chronic angina, and about 350,000 develop new-onset angina each year.[101] Unstable angina develops in approximately 750,000 Americans each year and is associated with subsequent MI in approximately 10%. Postinfarction angina is defined as the presence of angina or other evidence of myocardial ischemia in a patient with a recent (1 to 2 weeks) Q-wave or non-Q-wave MI.

Unstable angina and postinfarction angina are classified into subsets according to the triggering stimulus (A to C) and frequency of pain (I to III).[102] Class A indicates angina precipitated by an extracardiac or indirect stimulus such as an arrhythmia or hypotension that can be reversed by medical management. Class B indicates angina without such an extracardiac or indirect stimulus, and class C indicates angina in the presence of acute MI. Class I is new or accelerated angina without rest pain. Class II is angina occurring at rest within 1 month but not within 48 hours of ACS. Class III is angina at rest within 48 hours of an ACS.

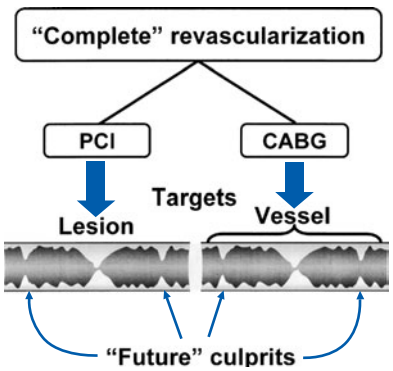

Figure 20-9. PCI is directed against specific culprit lesions. By bypassing diseased vessels, CABG treats both culprit lesions and future culprit lesions. *(Reproduced with permission from Opjie LH, Commerford PJ, Gersh BJ: Controversies in stable coronary artery disease. Lancet 2006; 367;69.)*

The initial approach to the patient with non-ST-segment-elevation ACS (NSTEMI) is pharmacologic stabilization, followed by risk stratification. The latter is based on multiple clinical, demographic, and electrocardiographic variables in addition to the use of serum biomarkers. In institutions with facilities for early angiography, patients at intermediate or high risk (the majority) undergo early angiography with a view toward revascularization. In many parts of the world, however, angiographic facilities are limited, and an alternative approach based on pharmacologic stabilization followed by mobilization and risk stratification using stress testing is employed.

The most recent randomized, controlled trials of aggressive versus conservative approaches to non-ST-segment-elevation ACS are the FRISC2, TACTICS, and VINO trials.[103–105] Despite differences between these trials, the results favor an aggressive strategy with a view toward revascularization in the majority of patients shown to be at high risk (e.g., older patients, diabetics, those with ST-segment depression on ECG, and those with elevated CPK-MB or serum troponins).

CABG versus medical therapy in ACS

The technical advances in PCI in the setting of ACS have relegated CABG largely to a secondary position in most cases. The special circumstances of postinfarction mechanical complications of papillary muscle rupture, ventricular septal defect, and shock are addressed specifically in other chapters of this text. It should be noted here, however, that two multicenter trials and one single-center randomized trial involving a total of 823 patients have evaluated the relative merits of CABG and medical therapy in unstable angina during the 1970s.[106–108] Patients with left main disease, poor LV function (ejection fraction $<30\%$), and age greater than 70 years were not included. In the VA cooperative study, improved survival and a lower rate of recurrent angina were shown with surgery,

and at both 5 and 8 years, there were fewer subsequent hospitalizations for cardiac reasons in the surgical group.[109] Interestingly, there was no difference in progression to Q-wave MI between medical and surgical groups.[109] Like the VA study, the National Cooperative Study Group Trial[106] showed no difference in progression to Q-wave MI but less severe subsequent angina with operation. Unlike the VA study, however, there was no survival difference at 2 years (90% in both groups). Of note, 32% of the medical group crossed over to surgery by 24 months. Since current medical therapy was not available to these patients, there is significant difficulty in extrapolating the results of these trials to current clinical practice. Finally, Bertolasi and colleagues reported a single-center study of 113 patients that demonstrated less subsequent angina, fewer infarctions, and a survival benefit for surgery in short-term follow-up.[107]

In the TIMI-IIIB trial, medical management followed by earlier delayed PCI or CABG resulted in 6-week mortality and nonfatal MI rates of 2.1% and 6.1% among 1473 patients with unstable angina or non-Q-wave MI (NQWMI).[108] This study compared the results of a strategy of initial stabilization followed by aggressive treatment involving routine angiography followed by revascularization in the presence of suitable anatomy with a conservative arm reserving angiography for those with recurrent angina or a positive stress test. At 42-day and 1-year follow-up, there was no difference in death or MI between the two groups. Subsequent subset analyses have demonstrated a trend in favor of an aggressive approach to revascularization over medical therapy in patients at higher risk, as characterized by an elevated CPK-MB fraction (NQWMI).[109] In the end, revascularization rates were similar, with only the timing of that revascularization event being different.

The Veterans Affairs Non-Q-Wave Infarcts and Strategies in Hospitals (VANQWISH) trial[111] was a similar design to TIMI-IIIB. A higher early mortality rate was observed in the invasive group than in the medical group possibly owing to the extraordinarily high perioperative mortality rate of 7.7% in the CABG group. The opposite result was found in the second Fragmin and Fast Revascularization during Instability in Coronary Artery Disease trial (FRISC II).[103] These investigators found a benefit with early revascularization, particularly among patients with elevated troponins. The reason for such different results among these studies is likely due to differences in patient populations studied. It is likely that higher-risk patients benefit from an aggressive approach, whereas lower-risk patients have less to gain and so are more likely to suffer adverse consequences.

The Angina with Extremely Serious Operative Mortality Evaluation (AWESOME) was reported in 2004,[112] comparing results from PCI and CABG. Patients were enrolled who had increased risk of adverse outcomes with CABG, including greater than one risk factor, prior CABG; ACS within 7 days; left ventricular ejection fraction (LVEF) $< 35\%$; age > 70 years; or intra-aortic balloon pump. Results suggested that PCI and CABG have similar outcomes for patients with ACS, even in those with low ejection fractions.

PCI for acute MI

Because of the rapidity with which vessel patency can be restored using percutaneous techniques, PCI has all but replaced CABG in the setting of acute ST-segment-elevation MI (STEMI). Both thrombolytic therapy and direct or primary angioplasty can restore coronary artery patency and flow during acute STEMI. In the absence of hemorrhagic concerns, however, thrombolytic therapy is more widely available and is standard early therapy for acute transmural MI when immediate angioplasty is unavailable.

In the few instances in which surgical revascularization must be undertaken following thrombolysis or acute angioplasty, perioperative bleeding is increased. Bleeding has been shown not to be excessive if glycoprotein IIb/IIa inhibitors are discontinued at least 2 hours preoperatively[113] or if a platelet transfusion is provided in the presence of abciximab.[114] Clopidogrel should be held for 5 days prior to surgery if possible.[115]

Several early myocardial reperfusion trials have assessed the role of routine adjunctive angioplasty given that not all arteries can be reopened by thrombolysis, that reocclusion occurs in some arteries opened initially, and that reocclusion is associated with increased morbidity and mortality.[116,117] In these studies, the addition of routine angioplasty to thrombolytic therapy did not enhance patency, improve left ventricular function, or reduce early mortality compared with a more conservative approach of ischemia-driven angiography, but did increase expense and vascular bleeding problems.[118–120] A meta-analysis of adjunctive PCI and thrombolysis versus thrombolysis only showed no early benefit of PCI except in patients who have clinical indications for early revascularization (e.g., postinfarction angina).[121] These studies were performed in an early phase of PCI, however, and the addition of stents as well as glycoprotein IIb/IIIa inhibitors and new lytics have renewed interest recently in a combined strategy.

Asymptomatic Coronary Artery Disease

The role of revascularization either by PCI or CABG versus medical therapy in the setting of asymptomatic CAD has been studied in the Asymptomatic Cardiac Ischemia Pilot (ACIP) trial.[122] Of 558 patients with CAD and medically controlled angina, treatment was randomized to either revascularization or medical therapy directed toward eliminating angina or eliminating ischemia during an ambulatory ECG. Revascularization was more effective than medical therapy in relieving ischemia, and CABG was superior to PCI (70% freedom from ischemia versus 46%; $p < .002$). Mortality at 1 and 2 years was superior for revascularization as compared with angina-directed medical therapy but not superior to ischemia-directed medical therapy.[57,123] The greatest benefit was among patients with the most severe disease. Importantly, many of these patients with "silent ischemia" on ambulatory ECG monitoring did have symptomatic angina at other times and thus were not truly asymptomatic.

The documentation of ischemia, however, is critical. Several studies emphasize the flaws in the assumption that one can identify future culprit lesions in the absence of symptoms or documentation of ischemia.[124] Among patients undergoing serial coronary arteriography who subsequently developed acute MI or unstable angina, the severity of stenosis at the time of initial angiogram is poorly predictive of the culprit lesion causing the acute ischemic syndrome.[124–127] In most cases, the severity of the lesion responsible for subsequent ischemia was less than 50%, and in many patients it was not present at all on the initial angiogram. The lack of benefit of prophylactic revascularization incidentally raises concern regarding the number of patients undergoing angioplasty who have not undergone stress testing to document objective evidence of ischemia when severe symptoms at the time of presentation were absent.[128] Bech and associates have demonstrated that fractional flow reserve exceeded 0.75 in 91 of 325 patients planned for PCI without noninvasive evaluation of ischemia and that among those patients, angioplasty had no impact on event-free survival or angina.[129]

The Elderly

Age is a predictor of operative risk in most models but is also a predictor of poor outcome with medical therapy in the presence of CAD. In the Swiss Multicenter Trial of Invasive versus Medical Therapy in the Elderly (TIME), briefly noted earlier, 301 patients over the age of 75 with chronic angina were randomized to medical therapy with or without invasive evaluation.[59] Of those undergoing angiography, two-thirds had revascularization. At the 1-year follow-up interval, there was no statistical difference in death or nonfatal MI rates. Symptoms and quality of life also were similar. However, there was a substantial increased risk of rehospitalization with revascularization in those who had undergone medical treatment. These data suggest that invasive evaluation should be offered to the elderly who are symptomatic only after adequate medical therapy.

The choice of mode of revascularization will be particularly affected in this group of patients by the presence of comorbidities that may increase the risk of surgical intervention, such as cerebrovascular disease, renal dysfunction, and pulmonary disease. The impact of a reduction in operative morbidity through off-pump coronary artery bypass (OPCAB) on this choice is as yet unclear. There are an increasing number of studies to suggest that it is in just this group of patients with comorbid conditions that off-pump surgery offers its greatest advantage over conventional surgery (see Chap. XX). The majority of these studies are not randomized, however, making their results less conclusive than one would hope. There are two retrospective and nonrandomized trials reviewing elderly patients who underwent OPCAB. There were more grafts in the standard CABG for both studies, but there were fewer strokes, incidences of prolonged respiratory failure, bleeding, and transfusions in the OPCAB group, and both ICU and hospital length of stay were reduced. Reoperations for bleeding, MI, renal failure, wound infections, and operative mortality were not significantly different.[130,131] Among the randomized trials, there has been no consistent advantage to OPCAB with respect to neurocognitive outcomes, a particularly important endpoint in the elderly.[132] A meta-analysis of both randomized and observational studies of OPCAB and standard on-pump CABG in diverse populations[133] has failed to demonstrate any difference except for a reduction in atrial fibrillation in the OPCAB group [odds ratio (OR) 0.59 (0.46–0.77)]. The impact, therefore, of newer technologies on modifying the indications for CABG in the elderly is as yet unclear.

Severe Left Ventricular Dysfunction

Left ventricular dysfunction is a predictor of increased operative risk for most cardiac surgical procedures, and in the early days of coronary revascularization, these patients were not offered CABG. As with age, however, LV dysfunction is also a strong predictor of poor outcome with medical therapy. Accordingly, more recently, significant LV dysfunction has been considered an indication rather than a contraindication for surgical revascularization. In some patients, LV function has been shown to improve—sometimes dramatically so—after revascularization, leading to the concept of a "hibernating" or "stunned" myocardium.[134–137] The identification of viable myocardium, which is potentially recoverable, depends on identification of preserved metabolic activity by positron-emission tomography (PET), cell membrane integrity by thallium-201 or technetium-99m single-photon-emission computed tomography (SPECT), or dobutamine stress echocardiography.[10,137,138]

Thus far, no prospective, randomized trials of medical versus surgical therapy in patients with severe LV dysfunction have been reported, although the National Institutes of Health (NIH)–sponsored trial entitled the Surgical Treatment for Ischemic Heart Failure (STICH) trial is underway. A number of retrospective analyses of the impact of revascularization on outcome in patients with LV dysfunction with or without demonstrable viability have been reported[139] (Fig. 20-10). Recently Allman and colleagues reported the results of a meta-analysis of these studies.[140] Their analysis demonstrated a 79.6% reduction in annual mortality (16 versus 3.2%; $p < .0001$) when patients with severe three-vessel disease and severely depressed LV function with evidence of viability underwent surgery versus medical therapy. Among those patients without demonstrable viability, the mortality rates were similar (7.7 versus 6.2%; p = NS). This study is subject to all the limitations of a retrospective surgical series, however, including, perhaps most important, the unaccountable effect of clinical judgment employed in selecting patients for one therapy versus another. The results, however, have been remarkably consistent over the years among virtually all studies, with the greatest benefit of surgical revascularization being sustained by the patients with the worst ventricular function.

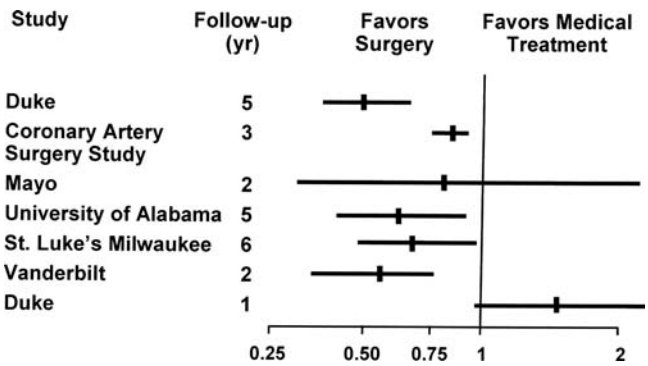

Figure 20-10. Relative risk of mortality for CABG compared with medical therapy in moderate to severe left ventricular systolic dysfunction, ranked in order of study quality. *(Reproduced with permission from Chareonthaitawee P, Gersch BJ, Araoz PA, et al: Revascularization in severe left ventricular dysfunction: The role of viability testing. J Am Coll Cardiol 2005; 46;567.)*

The relative roles of CABG and PCI in this population are not clearly defined despite the number of trials of angioplasty versus surgery. Patients with LV dysfunction may be at higher mortality risk following revascularization by PCI than by CABG, but the potential survival benefits of CABG have not been demonstrated, perhaps because these patients are underrepresented in these prospective, randomized studies. In a multicenter study of patients with LV dysfunction (ejection fraction <40%), slightly more than one-quarter of the patients were dead in the 2 years following multivessel angioplasty.[141] Similar results have been reported from other studies of PCI in patients with multivessel disease and LV dysfunction. Overall, the outcome with PCI appears less favorable than that obtained after CABG[61] possibly as a function of more complete revascularization in surgical patients.[142]

Completeness of revascularization may be particularly important in patients with LV dysfunction. An analysis of data from the CASS registry demonstrated that among patients with triple-vessel disease, 4-year survival depended on the number of vessels bypassed, particularly among those with more severe angina and those with worse ventricular function.[142] For PCI, completeness of revascularization of target arteries ranged from 57 to 61% in the prospective, randomized trials in which complete revascularization was not a protocol requirement (e.g., BARI, EAST, and CABRI). In the GABI and RITA trials, complete revascularization by PCI was targeted and was achieved in 86% in GABI and in 81 and 63% of patients with two- or three-vessel disease in RITA.[85,86]

Total Occlusions

In most patients with chronic, totally occluded coronary arteries, revascularization is not possible, although the advent of stent technology has offered some improvement in this area. In the randomized trials of multivessel PCI versus CABG, 35 to 37% of patients were excluded because of the presence of a chronic total occlusion of a coronary artery serving viable myocardium. Thus, the high proportion of trial patients with less than three-vessel disease, well-preserved ventricular function, and absence of chronically occluded arteries produces a study population that favors a higher incidence of complete revascularization by PCI and attenuated consequences of incomplete revascularization than expected in community practices. Among patients with severe angina, triple-vessel disease, and ventricular dysfunction, survival is greater in those with three or more coronary arteries bypassed than in those with only two vessels bypassed.[49,142] CABG improves survival in patients with three- and two-vessel disease with LV dysfunction compared with medical therapy. Although angioplasty may have a similar survival benefit, its influence on this high-risk subgroup has not been fully tested or reported.

Diabetes Mellitus

It has been recognized for many years that patients with diabetes mellitus are at higher risk following percutaneous[143] or surgical[144–146] revascularization. The BARI trial was the first trial large enough to identify significant differences in outcome between diabetic and nondiabetic patients. In this study, which included 353 diabetic patients, a survival benefit was observed among insulin-dependent patients undergoing CABG with an ITA graft as compared with those undergoing PCI. The explanation for this is not entirely clear, although an intriguing observation is that while the incidence of subsequent MI is similar between groups, survival following MI is superior among those who have undergone surgical revascularization.[147] In fact, diabetics suffering spontaneous Q-wave MI were more than 10 times as likely to die of their infarction if they had been treated with PCI compared with CABG. No such protective effect was seen among nondiabetic patients either with or without Q-wave MI. This survival difference was even more pronounced at 7 years, with 76.4% of diabetics in the surgical arm alive compared with 55.7% in the angioplasty arm.[148]

The physiologic basis for this difference remains a matter of speculation, although the completeness of revascularization may be a factor. Because of the significant incidence of restenosis after PCI in diabetics, Van Belle and colleagues[149] analyzed ejection fraction at 6 months and long-term cardiac mortality and morbidity among 513 diabetic patients stratified according to the presence of occlusive restenosis ($n = 94$), nonocclusive restenosis ($n = 257$), and no restenosis ($n = 162$). The mortality rose with restenosis (24% without restenosis, 35% with nonocclusive restenosis, and 59% with occlusion), and ejection fraction fell with occlusion (decrease of 4.8 $\pm$ 12.6%). Coronary mortality was strongly predicted by coronary occlusion by multivariate analysis.

The results of the BARI trial prompted retrospective post hoc analyses of several earlier trials. The results have been variable. An analysis of diabetic patients from the CABRI trial at 8 years demonstrated a mortality rate of 3.5% for CABG patients versus 15.6% for PCI patients.[150] There

also was a nonsignificant trend for better survival among diabetic patients treated surgically in the EAST trial.[151] A meta-analysis of pooled data pertaining to diabetic patients from CABRI, EAST, and RITA, however, found similar 5-year mortality rates following CABG or PCI.[152]

Several other data bank studies also have been conducted. The Northern New England Cardiovascular Disease Study Group evaluated survival 5 years after treatment among 7159 diabetic patients with multivessel disease who were treated with CABG or PCI between 1992 and 1996.[153] Of this group, 38.6% of patients were clinically and angiographically similar to those randomized in BARI. Patients were treated according to physician preference. Those undergoing CABG were more likely to have three-vessel disease and tended to be older with greater degrees of ventricular impairment and obstructive lung disease. There were more women and more urgent interventions in the PCI group. After adjusting for these variables, PCI was associated with a significantly greater mortality rate at 5 years [risk ratio (RR) 1.49, 95% confidence interval (CI) 1.02–2.17; $p = .037$) and particularly among diabetics with three-vessel disease [hazard ratio (HR) 2.01, 95% CI 1.04–3.91; $p = .038$].

Diabetes is a condition characterized biologically by an inflammatory, proliferative, and prothrombotic state. This may account in part for the increased risk of restenosis and occlusion. Since diabetics tend to have more diffuse disease, the importance of complete revascularization, which is achieved more often surgically than percutaneously, may be enhanced. Another explanation may have more to do with patient selection than vascular biology. It has long been recognized from the previously cited studies that the survival advantage of CABG over medical therapy is greater the more extensive the coronary disease, and more recent studies of PCI versus CABG have demonstrated similar trends. Diabetic patients tend to have more extensive disease, and in BARI, diabetic patients had a higher frequency of three-vessel disease, diffuse disease, proximal LAD artery disease, and LV dysfunction.

In this respect, it is interesting to note that in community studies[154] and the BARI registry, although diabetic patients have a poorer outcome with both PCI and CABG in comparison with nondiabetic patients, there were no significant differences in outcomes between these therapies in the diabetic patient subgroup. It must be emphasized that in these nonrandomized trials in which the selection of therapy was at the discretion of the physician and the patient, a very clear trend was noted. The "sicker" patients with left ventricular dysfunction and triple-vessel disease were far more likely to undergo CABG than patients with double-vessel disease and preserved LV function. Therefore, these registry studies suggest that although the differences between CABG and PCI in diabetic patients may be due to altered vascular biology, these differences are magnified by the process of randomization, in which patients who probably would have been treated with CABG in clinical practice were randomized to PCI.

From a clinical standpoint with regard to patient selection for coronary revascularization and the method of revascularization, the assessment of diabetic patients should be made on standard principles, namely, the severity and extent of coronary disease, the potential for complete revascularization, the presence or absence of LV dysfunction, and the technical suitability of the lesions for PCI. The results of the aforementioned studies suggest that a preference for surgical over percutaneous revascularization is, at this time, appropriate among diabetic patients—at least those with extensive disease and/or ventricular dysfunction. This recommendation may change if new technologies such as DESs and antiplatelet agents are successful in reducing the risk of restenosis and occlusion. DESs are being used with greater frequency owing to subset analysis of the TAXUS IV and SIRIUS trials showing a significant decrease in restenosis. However, these studies were not powered to determine restenosis rates in diabetic patients, and results may have been due to chance alone.[155–157] Furthermore, the potential impact of risk-factor reduction may alter the risk:benefit balance in the future in this important and increasing subset of patients presenting with CAD. Current data suggest that the decreased incidence of repeat revascularization, cardiac rehospitalization, and recurrent angina can be reduced to the level of nondiabetic patients if diabetic patients maintain optimal glycemic control (HbA1c $\leq$ 7%).[158] Irrespective of the mode of therapy, an aggressive approach to risk-factor modification is required.

End-Stage Renal Disease

End-stage renal disease (ESRD) is a growing problem. Cardiovascular disease is the most common cause of death among those with ESRD, and therefore, there likely will be high rates of revascularization required in these patients in the future.[159] Comorbidities complicating surgical or percutaneous revascularization, such as diabetes, hypertension, and calcified vessels, are more common in patients with ESRD, increasing the risk of intervention. A study conducted by the Northern New England Consortium found dialysis-dependent patients with renal failure to be 3.1 times more likely to die after CABG after adjusting for known risk factors [OR 3.1 (2.1–3.7); $p < .001$].[160] This study also found significantly increased rates of mediastinitis (3.6 versus 1.2%) as well as postoperative stroke (4.3 versus 1.7%).[160] The long-term survival also was decreased, with renal failure found to be a highly significant predictor of mortality after adjustment.[161] Despite these risks, the prognosis without surgical correction of CAD is poor. Revascularization in patients with ESRD is associated with improved survival compared with medical management.[162]

Carotid Artery Disease

Stroke is a devastating complication of cardiac surgery. The mortality rate among individuals suffering a postoperative cerebrovascular accident has been reported to be as high as 24.8% with a mean hospital stay of 28 days.[163] The source of perioperative stroke may be thromboembolic from the heart

itself, atheroembolic from the aorta, or a result of carotid artery disease. Among these, carotid artery disease is perhaps the most readily addressed surgically. Accordingly, current AHA/ACC guidelines recommend carotid artery screening for patients older than 65 years of age and those with left main coronary artery stenosis, peripheral vascular disease, a history of smoking, a history of transient ischemic attack or stroke, or carotid bruit on examination.[22] Conversely, uncorrected coronary artery disease is the most common source of mortality and morbidity after successful carotid endarterectomy.[164] Hence, the management of combined carotid artery and coronary artery disease is a topic of profound clinical importance encountered with significant frequency.

The clinical implications of carotid artery disease reflect the degree of atherosclerosis present. In a recent meta-analysis, perioperative stroke risk rises from 2% when a carotid stenosis is less than 50% up to 12% among patients with a unilateral occlusion.[165] Among those with bilateral high-grade stenoses (50 to 99%), the stroke risk has been estimated to be approximately 5%.[165]

While the benefits of carotid endarterectomy (CEA) are clearly established in symptomatic carotid artery stenoses in both the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[166] and the European Carotid Surgery Trial (ECST),[164] the management of asymptomatic carotid artery disease is an ongoing controversy. The Asymptomatic Carotid Atherosclerosis Study (ACAS)[167] and the Asymptomatic Carotid Surgery Trial (ACST)[168] are large trials that enrolled 1662 and 3120 patients, respectively. ACAS did not demonstrate a significant reduction in the absolute risk of disabling or fatal stroke with surgery, whereas ACST reported a statistically significant absolute risk reduction of 2.5%. A recent *Cochrane Review*[169] concluded that despite a 3% perioperative stroke or death rate, CEA for asymptomatic carotid stenosis reduces the risk of any stroke by approximately 30% over 3 years. In a natural history study of patients undergoing cardiopulmonary bypass, 582 patients were screened with carotid artery ultrasound. Despite the exclusion of patients with recent neurologic symptoms, 70 patients (12%) had one carotid artery stenosis equal to or greater than 80%, and 50 patients (8.6%) had bilateral lesions of at least 50%.[170] Thus, this issue will continue to be debated in the future because its relevance to cardiac surgery is of obvious importance.

The AHA/ACC guidelines currently recommend CEA before or concomitant with CABG in patients with any symptomatic carotid stenosis. CEA is also recommended for asymptomatic patients with a unilateral or bilateral internal carotid stenosis of at least 80%.[22]

Gaudino and colleagues have shown an improvement in freedom from late stroke and TIA after combined CEA-CABG in patients with asymptomatic, unilateral high-grade stenoses from 75 to 98% at 10 years.[171] Similarly, among patients undergoing concomitant CEA and CABG, Akins and colleagues[172] and Kolh and colleagues[173] have reported 10-year actuarial event-free survivals of death (40 and 50%), MI (87 and 84%), and stroke (82 and 93%).

While the value of addressing both cardiovascular and cerebrovascular conditions is demonstrable, the superiority of a combined versus sequential approach remains controversial. Some centers perform CEA followed by CABG 1 to 5 days later, whereas others perform concomitant procedures. In a review, the cumulative risk of 8.4% for a combined endpoint of stroke and death of a staged procedure is not statistically different from the risk of a combined procedure (7.4%).[174] The increased operative risk associated with patients with carotid disease is attributable to the comorbidities of those patients with carotid disease rather than to the procedure itself.[175] Thus, the timing of CEA and CABG should be chosen based on patient and center preference. The recent advent of carotid artery stenting complicates matters further, with the place of this new technology in this setting still undefined.[176]

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CHAPTER 21

Myocardial Revascularization with Percutaneous Devices

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The increased popularity of surgical coronary revascularization was accompanied by the improved performance of diagnostic coronary angiography. As the diagnostic technique evolved to a safe and easily performed procedure, engineering advances offered the possibility of improving coronary blood flow capacity using catheter-based transluminal methods. In 1974, Andreas Gruentzig developed the double-lumen balloon catheter that was later miniaturized for use in coronary arteries.[1,2] Soon afterward, techniques for percutaneous transluminal coronary angioplasty (PTCA) expanded as technical breakthroughs were applied to subselective catheters, devices, guidewires, and balloon materials. Undoubtedly the most important advance in percutaneous revascularization has been the coronary stent, an expandable metal buttress that reinforces a balloon-dilated vessel. Not only does the stent provide mechanical support, preventing early vascular recoil and closure, but it also provides a platform for local drug delivery. The proliferation of techniques for expanding a coronary lumen has produced a more broadly encompassing nomenclature, namely, percutaneous coronary intervention (PCI) or percutaneous coronary revascularization (PCR).

BALLOON ANGIOPLASTY

Principles

Early balloon angioplasty procedures used a bulky balloon catheter with a small length of steering wire attached to its tip. However, severe technical limitations restricted percutaneous techniques to low-risk patients with proximal discrete coronary artery stenoses, and their outcomes lacked predictability. Predicated on the advances made in guiding catheters, guidewires, lumen-expansion tools, and antithrombotic therapy, higher-risk patients became candidates for percutaneous therapy. Therefore, a protocol for safe, successful vascular manipulation was required. Over time, because of the more complex, challenging cases that cardiovascular surgeons have treated, several principles have been recognized (Table 21-1).

Tools

Guiding catheter

The guiding catheter differs from diagnostic catheters in both shape and construction. A wire-braid-supported thin catheter wall allows for a larger central lumen and maintains sufficient mass, rigidity, and support to allow the advance of subselective catheters to the distal regions of the coronary bed. Slight modification in guiding catheter shape enables coaxial alignment of the catheter with the treated vessel while simultaneously maintaining contact with the opposing wall of the aorta or aortic cusp. The anatomy of the ascending aorta and origin of the treated coronary artery determine the shape of the guiding catheter that will provide the most secure positioning (Fig. 21-1). The choice of guiding catheter often is the deciding factor for success when approaching challenging anatomy or when complications increase procedural difficulty. Guiding catheter manipulation is a common cause of procedural complications that necessitate urgent coronary artery bypass surgery.

Guidewire

The guidewire represents an avenue of access to all points traversed. Therefore, when the guiding catheter position remains secure, the guidewire allows control of the distal vessel. The many different wires vary in stiffness, coatings, diameter, and design of the distal steering tip. For most procedures, the chosen wire is a 190- to 300-cm monofilament that is 0.0254 to 0.0356 cm in diameter with either a graded tapering segment welded to the tip or a gradual taper of the monofilament. The long body of the wire allows applied

Table 21–1.

Principles of Percutaneous Coronary Intervention

1. The patient's outcome is a function of age and comorbidity.
2. The procedure's outcome is a function of anatomy and proper planning (i.e., sequence and equipment choices such as guidewires and device).
3. Proximal and distal control of the treated vessel are maintained.
   a. Choose proper guide catheter support.
   b. Maintain distal wire position.
   c. Keep the guide, device, and distal wire tip visible during any movement.
4. Needs and limits to treatment options such as devices, adjuvant medical therapy, contrast use, and circulatory support are determined by
   a. Vascular access
   b. Clinical setting (e.g., stable angina or acute myocardial infarction)
   c. Ventricular function
   d. Comorbidity: diabetes mellitus, renal insufficiency
5. The following factors can lead to failure:
   a. Incomplete understanding of the three-dimensional anatomy of the course to be taken and lesion to be treated
   b. Unrealistic interpretation of
      i. The capacity of available techniques to achieve success
      ii. The allowance of specific anatomy to accept percutaneous manipulation
      iii. Ignorance or inattention to technique in subselective device movement
   c. Inattention to anticoagulation
   d. Inattention to catheter hygiene (minimizing blood and contrast stagnation within the guiding catheter or other devices)

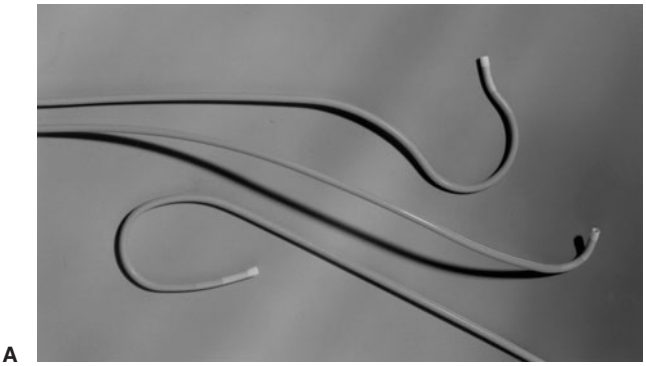
torque to be transmitted to the distal steering tip. The central wire core at the tip is "plastic," or malleable, and may be shaped by the operator. In many wire designs, a wire coil wrapped around the central filament projects a blunter, less traumatic tip to the vessel that it must traverse. In addition, this superficial coil proffers elasticity to the shape created by the operator, preventing the filament's deformation during attempts to guide the wire to its desired destination. This shaped, soft steering tip eases access to tertiary branches of the coronary tree. This easily deflected wire is the safest choice but may lessen the probability of successfully crossing certain types of lesions, such as a total occlusion, particularly when an occlusion has been present for more than a month.[3,4] In these settings, a stiffer wire tip with a bonded, hydrophilic coating, rather than the wire coil, frequently is chosen. While increasing the likelihood of crossing the lesion successfully, these stiffer, "slicker" wires also increase the risk of such complications as creation of a subintimal wire course and dissection or perforation of the vessel (Fig. 21-2). Variations in the body wire's stiffness influence support for subselective device delivery in a challenging or tortuous anatomy.

Tools for lumen expansion

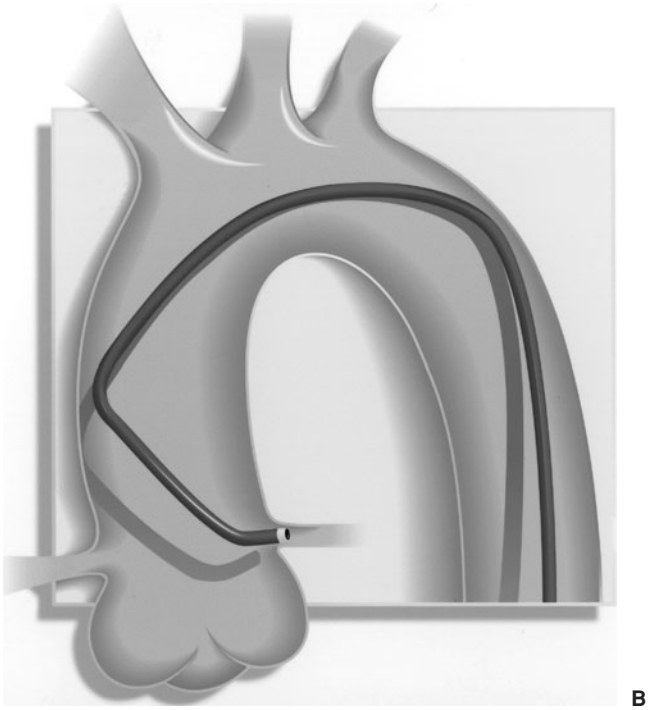
The vast bulk of subselective devices for coronary artery manipulation are balloon inflation catheters or some variation of this theme. The components of the balloon catheter are the proximal shaft, the distal shaft on which the balloon is placed, and the tip. The proximal shaft is made as rigid as possible to allow sufficient transmission of force applied by the operator to the distal aspect of the device. The balloon shaft generally is made of thinner material and is thus more deformable with a lower profile. The device tip must offer the lowest possible profile while advancing into the coronary arteries to minimize friction that could oppose its advance. A central lumen allows the device to track along the guidewire.

Balloon catheter designs vary in the placement of the proximal opening of the central lumen. The "on the wire" design has a central lumen extending the length of the catheter. This design affords the best traceability and capability to maneuver through difficult anatomy but requires an assistant to manipulate the wire during device advance. The "monorail" design has a central lumen extending only through the distal balloon shaft of the catheter. The remaining catheter shaft communicates only with the balloon lumen. This design, though less traceable, allows the procedure to be performed without the requirement for an assistant.

Properties of the angioplasty balloon include compliance, maximally tolerated pressure, profile, and friction



A



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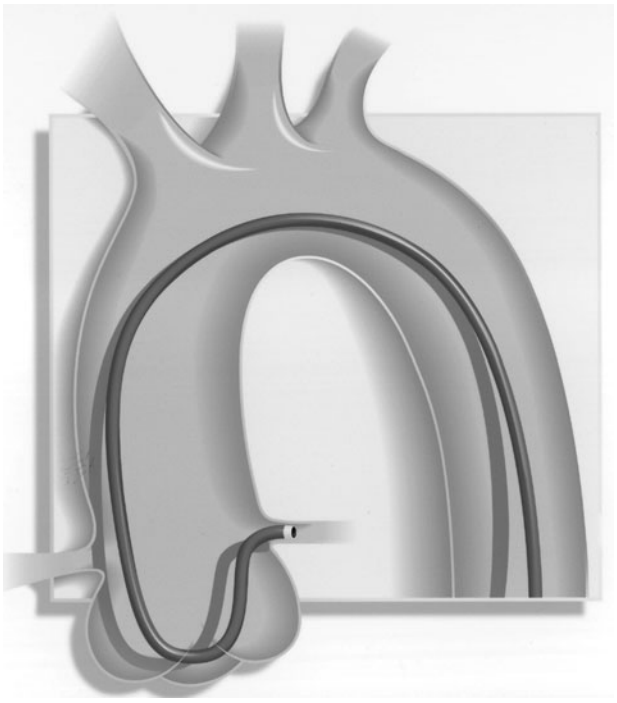

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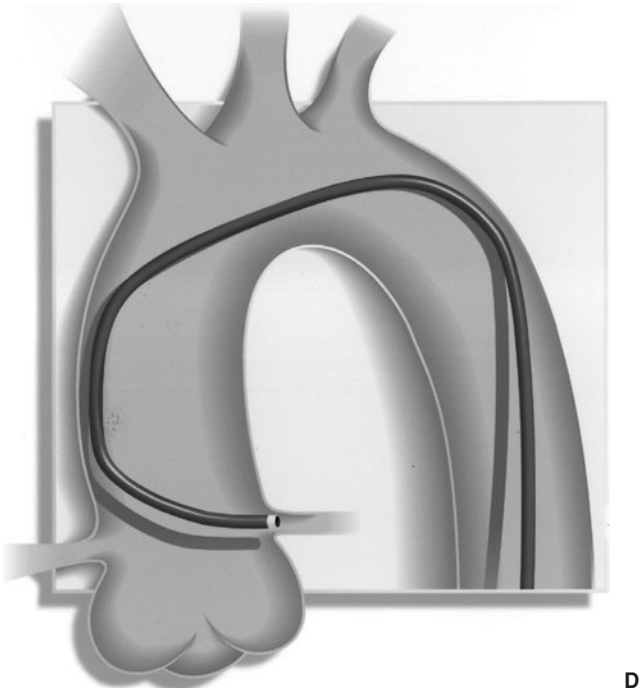
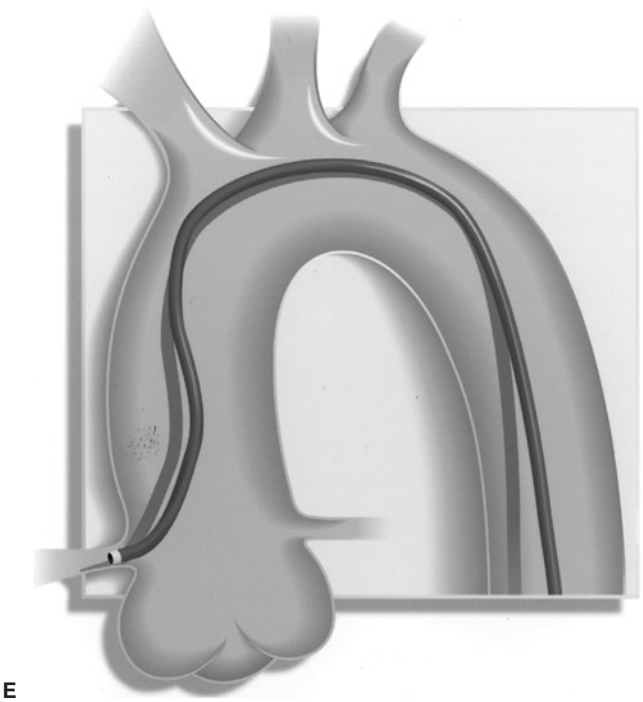


D

Figure 21-1. Commonly used guiding catheters are shown in the relaxed state (*A*) and as engaged with the coronary ostia in preparation for PCI: left Judkins (*B*), left Amplatz (*C*), XB (extra backup) (*D*), *(continued)*

coefficient. Compliance, or growth under pressure, and maximally tolerated pressure are a function of balloon wall thickness and material. Compliance is divided into three categories: noncompliant, semicompliant, and compliant. Noncompliant balloons typically are made from polyvinyl chloride (PVC), polyethylene terephthalate (PET), and high-density polyethylene and polyolefin copolymer (HDPE/POC). Polyolefin copolymer balloons are compliant and vary up to 15% in diameter when exposed to nominal inflation pressure. PET balloons are the most noncompliant, with less than 5% variation even at high pressure. The thin-walled, compliant balloon has the lowest deflated profile,



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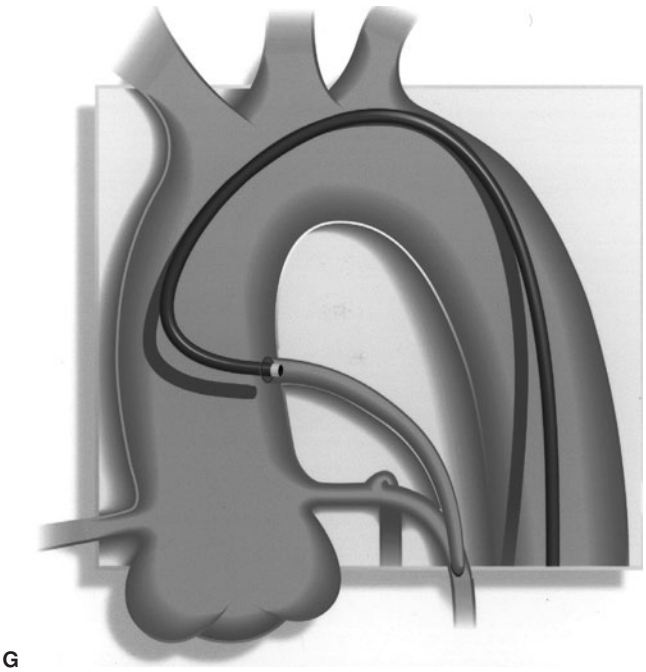


G

Figure 21-1. *(continued)* right Judkins (*E*), right Amplatz (*F*), and left coronary bypass (*G*). (*Reprinted with permission from Cordis Corporation, a Johnson & Johnson company.*)

allowing the device to pass through the most severely occluded vessels. However, the balloon may expand nonuniformly or lengthen when exposed to high pressures, such as pressures in excess of 20 atm (15,200 mm Hg), which are required to dilate hard and heavily calcified stenoses or stents. A variety of balloon coatings may be used to reduce the friction coefficient or protect from abrasion (as in passing a stent).

Antithrombotic therapy

During an angioplasty procedure, blood may stagnate in the guiding catheter or near the treated lesion when a wire or device is placed within the lumen of the target lesion. In addition, metallic components of the guidewire or other devices attract fibrinogen, thus stimulating thrombosis. Therefore, a thrombus may form easily unless prevented with intense anticoagulation therapy (Table 21-2). Most

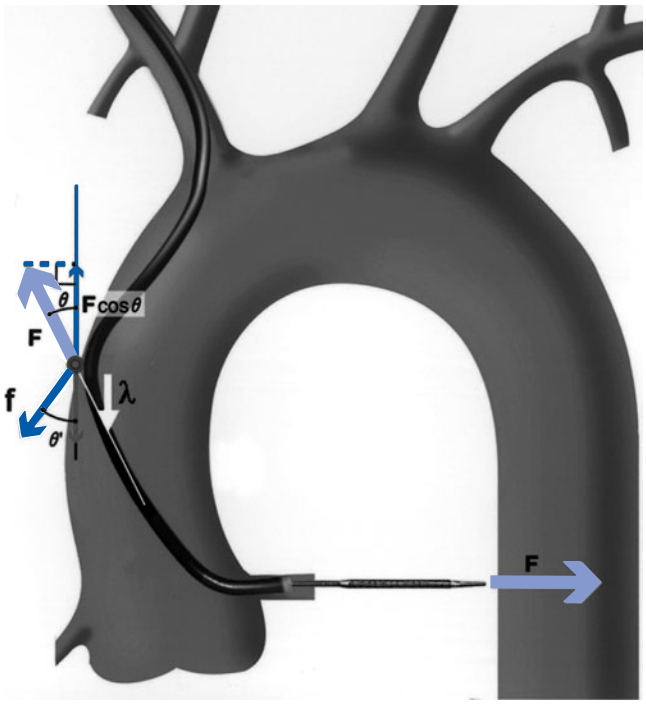


Figure 21-2. Support for subselective device introduction into the coronary vessels is determined primarily by the shape of the guiding catheter in relation to the anatomy of the ascending aorta and origin of the left main coronary artery. Shown graphically, advance of the device forces the catheter backward. This movement is opposed by the alignment of the catheter with the coronary artery and by friction developing through contact between the primary curve of the catheter and the opposing wall of the aorta. (*Reprinted with permission from Ikari Y, Nagaoka M, Kim JY, et al: The physics of guiding catheters for the left coronary artery in transfemoral and transradial interventions. J Invas Cardiol 2005;17:636*)

angioplasty procedures are performed with unfractionated heparin anticoagulation titrated to an activated clotting time (ACT) value of more than 300 seconds.[5] Alternative anticoagulants such as low-molecular-weight heparins and direct antithrombin antagonists may be used.[6–10] However, none of these agents has proven to be superior to unfractionated heparin. Antiplatelet therapy also reduces the risk of thrombosis at the treated lesion. In addition to aspirin and thienopyridines, glycoprotein IIb/IIIa complex (Gp IIb-IIIa) inhibitors may be employed in specific circumstances. Gp IIb/IIIa complex inhibitors are unique in their ability to impair platelet-platelet aggregation regardless of the type or intensity of stimulus. Anticoagulation is titrated to a lower intensity, an ACT of 200 to 250 seconds, when Gp IIb/IIIa inhibitors are used. When this reduced-intensity anticoagulation regimen is used in conjunction with Gp IIb/IIIa inhibitors, hemorrhagic complications are less frequent without increased thrombotic complications.[11]

Two types of Gp IIb/IIIa inhibitors are available: an antibody derivative with high receptor affinity (e.g., abciximab) acting as a noncompetitive inhibitor with a long duration of effect and small-molecule competitive antagonists (e.g., eptifibatide or tirofiban) with a short duration of effect. The ability of these drugs to induce a temporary thrombasthenic state has proved remarkably effective in reducing the risk of percutaneous revascularization in the setting of unstable angina or acute myocardial infarction (MI).[12–15]

Mechanisms

Balloon angioplasty transmits increased intraluminal pressures circumferentially to the rigid intimal surface of the diseased vessel. Since atherosclerotic lesions typically are heterogeneous in their circumferential distribution and physical characteristics, the nondiseased or less diseased wall may be overstretched during balloon inflation. In most instances, the lesion segment with the greatest structural integrity is a focal point for applied stress. Adjacent regions of the vascular wall shift, and the diseased, inelastic intima fractures. Although this mechanism allows balloon expansion and an increase in luminal diameter, extension of the fracture into the intima-media border creates a dissection plane whose growth will be determined by the mechanical characteristics of the lesion and the amount of force applied. If growth of the dissection plane results in significant displacement of the diseased intima, the vessel will close. This event, termed *abrupt* or *acute occlusion*, complicates about 10% of balloon angioplasty procedures. Overstretching the minimally diseased or nondiseased wall without creating plaque fracture typically results in early recoil of the treated lesion to its original state. Occasionally, percutaneous angioplasty produces an angiographic appearance of near-total resolution of coronary artery stenosis with limited, invisible fracture of the intima. In the majority of instances, however, a small dissection may be visible, and 30 to 50% of stenosis remains.

After balloon deflation, the lesion, whose diseased endothelium may have been sparse to begin with, is now devoid of protection and rich in thrombogenic material. Platelet accumulation and thrombus formation are limited by flow and intense antithrombotic therapy. The small amount of thrombus that accumulates provides the stimulus and framework for colonization by inflammatory cells and myofibroblasts. Under the guidance of locally produced cytokines, myofibroblasts colonize, multiply, and deposit ground substance, creating the histologic appearance of intimal hyperplasia. Cell multiplication slows as the lesion is covered by endothelium, and ground substance is replaced by collagen-rich connective tissue. In addition, mechanical injury to the media and adventitia results in scar formation whose contracture may reduce vessel cross-sectional area, a phenomenon termed *negative remodeling*.[16,17] Encroaching intimal hyperplasia that peaks in volume about 3 months after the inciting injury, combined with negative remodeling, results in restenosis after 40 to 50% of balloon angioplasty procedures.[18–20]

Outcomes

In approximately 2 to 10% of balloon angioplasty procedures, intimal dissection, thrombosis, and perhaps medial

Table 21–2.

Adjunctive Pharmacologic Therapy for PCI

	Use	Setting	Dose	Duration of effect	Duration of therapy	Complication
Aspirin	Antiplatelet	All PCI	81 mg	5–7 d	Permanent	GI bleeding
Clopidogrel	Antiplatelet	All PCI	600 mg 6 h before PCI; 75 mg/d	5–7 d	1 y	Bleeding TTP (rare)
Abciximab	Antiplatelet	ACS	0.25 μg/kg+0.125 μg/kg/min	72 h	12 h	Bleeding Thrombocytopenia
Eptifibatide	Antiplatelet	ACS	180 μg/kg bolus; repeat after 10 min+infusion 2 μg/kg/min	4 h	12–72 h	Bleeding
Tirofiban	Antiplatelet	ACS	0.4 μg/kg/min for 30 min+ 0.1 μg/kg/min	4 h	12–72 h	Bleeding
Heparin	Anticoagulation	All PCI	100 IU/kg *60 IU/kg	6 h	During procedure	Bleeding Thrombocytopenia Thrombosis
Bivalirudin	Anticoagulation	UFH alternative	1 mg/kg bolus+2.5 mg/kg/h for 4 h	2 h	During procedure + 4–6 hours if no clopidogrel bolus	Bleeding
Argatroban	Anticoagulation	UFH alternative	350 mcg/kg bolus+ 25 mcg/kg/min	2 h	During procedure + 4–6 hours if no clopidogrel bolus	Bleeding
Enoxaparin	Anticoagulation	UFH alternative	1 mg/kg *0.7 mg/kg	6 h	During procedure	Bleeding
Dalteparin	Anticoagulation	UFH alternative	100 IU/kg *70 IU/kg	6 h	During procedure	Bleeding
Acetylcysteine	Contrast nephropathy prophylaxis	GFR <60 ML/min	600 mg every 12 h	Unknown	Begin 12 h before and continue for 12 h afterward	None
Verapamil/diltiazem/nicardipine	Vasodilator	No/slow-reflow	0.1–0.5 mg IC	20–30 min	As needed	Hypotension Bradycardia
Nitroprusside	Vasodilator	No/slow-reflow	30 μcg IC	30–60 s	As needed	Hypotension
Adenosine	Vasodilator	No/slow-reflow	50 μcg IC	30 s	As needed	Bradycardia

**Recommended dose in conjunction with glycoprotein IIb/IIIa inhibitor therapy.*

PCI = percutaneous coronary intervention; GI = gastrointestinal; TTP = thrombotic thrombocytopenic purpura; ACS=acute coronary syndrome; UFH=unfractionated heparin; GFR=glomerular filtration rate; IC = intracoronary.

Table 21–3.

Causes of Death After PTCA[25]

Low-output failure	66.1%
Ventricular arrhythmias	10.7%
Stroke	4.1%
Preexisting renal failure	4.1%
Bleeding	2.5%
Ventricular rupture	2.5%
Respiratory failure	2.5%
Pulmonary embolism	1.7%
Infection	1.7%

PTCA = percutaneous transluminal coronary angioplasty.

smooth muscle spasm combine to produce abrupt closure.[21,22] Abrupt closure may be treated successfully with repeat balloon inflation but is treated more commonly with stent implantation.[23] The specter of abrupt closure and MI or emergency bypass surgery and its complications historically has limited the application of balloon angioplasty.

In patients with stable angina, the mortality rate from a balloon angioplasty procedure is 1% at 1 month.[24] About half the deaths are the result of a procedural complication, and most are related to low cardiac output[25] (Table 21-3). Although the incidence of restenosis (>50% diameter stenosis during follow-up) is 40 to 50% within 6 to 9 months of a PTCA procedure,[19,20,26] only 25% of patients report recurrent angina that warrants further investigation.[27] Patients with restenosis suffer an increased risk of MI and coronary artery bypass surgery.[28]

DEVICE-ASSISTED ANGIOPLASTY

Stent

Two major failings that hamper balloon angioplasty are abrupt closure and restenosis. These failings stimulated the development of a myriad of devices with the goal of reducing either the risk of the procedure, the risk of restenosis, or both. Only the coronary stent has been shown to have an advantage over balloon angioplasty, except in the case of lesions with severe calcification (Table 21-4). There are numerous coronary stent designs, but the majority of those in current use consist of a stainless steel (or alloy such as cobalt chromium) cylinder that has been "carved," creating a so-called slotted-tube design. Expansion of the stent creates a series of interlocking cells, resembling a cylindrical meshwork (Fig. 21-3). The stent thus is deformable, but when expanded, it maintains sufficient rigidity to act as scaffolding after deflation of the angioplasty balloon. Intimal disruption thus is contained and far less likely to propagate and occlude the treated vessel. In addition, the rigid framework left behind becomes part of the vessel wall, addressing the issue of remodeling, one of the mechanisms of restenosis.

A stent allows safe expansion of the vessel beyond that typically achieved with PTCA at the time of balloon expansion; however, stent use increases thrombotic and inflammatory responses of the vessel wall. The increased injury and a foreign-body response to stent struts result in a more intense and prolonged local inflammatory response.[29] As a result,

Table 21–4.

Devices Used for Coronary Angioplasty

	Experience	Ease of use	Complications	Efficacy	Lesion type
POBA	++++	++++	+	+++	Any
Cutting balloon	+	++	++	+++	Calcified lesion, ISR, bifurcation
Rotational atherectomy	+++	+	+++	+++	Heavily calcified, nondilatable ISR
Directional atherectomy	+	+	+++	+	Bifurcation, ostial lesion
Laser atherectomy	++	++	++	++	Calcification, ISR, thrombus
Aspiration (mechanical)	++	+	+	++	Thrombus
Aspiration (manual)	+	+++	+	++	Thrombus

POBA = plain old balloon angioplasty; ISR = in-stent restenosis.

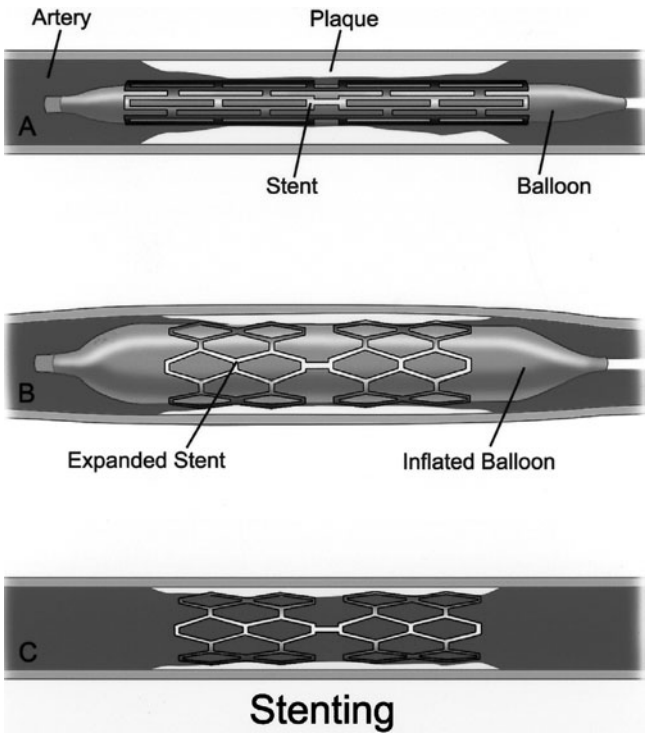


Figure 21-3. The coronary stent is a metallic "meshwork" that increases its rigidity when coldworked by balloon expansion. Buttressing of the vascular wall, propagation of dissection, and early vascular recoil are reduced significantly. (*Reprinted by permission from Texas Heart Institute, www.texasheart.org.*)

stent placement paradoxically exacerbates intimal hyperplasia.[30,31] Using the late (6 or 9 months) loss in lumen diameter after stent implantation as a measure of intimal hyperplasia, even the most modern stent designs fall within a range of about 0.8 mm, more than twice the loss incurred after PTCA (0.32 mm). As a result, when examining restenosis after angioplasty, the impact of stent PCR is rather small in comparison with that of PTCA.[30,31] The bulk of intimal hyperplasia and risk of restenosis are functions of the size of the treated lumen on completion of the procedure, the length of the treated lesion, and the presence of unstable angina, hypertension, and diabetes mellitus[32–35] (Table 21-5). Generally, for a 3-mm artery with a lesion length of 20 mm or less, the risk of restenosis at 6 months is 15 to 30%.[30,31,36–38] Long-term follow-up studies suggest that a stent that does not reocclude during the first 6 to 9 months after implantation is not subject to late, rapid disease progression.[37–41]

By reducing the likelihood of both abrupt closure requiring emergency coronary artery bypass surgery and restenosis, stent-assisted angioplasty is more effective than routine balloon angioplasty for virtually any type of coronary artery lesion. However, coronary artery stents were not proven to be safer than PTCA when stent placement was used as a "bailout" option in randomized clinical trials.[42] Nonetheless, registry data describe a risk for emergency surgery of only 0.3 to 1.1% and a procedural mortality of less than 1%.[43–46] The likelihood of a procedural complication

Table 21–5.

Approximate Risk of Restenosis Based on Final Lumen Diameter and Stent Length

	Final lumen diameter (mm)				
	2.0	2.5	3.0	3.5	4.0
Stent length (mm)	**Percent risk**				
15	32%	22%	14%	8%	4%
30	42%	30%	20%	11%	7%
45	52%	39%	28%	15%	10%
60	60%	47%	35%	20%	13%

Summarized and modified from ref. 34.

may be estimated based on lesion characteristics[47] (Table 21-6). Depending on lesion characteristics and the number of lesions treated, after 1 year, 5 to 10% of patients will require coronary artery bypass surgery, and 15 to 20% will undergo a second PCR procedure.[48–51] After 5 years, 10 to 15% of patients require another revascularization procedure because of the development of severe stenosis at an untreated site.[40] Diabetes increases the risk for adverse outcomes by increasing the risk of restenosis and disease progression at untreated sites.[52–54]

As noted previously in the description of the guidewire, iron components of stent struts attract fibrinogen and offer a site for platelet attachment and thrombosis. The increased risk of thrombosis at the treated site persists until endothelialization is complete. As a result, more intense antithrombotic therapy is required during the procedure and for up to 1 year afterward.[55,56] Before the use of preprocedural thienopyridine antiplatelet drugs, an intense antithrombotic regimen was used consisting of a Gp IIb/IIIa inhibitor and postprocedural warfarin anticoagulation in combination with aspirin.[11,30,31] However, the addition of thienopyridine antiplatelet drugs to aspirin therapy has proved more effective than warfarin anticoagulation. When given before the procedure, antiplatelet therapy provides sufficient protection so as to allow stent implantation in a stable patient without the need for Gp IIb/IIIa inhibitor therapy.[57–60]

A stent may be used as a drug-delivery system. However, rather than simply applying a drug to the stent surface, from which it will dissipate quickly, drug delivery is controlled by using a surface polymer or by altering the design or the material used to construct the stent.[61] This method of drug delivery, called a *drug-eluting stent* (DES), allows the drug to be applied at high concentrations at the site of interest and reduces the probability of systemic toxicity.

Table 21–6.

Risk Factors for Ischemic Events After Stent Placement[47]

Strongest correlates		
Nonchronic total occlusion		
Degenerated SVG		
Moderately strong correlates		
Length ≥ 10 mm		
Lumen irregularity		
Large filling defect		
Calcium + angle ≥ 45°		
Eccentric		
Severe calcification		
SVG age ≥ 10 years		
	Outcomes	
Group	**Definition**	**Death/MI emergency CABG**
Highest risk	Either of the strongest correlates	12.7%
High risk	≥3 moderate correlates	8.2%
Moderate risk	1–2 moderate correlates	3.4%
Low risk	No risk factors	2.1%

SVG = saphenous vein graft; MI = myocardial infarction; CABG = coronary artery bypass graft surgery.

A number of drugs have been studied. To date, the most effective drugs prevent replication of myofibroblasts that colonize the treated lesion.[62–64] Drug-eluting stents reduce the primary determinant of restenosis by 50 to 100%, as determined by quantitation of late lumen loss after angioplasty (Fig. 21-4). In large-scale clinical trials, this reduction corresponds to an angiographic restenosis rate of 4 to 6%, with a very low likelihood of a repeat procedure on the same lesion.[62,63,65] Studies examining the efficacy of the DES introduced new nomenclature to the follow-up endpoints. The most useful follow-up endpoint is termed *target vessel failure* (TVF), signified by cardiac death, MI, or repeat revascularization of the treated vessel. One year after the procedure, TVF is reduced from 19.4 to 21% with a bare-metal stent (BMS) to 8.8 to 10% with a paclitaxel or sirolimus DES.[50,51]

DES placement reduces the risk of angiographic restenosis and the need for repeat revascularization procedures for native coronary artery lesions, small vessels, chronic total occlusion, and saphenous vein grafts in patients with MI and diabetes mellitus[50,66–71] (Table 21-7). In fact, reduced rates of repeat intervention after DES placement have been reported for every type of lesion studied, except bifurcation lesions, where the risk of restenosis remains significant, and the risk of potentially fatal early thrombosis is as high as 3.5%.[69,72,73] However, the impact of DESs on failure of long-term treatment and repeat procedures does not translate to a reduced risk of procedure-related complications.[74] Because of the effect of the eluted drug or perhaps the polymer itself, endothelialization is delayed after DES implantation, peristent inflammation is prolonged, and local production of tissue factor may be enhanced.[75–78] After 1 month, thrombosis caused by DES placement is seen in approximately 0.3 to 0.7% of patients.[73,79,80] Late thrombosis is associated with the treatment of complex lesions, diabetes mellitus, renal failure, depressed left ventricular ejection fraction (LVEF), and withdrawal of dual antiplatelet therapy.[73,79,80] The treatment time required for dual antiplatelet therapy using aspirin and a thienopyridine after DES is

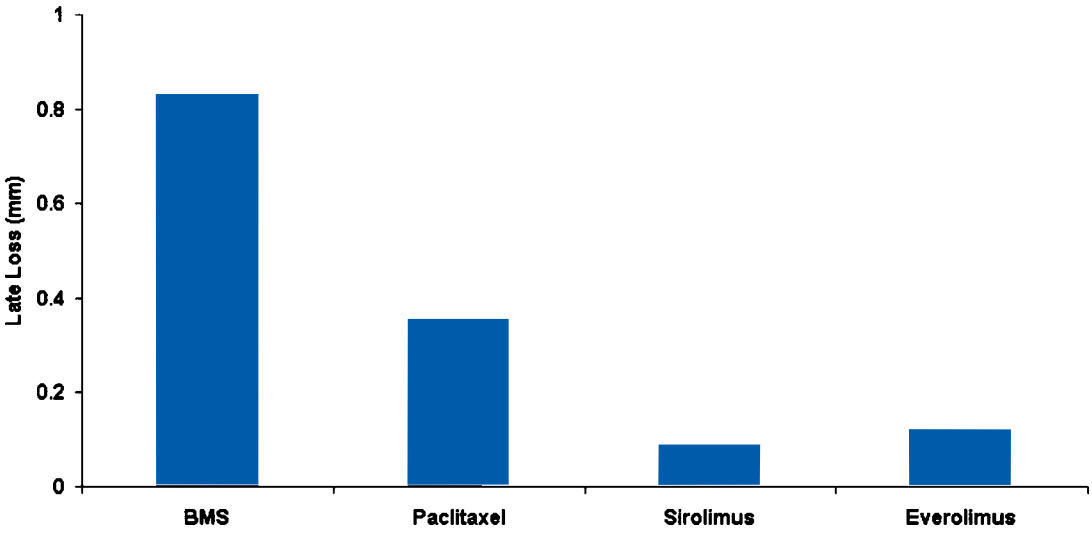


Figure 21-4. The effect of various stents on intimal hyperplasia in randomized trials is shown. A bare-metal stent's intimal hyperplasia thickness, or late loss, shown on the left, is compared with the late loss of drug-eluting stents shown at the right. BMS = bare-metal stent.

much longer than after BMS implantation. Current guidelines call for dual therapy for 3 months after sirolimus DES and 6 months after paclitaxel DES. However, clinical trial evidence that is not device-specific suggests that dual therapy should be continued for up to 1 year after any stent-related coronary revascularization.[55,56] The prolonged need for dual antiplatelet therapy has raised concerns about the timing of noncardiovascular surgeries following DES implantation.

Other Devices

Perfusion balloons

Before the routine use of coronary stents, abrupt closure owing to dissection could be treated with repeat balloon inflation and, if unsuccessful, with coronary artery bypass surgery. Prolonged balloon inflation generally was necessary for successful restoration of patency, but in the event of

Table 21–7.

The Clinical Impact of Drug-Eluting Stents

Population	Endpoint	BMS (%)	DES (%)
Total[50,51]	TVF	20–24.1	9.9–10.8
Diabetes mellitus[212]	MACE 9 mos.	27.2–36.3	11.3–15
Insulin-treated[213]	MACE 9 mos.	31.5	19.6
Myocardial infarction[214]	TVR 8 mos.	32	18
"Complex" lesions[215]	TLR 12 mos.	29.8	2.4
Long lesion small vessel[216–218]	MACE 9 mos.	18.3–22.6	4-8
Small vessel[70]	MACE 8 mos.	31.3	9.3
Bifurcation[72,219–221]	TVR 6 mos.	13.3–38	8.6–19
Restenosis[222]	TVR 6 mos.	33	8–19
Saphenous vein graft lesion[69]	MACE 6 mos.	28.1	11.5

BMS = bare-metal stent; DES = drug-eluting stent; TVF = target vessel failure; MACE = major adverse cardiac event; TVR = target vessel revascularization; TLR = target lesion revascularization.

failure, transport for emergency surgery often was accompanied by severe ischemia of the treated territory. As a result, balloon catheters with a short third-lumen opening just proximal and distal to the balloon were developed. These catheters, or "perfusion balloons," allowed for prolonged balloon inflation with far less ischemia and could be used to ameliorate the severity of ischemia during transport for surgery after an unsuccessful procedure.[81] Since the introduction of the coronary stent, perfusion balloons are used rarely.

Atherectomy

When introduced, the concept of reducing the bulk of the obstructing atheroma was quite attractive. The idea was to reduce vessel wall thickness or "debulk," allowing for balloon expansion at lower pressure. With less force applied for lumen expansion, theoretically the likelihood of abrupt closure would be reduced, as would the degree of arterial injury at the time of treatment. In some instances, balloon angioplasty even could be avoided. Several devices used to debulk have been developed and studied, including directional coronary atherectomy, high-frequency rotational atherectomy, percutaneous transluminal rotational ablation, and laser ablation. Unfortunately, when subjected to rigorous examination, debulking devices provide no incremental gain over plain balloon angioplasty in achieving procedural success or avoiding restenosis.[82–85] Although each device has developed a specific niche (see Table 21-4), their routine use generally is associated with an increased risk of procedural complications, including perforation and MI.[84,86,87]

Directional atherectomy

Directional coronary atherectomy is a procedure that uses a metal cylinder containing an opening, or "cutting window," opposing a balloon. When placed over a lesion, balloon inflation forces the cutting window into contact with the atheroma. The surface of the atheroma is lathed into a metallic reservoir. The SilverHawk atherectomy catheter (SilverHawk Technology, Redwood City, CA), a more recent iteration of directional atherectomy, uses the shape and orientation of the catheter (SilverHawk) to better orient the atherectomy. Directional atherectomy is limited by a modest degree of lumen enlargement, a frequent need for adjunctive angioplasty, and high rates of restenosis and complications. Thus directional atherectomy offers no advantage over conventional balloon angioplasty.[87]

Rotational atherectomy

The Rotablator (Boston Scientific Corporation, Natick, MA) is an olive-shaped device that is coated with diamond chips. The Rotablator is attached to a flexible shaft that is attached to an electrical motor. The motor creates rotation of the device or "burr" at very high speeds. The device is designed to abrade a rigid atherosclerotic intima, creating microemboli that are small enough to pass through the coronary microcirculation without incident.

Abrasion and microembolization are effective means of facilitating balloon angioplasty or stent implantation in heavily calcified lesions. However, the concept is not without failings. Impaired microcirculatory flow after rotational atherectomy is substantially more common than after plain balloon angioplasty.[88,89] Microembolization is likely to exacerbate ischemia and therefore is contraindicated when there are thrombotic lesions or impaired microcirculatory flow associated with recent MI. Use of this device is also associated with an increased risk of perforation in highly angulated lesions. It is, however, useful as an initial treatment method for very rigid, heavily calcified lesions because the procedure allows stent implantation where it otherwise would not have been possible.

Laser ablation

Lasers have been used to heat a catheter tip, to heat tissue abutting the angioplasty balloon, and to assist wire passage through chronic total occlusions, as well as for direct application to the lesion, for vaporizing tissue, and for direct application to myocardium.[90–95] Similar to the atherectomy devices, laser phototherapy devices are intended to perform safe and effective lesion debulking and to reduce the thrombus burden. With the exception of severely calcified lesions and, perhaps, lesions with a heavy thrombus burden, laser therapy is similar to atherectomy in offering little benefit over balloon angioplasty because laser therapy increases the risk of procedural complications.[85,87,93,96,97] Percutaneous transmyocardial laser revascularization yields no clinical improvement and promotes an additional risk of MI.[95] Also as in rotational atherectomy, specific lesions or circumstances may warrant its use (Fig. 21-5).

Aspiration devices

A number of coronary aspiration devices are available to reduce the risk of distal embolization and to diminish the local concentration of prothrombotic and vasoactive substances. These devices range from a simple end-hole catheter attached to a syringe to a complex suction catheter with or without an associated mechanical disrupter. These devices forcibly extract components of the thrombus or atheroma.[98] Their use may improve flow after treatment of thrombus-laden lesions or saphenous vein grafts[99] (Fig. 21-6). However, this effect has not been established with certainty.[100]

Embolic protection devices

During balloon angioplasty, mechanical dissolution of thrombus, if present, may result in macroembolization and distal vessel occlusion. The high-pressure manipulation of an atheromatous lesion also may free cholesterol crystals and other components of the lesion, resulting in distal microembolization, thrombosis, and slow- or no-reflow phenomenon.[101–105] Several devices have been developed to reduce the frequency or impact of distal embolization. These devices may be placed distal or proximal to the treated lesion. Distal devices are mounted on the guidewire

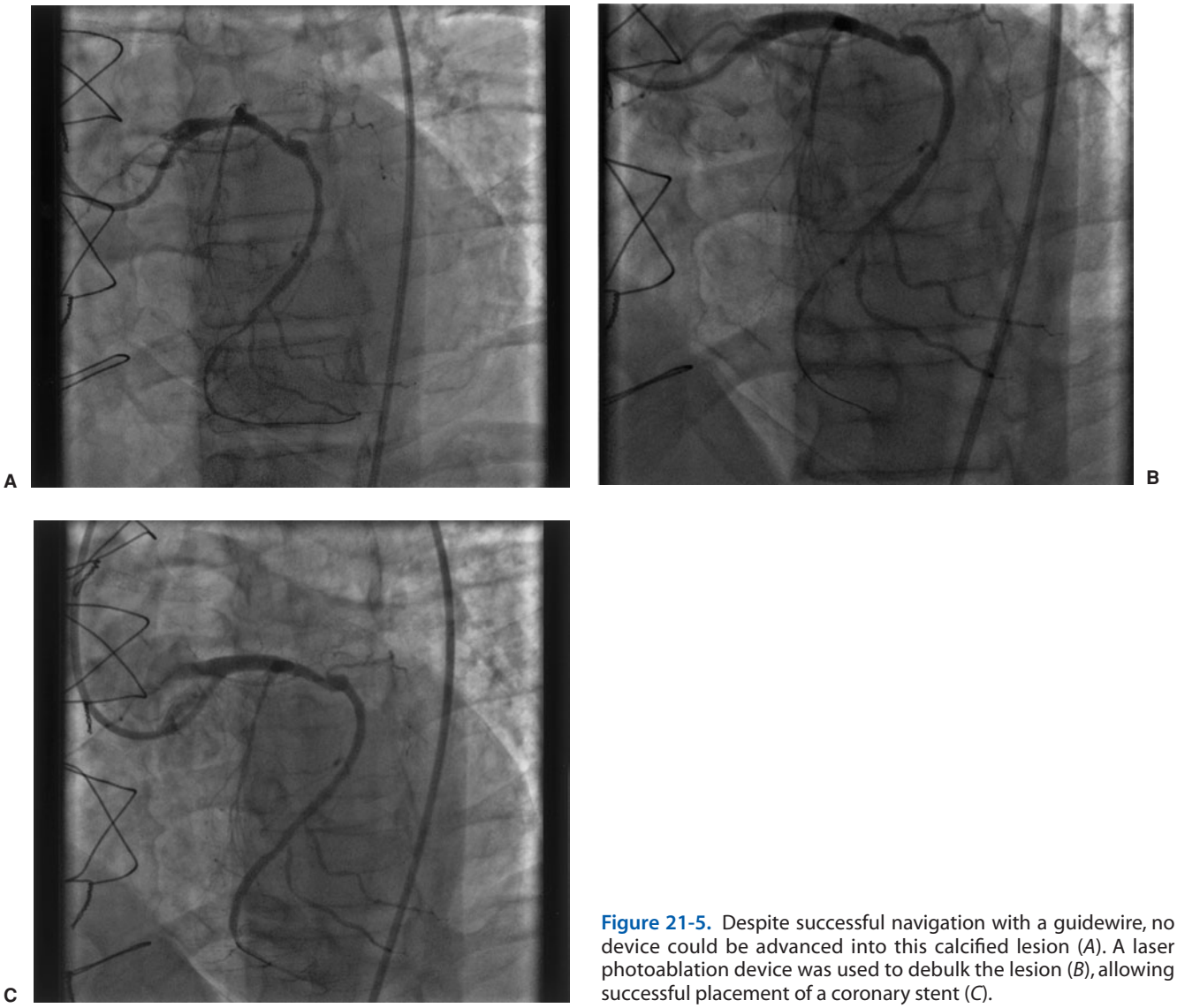


Figure 21-5. Despite successful navigation with a guidewire, no device could be advanced into this calcified lesion (*A*). A laser photoablation device was used to debulk the lesion (*B*), allowing successful placement of a coronary stent (*C*).

and use either a suspended micropore filter to trap particulate matter of 100 to 150 μm or larger or balloon occlusion of the treated vessel with posttreatment aspiration to capture embolized material. Proximally placed devices temporarily interrupt flow and aspirate the treated vessel. The PercuSurge GuardWire Plus (Medtronic, Minneapolis, MN) is a balloon occlusion and aspiration device that underwent testing in vein grafts in the Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial. The trial demonstrated a 42% reduction in creatine kinase (CK) elevations and more than a 50% reduction in the no-reflow phenomenon.[106] Unfortunately, these results did not apply to patients with MI.[107]

The FilterWire EX (Boston Scientific, Natick, MA) has a self-expanding wire loop attached to the guidewire (Fig. 21-7). This self-expanding loop suspends a micropore filter shaped somewhat like a windsock and ensures good apposition to the wall of the treated vessel. Theoretically, smaller particles, cytokines, and procoagulant molecules may pass through the filter. However, a direct comparison between the filter wire and guardwire revealed no difference in the degree of protection against distal embolization.[108]

Imaging devices

Angiographic imaging allows imaging of the coronary lumen but may be unreliable in the setting of severe calcification, difficult branching patterns, or previously placed coronary stents. Furthermore, a thrombus that may increase the risk of PCR may go undetected by standard angiographic imaging. Therefore, a number of alternative imaging methods have been developed to improve diagnosis, to plan revascularization efforts, and to evaluate the success of

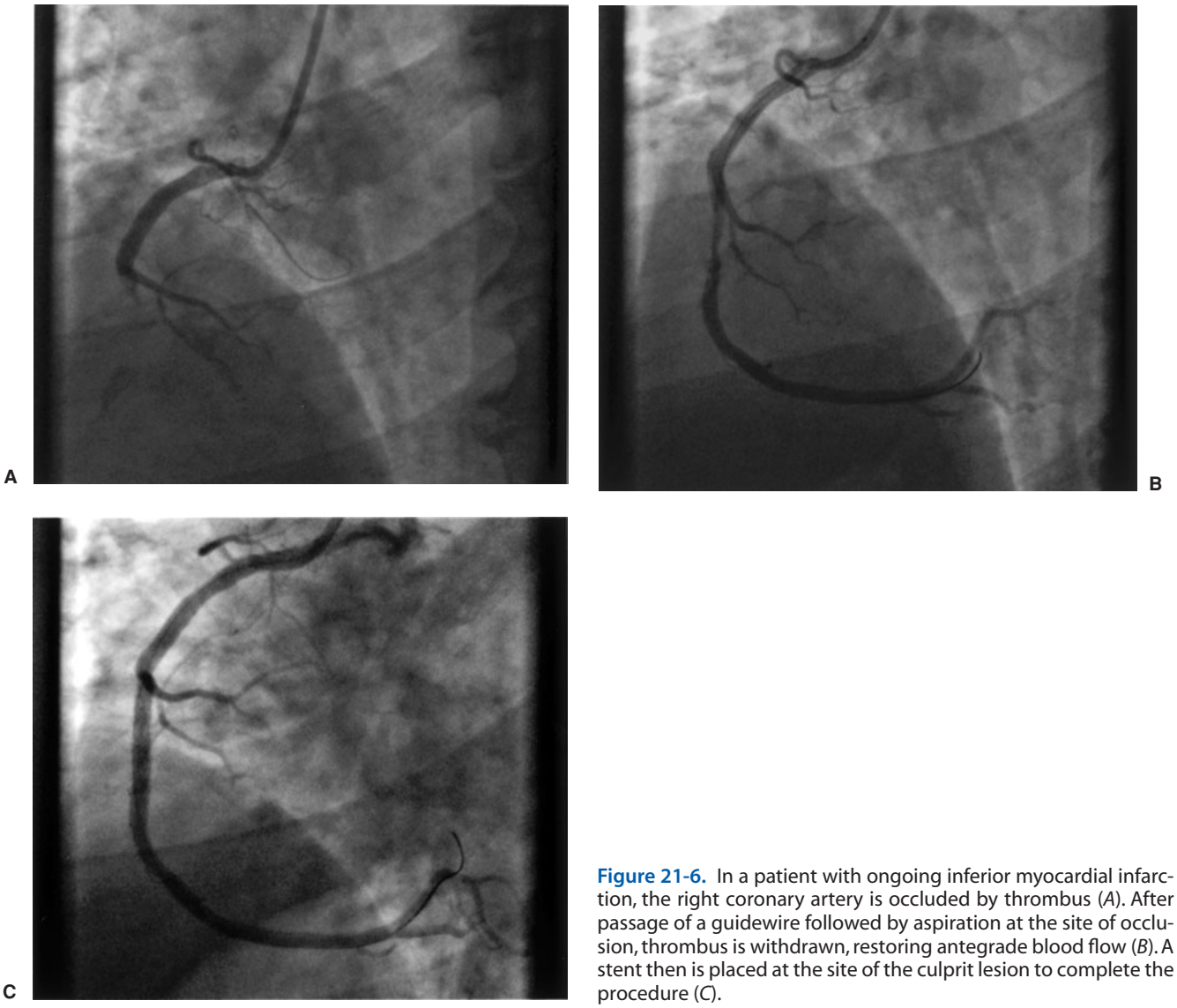


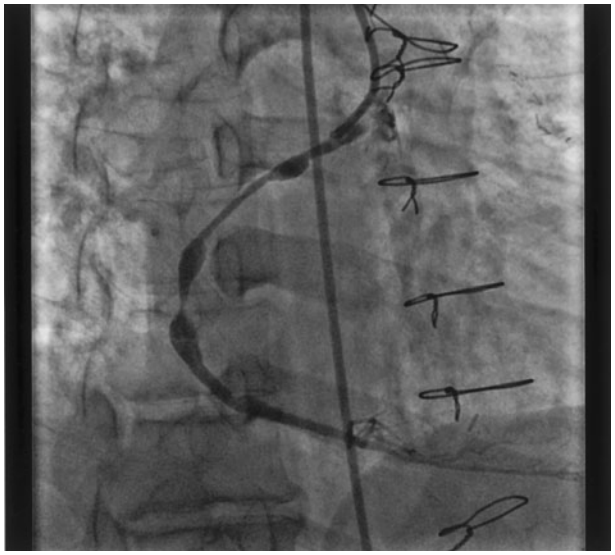
Figure 21-6. In a patient with ongoing inferior myocardial infarction, the right coronary artery is occluded by thrombus (*A*). After passage of a guidewire followed by aspiration at the site of occlusion, thrombus is withdrawn, restoring antegrade blood flow (*B*). A stent then is placed at the site of the culprit lesion to complete the procedure (*C*).

such efforts. Angioscopy or fiberoptic imaging requires occlusion of the imaged vessel and perfusion with saline. While a useful tool to investigate the presence or components of thrombus within coronary vessels, angioscopy has not been a useful adjunct to PCR.[109] In contrast, intracoronary ultrasound imaging has proved especially useful. Ultrasound imaging allows accurate determination of vessel size, luminal reduction, lesion components, and progress associated with revascularization attempts. Ultrasound guidance for stent implantation is associated with a greater than 30% reduction in the need for repeat procedures.[110] Of equal importance, intracoronary ultrasound is an invaluable research tool used to investigate the accuracy of contrast angiography and the impact of mural lesion components on complications and outcomes after angioplasty. Intracoronary ultrasound also provides precise, accurate information about the impact of various DESs on intimal hyperplasia.[111,112]

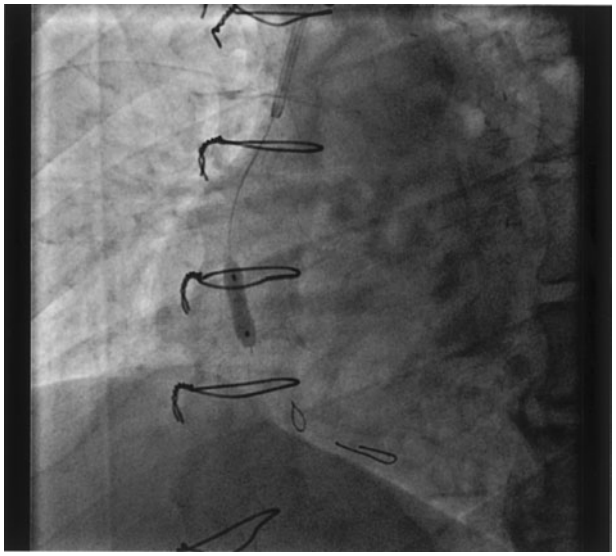
Devices that measure lesion severity

The hemodynamic significance of coronary lesions, the appropriateness of a treatment, and the success of treatment may be determined by the following two means: a guidewire that measures the velocity of blood flow within coronary arteries or a calculation that measures pressure distal to a coronary lesion.

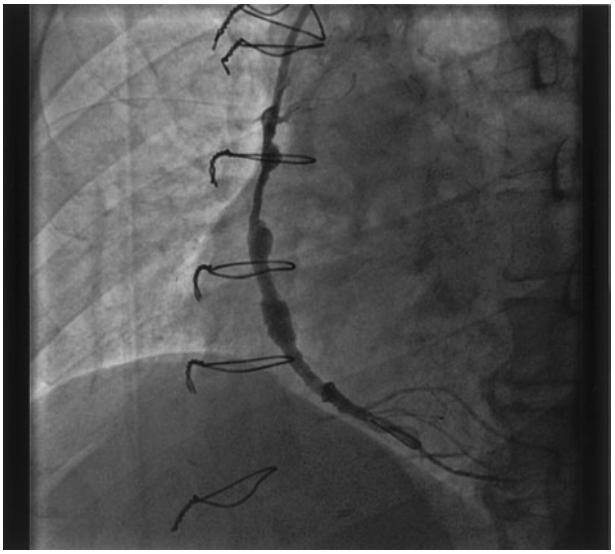
A miniaturized Doppler-equipped guidewire with a 12-MHz transducer uses a pulsed interrogation that samples 5.2 mm beyond the guidewire tip at an angle of 14 degrees on either side. Assuming that the cross-sectional area of the



A



B



C

Figure 21-7. In this aged and degenerated saphenous vein graft, any manipulation is likely to result in distal microembolization, slow flow, and infarction (*A*). Placement of a distal filter wire may prevent embolization proximal to the device during placement of a stent (*B*). The self-expanding ring can be seen closely apposed to the walls of the saphenous vein graft, allowing flow through the centered filter (*C*).

interrogated vessel remains constant during all measurements, the ratio of velocities measured reflects the ratio of blood flow between any two measurements. The most important and reliable parameter that a flow probe measures is the ratio of resting flow to vasodilated coronary flow, a value known as *coronary flow reserve*. When measured using the Doppler probe, the value is termed *coronary velocity reserve* (CVR). As a coronary lesion becomes flow-limiting, attempts to normalize tissue perfusion by autoregulation result in arteriolar dilatation at rest. Therefore, the administration of an arteriolar vasodilator such as adenosine will have little additional effect on flow velocity. The absence of an appropriate increase in velocity during adenosine- or dipyridamole-induced arteriolar vasodilation produces abnormal flow reserve. A CVR greater than 2.0 indicates hemodynamically significant lesions.

CVR measurement reflects changes in flow relative to an assumed normal baseline state but is subject to error when baseline flow is abnormal. Examples of abnormal states include left ventricular (LV) hypertrophy, fibrosis, and perhaps anemia. In addition, abnormally large or small driving pressure gradients may fall outside the range of normal coronary autoregulation, altering the basal-to-hyperemic ratio. Failure to achieve arteriolar dilatation in response to adenosine or dipyridamole will produce an abnormal calculated flow reserve. Examples that affect arteriolar dilatation include diabetes mellitus, amyloidosis, and recent caffeine or theophylline ingestion.

Under normal conditions, epicardial vessels present little detectable resistance to flow. Therefore, driving pressure (P_{Ao}) and arteriolar resistance pressure (P_{RA}) determine maximal coronary blood flow. The presence of a flow-limiting coronary lesion will cause some of the driving pressure to be lost, so maximal flow will depend on the distal coronary pressure (P_d)-to-P_{RA} gradient and arteriolar resistance. Therefore, the fraction of maximal basal flow that remains possible in the presence of the lesion is

$$\dot{O}_{lesion}/\dot{O}_{no\ lesion} = (P_d - P_{RA}/R_{basal})/-(P_{Ao} - P_{RA}/R_{basal})$$

Canceling resistance and assuming that right atrial pressure remains constant results in a very simple relationship:

$$\dot{O}_{lesion}/\dot{O}_{no\ lesion} = P_d/P_{Ao}$$

This ratio, called the myocardial *fractional flow reserve* (FFR), is obtained after the administration of adenosine. An FFR of 0.75 or less identifies a hemodynamically significant lesion.[113]

BRACHYTHERAPY

Prior to the advent of the DES, restenosis after angioplasty or stent implantation could be treated by medical therapy, by repeat angioplasty, or by coronary artery bypass surgery. The frequency of restenosis led to a large population of patients with multiple treatment failures, intractable symptoms, and prohibitive risks for surgical treatment. Because a proportion of the cell population colonizing a treated lesion and contributing to restenosis arose from the media of the treated lesion, radiation therapy to prevent colonization and cell replication was proposed. The well-recognized dangers of high-dose, external-beam radiation limited dosing to local application, but this therapy still was seen as a substantial risk. When used as a treatment for de novo coronary lesions, radiation brachytherapy increased both short- and long-term complications.[114] However, for the treatment of refractory in-stent restenosis, limited successes have been observed.[115,116]

Radiation sources may be classified according to the energy of the emitted particle. Gamma radiation, at the high end of the electromagnetic spectrum, refers to an emitted photon with short wavelength and high energy that is able to penetrate deeply into tissue and surrounding structures. Therefore, short-term application of gamma radiation may allow for delivery of a significant tissue dose. Beta radiation refers to lower-energy and less penetrating electrons released from a radioactive isotope. Both forms of radiation have been used for coronary brachytherapy to prevent repeat stent restenosis. However, beta-radiation sources are handled more easily and may be applied to coronary stents for local delivery over a long period of time. Gamma-radiation sources are dangerous to handle, require special training, and may be applied only briefly in specially shielded catheterization laboratories. Beta-radiation sources include strontium-90, yttrium-90, and phosphorous-32. Strontium and yttrium are metallic and may be delivered to the site of interest as a "wire." Phosphorous-32 may be incorporated into a coronary stent. Gamma sources are limited to iridium-192, which must be delivered as pellets advanced through a specially designed catheter.

Radiation brachytherapy reduces the risk of repeat in-stent restenosis from 54 to 58% and, after 6 months, reduces restenosis from 17 to 27% in native vessels and saphenous vein grafts.[117–120] Treated patients have a greater risk of restenosis and repeat intervention during long-term follow-up, suggesting a catchup phenomenon, but an advantage over placebo is maintained through 5 years.[119,121–124] Unlike gamma radiation, the localized delivery of beta radiation also causes vigorous intimal hyperplasia to form adjacent to the treated site, creating a "candy wrapper" restenosis appearance.[125] The local effects of radiation create a prothrombotic state and an increased risk of thrombosis at the treated site.[115,126–128] Therefore, dual antiplatelet therapy is required for at least 1 year after the procedure.[129] This form of therapy likely will be abandoned with the advent of DESs, whose efficacy probably is equal to or greater than that of radiation.

CIRCULATORY SUPPORT

Performance of a percutaneous revascularization procedure includes an obligatory period of ischemia in the treated region. The duration of ischemia may be prolonged in the event of abrupt closure or distal embolization, and recovery may be incomplete or delayed for a period of days, as in the treatment of acute MI. For patients with depressed LV systolic function or for those in whom the treated territory is large, there is a risk for developing cardiogenic shock during and after the procedure. This risk substantially increases the possibility of acute renal failure, stroke, and death. The likelihood of shock complicating an angioplasty procedure may be predicted by using a scoring method that incorporates the extent and severity of systolic dysfunction present before the procedure and the extent that can be expected as a result of the procedure[130–132] (Table 21-8). Elective placement of

Table 21–8.

A Score Predicting the Need for Circulatory Support[132]

Six arterial segments	**LAD, D_1, S_1, OM, PLV, PDA**
Score 1	Target lesion or any additional lesion >70% diameter stenosis
Score 0.5	Subtended region is hypokinetic but has no stenosis
For a score >3	Consider IABP

LAD = left anterior descending artery; D_1 = first diagonal branch; S_1 = first septal branch; OM = obtuse marginal branch; PLV = posterior left ventricular artery; PDA = posterior descending artery; IABP = intra-aortic balloon pump.

an intra-aortic balloon pump (IABP) is associated with a reduced risk of hypotension and major complications.[133]

Intra-aortic balloon counterpulsation has been used to assist the performance of percutaneous angioplasty for a number of years, but the assistance provided by an IABP may be insufficient for patients with severely impaired systolic function or for those who develop cardiogenic shock after MI. The percutaneous left ventricular assist device (PLVAD) is a miniaturized axial-flow pump that is being used increasingly for support of patients in shock or during high-risk angioplasty procedures.[134] The PLVAD is capable of providing up to 4 L of additional blood flow per minute. Although it can providing superior circulatory support, the PLVAD has not shown any survival advantage when compared with the IABP, and vascular access-site complications are more frequent with the PLVAD.[135]

COMPLICATIONS OF PCR

In addition to abrupt closure and restenosis, there are several other potential complications of PCR that may influence the risk:benefit ratio for an individual patient. These complications include bleeding, vascular access-site complications, stroke, radiocontrast nephropathy, and MI owing to distal embolization.

Hemorrhage

During the introduction of coronary stent implantation, heparin therapy often was maintained after sheath withdrawal, resulting in groin access-site complications in as many as 16% of patients.[136] Modifications in groin access technique, pharmacologic therapy, and sheath withdrawal have reduced this risk substantially. Bleeding that requires transfusion or results in hemodynamic instability occurs in 0.5 to 4% of PCR procedures, depending on patient variables (e.g., age, gender, and peripheral vascular disease), procedural variables (e.g., location of femoral arteriotomy and duration), and pharmacologic variables (e.g., intensity of antithrombotic therapy).[5,137,138] Risk factors for vascular access-site complications potentially requiring surgical repair (e.g., pseudoaneurysm, arteriovenous fistula, laceration, and retroperitoneal hematoma) are similar to risk factors for bleeding.[139–141] A number of devices have been designed to improve femoral hemostasis after sheath removal, but none has proven superior to standard compression hemostasis.[142]

Because of the size of equipment used for angioplasty procedures, femoral access has been and remains the preferred approach. However, with the availability of lower-profile equipment, the radial artery is being used with greater frequency, which results in a reduction in bleeding and access-site complications.[143]

Ischemia

Stroke complicates approximately 0.18% of PCR procedures.[144] Its occurrence is associated with increased age, depressed LVEF, diabetes mellitus, saphenous vein graft intervention, and complicated or prolonged procedures requiring the placement of an intra-aortic balloon pump.[145]

MI complicates 5 to 30% of PCR procedures, depending on the definition of infarction.[146] Using a definition of new Q wave, the incidence is 1%.[147] When any elevation of MB fraction of CK (CK-MB) is used as the definition, as many as 38% of patients have periprocedural MI.[146] Use of more stringent definitions of infarction, such as greater than three or 10 times the upper limit of normal, reduces the reported values to 11 to 18% or 5%, respectively.[147–149] Actually, any elevation carries prognostic significance, but elevation above three times the upper limit of normal is accepted as a definition of periprocedural MI. Elevated levels of troponin I (23 to 48%)[149–151] after PCR are even more frequent, although the prognostic significance of minor elevations is questionable.

Transient coronary occlusion during PCR may result in a periprocedural MI. However, elevated markers of myocardial injury may be seen following apparently uncomplicated procedures.[146] One mechanism for such events is microscopic distal embolization. When severe, microscopic distal embolization of a coronary artery creates an angiographic appearance of slow vessel filling termed *no-* or *slow-reflow*. No-reflow is seen most often in the setting of saphenous vein graft angioplasty but also may complicate rotational atherectomy and primary PCR for acute MI. Methods of quantifying abnormal flow following PCR include a subjective estimation of flow velocity, the Thrombolysis in Myocardial Infarction (TIMI) flow rate (III, normal; II, slow; I, minimal contrast material flow beyond the treated site; and 0, no flow), and the more objective method of corrected TIMI frame count. Individual frames of the angiographic image are counted from the time of contrast material entry into the treated vessel until a predetermined distal landmark is reached. Because of somewhat slower flow in the longer left anterior descending artery, flow in this vessel is modified mathematically, or "corrected," in order to normalize values with the right and circumflex coronary arteries.[152]

No-reflow may be a brief and self-limiting phenomenon, but when prolonged, it is associated with increased mortality.[153] Pharmacologic manipulations, including intracoronary verapamil,[154] adenosine,[155] and nitroprusside,[156] may be used in an attempt to prevent or treat no-reflow phenomenon (see Table 21-2).

Perforation of the coronary artery complicates 0.5% of angioplasty procedures,[157–159] and its frequency increases almost 10-fold when ablation devices are used (ablation 1.3% versus PTCA 0.1%; $P < .001$).[157] Coronary artery perforation occurs more frequently in elderly and female patients.[157,159] Perforations are classified by severity as type I (a visible extraluminal crater without extravasation), type II (pericardial or myocardial blushing; Fig. 21-8), and type III (1 mm diameter perforation with contrast material streaming). Type I and II perforations typically are the result of improper guidewire manipulation or placement. Type I perforations (26%) may be treated nonsurgically 95% of the

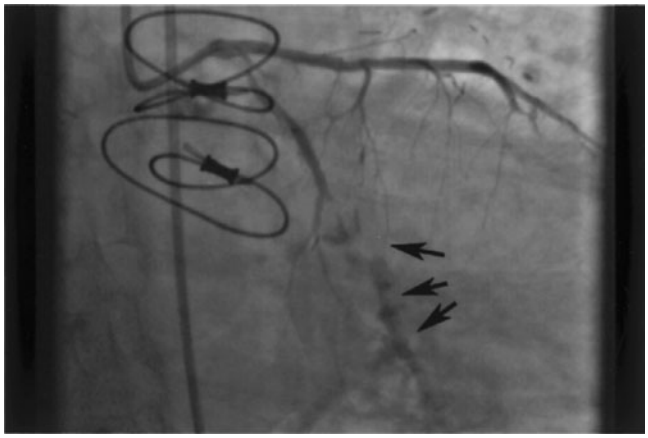


Figure 21-8. In the setting of early saphenous vein graft closure with myocardial infarction and postinfarction angina, attempts to access the culprit native vessel with a stiff guidewire have led to coronary perforation. Shown in this injection of the left coronary artery are occlusions of the left anterior descending and left circumflex coronary arteries. Staining is seen (*arrows*) in the region of the attempted recanalization of the left circumflex coronary artery identifying perforation (type II). The patient was treated successfully with reversal of anticoagulation and temporary occlusion of the circumflex using the PTCA balloon. PTCA = percutaneous transluminal coronary angioplasty.

time and are rarely fatal. Type II perforations (50%) require surgery 10% of the time and are associated with a 13% mortality rate. Type III perforations (26%) carry a mortality rate of 63%.[157]

Pericardial tamponade is frequently but not invariably associated with coronary artery perforation. The overall incidence of tamponade after PCI is 0.12% and doubles when ablation devices are used. PCI-associated tamponade is recognized 55%[160] of the time during or after the procedure while the patient is still in the catheterization laboratory and 45% of the time after the patient leaves the laboratory. A minority of episodes of late tamponade (13%) are associated with recognized coronary artery perforation. Tamponade requires surgical treatment in 39% of patients, is closely associated with MI complicating PCR, and carries a mortality rate of 42%.[160]

The covered stent that was developed for, but failed to reduce the risk of, saphenous vein graft restenosis[161] presently is used as a rescue device after coronary artery perforation or for the treatment of coronary or saphenous vein graft aneurysms[162] (Fig. 21-9). When a covered stent is used for the treatment of coronary artery perforation, the need for emergency surgery is reduced, and the outcome of coronary artery perforation is improved. A small number of patients, however, still will require surgery.[163]

Toxicity

Acute renal failure following exposure to radiocontrast material, or *radiocontrast nephropathy* (RCN), is poorly understood. Its occurrence is a function of age, congestive heart failure, hemodynamic instability, diabetes mellitus, preexisting renal insufficiency, anemia, peripheral vascular disease, and the amount of contrast material administered.[164–166] The incidence of RCN after coronary angiography is 5 to 6%, with the nadir of renal function occurring 3 to 5 days after the procedure.[167] Even a transient decline in renal function leads to an increased risk of ischemic cardiovascular events during follow-up, and renal failure requiring hemodialysis is seen in about 10% of patients with RCN, increasing both short- and long-term mortality.[164,166,168]

Attempts to limit the incidence of RCN have included the use of calcium channel antagonists, aminophylline, *N*-acetylcysteine, fenoldopam, dopamine, atrial natriuretic peptide, sodium bicarbonate, hemofiltration, and iso-osmolar nonionic contrast material and maintenance of brisk urine flow with crystalloid solution and diuretics.[167,169–177] Unfortunately, few of these methods have produced the desired result.

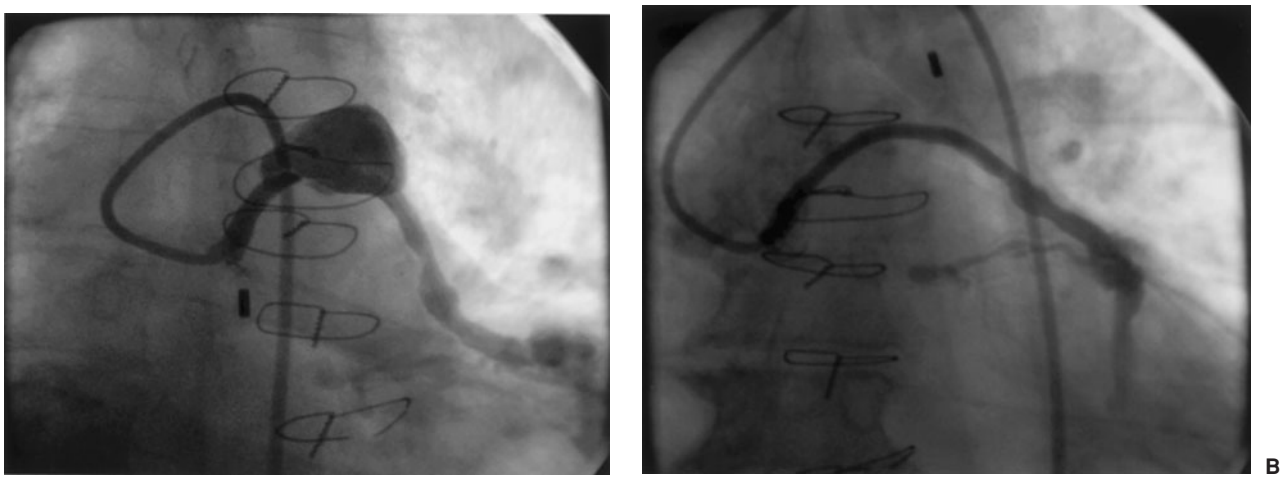


Figure 21-9. A large saphenous vein graft aneurysm (*A*) is treated with a covered stent (*B*).

Iodixanol, an iso-osmolar nonionic contrast agent, reduced the incidence of RCN following noncardiac angiography.[177] Giving four oral doses [600 mg each of *N*-acetylcysteine (two doses on the day before and two on the day of the procedure)] has met with varied outcomes in several studies but appears to be beneficial.[172,178] Administering crystalloid solution in volumes sufficient to maintain brisk urine flow, perhaps aided by alkalinization of urine pH, is the most effective intervention to ensure an adequate volume state.[167,170,171] Forced diuresis with diuretics is of minimal or no additional value, and the use of dopamine to reduce the likelihood or duration of RCN may be harmful.[170,175]

SPECIAL CIRCUMSTANCES

Acute Coronary Syndromes (ACS)

Successful PTCA within the first 6 hours of ST-segment-elevation MI is at least as effective as, and perhaps more effective than, thrombolytic agents in limiting myocardial damage and improving in-hospital survival. The incidence of recurrent ischemia is reduced, LV function may be better preserved, and there is no significant risk of intracranial hemorrhage.[179,180]

Patients undergoing urgent PTCA have a 20 to 40% risk of experiencing recurrent angina, restenosis, or repeat revascularization. Stents are more effective than PTCA, especially when used in combination with a potent antiplatelet regimen.[181–183] Their comparison with thrombolytic therapy has been far more favorable in both early and late outcomes.[180,184,185] The routine use of coronary stents for acute MI is associated with a restenosis rate of 17% and a 6-month event-free survival of 83 to 95%.[186–190] DESs are safe for use in patients with acute coronary syndromes[67,191,192] and reduce the risk of any adverse event from 17 to 9.4% at 300 days.[67]

Routine angioplasty following full-dose thrombolytic therapy was associated with an increased risk of complications owing to rethrombosis, bleeding, and intramural coronary artery hematoma, which could produce abrupt vessel closure. However, with the use of stents and Gp IIb/IIIa antagonists, there is no longer an increased complication risk associated with PTCA, and repeat hospitalization for revascularization has been reduced substantially.[193,194] After failed attempts at thrombolysis or for patients with cardiogenic shock who received thrombolysis, stent revascularization increases myocardial salvage and reduces the risk of death, heart failure, or reinfarction.[195–197]

Prior Coronary Artery Bypass

Stent implantation with the assistance of embolic protection devices is the preferred method for percutaneous treatment of saphenous vein grafts.[106,198] The use of distal embolic protection reduces the risk of periprocedural MI from 14.7 to 8.6%.[106] Unfortunately, diseased grafts have a high probability of developing new lesions, reducing the long-term event-free survival rate. After stent implantation, overall survival is 79% at 4 years, but survival free of MI or another revascularization procedure is only 29%.[199–203] DESs reduce the risk of restenosis after saphenous vein graft PCR but will not affect the likelihood of progression elsewhere in the diseased graft.[69]

THE FUTURE

The future of interventional cardiology lies in reducing procedural risk and extending treatment durability. For many patients, the goal of providing durable treatment success has been very nearly achieved with the introduction of DESs, an approach that has yet to be fully explored. However, a DES does not reduce procedural risk, and problems remain for patients with diffuse atherosclerosis, diabetes mellitus, bifurcation lesions, and acute coronary syndromes.

Ironically, the goal of reducing procedural risk has been pursued most effectively for saphenous vein graft revascularization with the development of distal embolic protection devices. However, for native-vessel intervention, particularly during acute coronary syndromes, further advances likely will be pharmacologic rather than technical. Drawing on observations made in ischemic preconditioning, modification of myocardial energy metabolism with drugs such as ranolazine, perhexeline maleate, and others represents a means of improving the heart's ability to withstand ischemia, thus temporizing the impact of temporary vascular occlusion and macro- or microembolization.[204–206] In addition, inhibitors of the protein kinase family of enzymes, central to intracellular signaling, also may improve the heart's ability to withstand ischemia as well as reduce the severity of reperfusion injury.[207–209]

Local drug delivery has met with great success in reducing the problem of restenosis. However, there are numerous methods of modifying the physiology driving intimal hyperplasia after stent implantation. New DES platforms offer the alternative of eluting multiple drugs at different rates, reducing the need for systemic medical therapy such as prolonged dual antiplatelet therapy. One active area of research is the development of stents capable of delivering drug therapy without dependence on a coating polymer. In addition, complex molecules that can be absorbed by the body are being developed as stent platforms. The use of such a stent, one that delivers antithrombotic and antiproliferative drug therapy, could, conceivably, allow PCR protection from acute closure, recoil, thrombosis, and restenosis without contributing to vessel rigidity—which increases the difficulty of subsequent procedures.

A growing number of patients who are surviving long-term with severe multivessel coronary artery disease remain hampered by severe angina pectoris. In many instances, years of slow, steady disease progression have left extensive collateral vessels that prevent infarction and the near or complete loss of major branch vessels. These patients currently have no option for percutaneous or surgical revascularization.

The promise of direct myocardial revascularization remains unfulfilled, and percutaneous attempts appear to be harmful.[210] The modification of vascular growth and remodeling that was hoped for with the administration of specific growth factors proved too complex to achieve predictable results. However, the use of stem cells, perhaps the most efficient producers of cytokines and growth factors in their proper sequence, has met with early success. Direct injection of stem cells into regions of ischemic myocardium improves walking time and reduces the frequency of angina attacks.[211]

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CHAPTER 22

Myocardial Revascularization with Cardiopulmonary Bypass

Enrique Góngora • Thoralf M. Sundt, III

Coronary artery disease (CAD) remains the single largest killer of Americans. Accounting for almost half a million deaths per year, CAD imposes a particular burden on the elderly, with more than 80% of all CAD deaths occurring in those over age 65.[1] Given projections that the number of Americans older than 65 years of age will double from 30 million currently to 62 million over the next 25 years,[2] and the anticipated increase in the prevalence of important risk factors for CAD such as diabetes mellitus and obesity,[3] the need for coronary revascularization in the next two decades can be expected to increase.

The role of surgical revascularization vis-à-vis percutaneous coronary interventions (PCI) continues to mature, as the latter field has evolved from balloon angioplasty to near routine coronary stenting complemented by "cutting balloon" angioplasty, rotational atherectomy, directional atherectomy, laser angioplasty, and radiation brachytherapy. Between 1999 and 2002 the use of percutaneous techniques increased at a rate of 6.8% annually with a 1.9% annual decrement in the number of coronary artery bypass graft (CABG) procedures performed.[4] In 2002, an estimated 959,000 Americans required coronary revascularization, according to the Centers for Disease Control and Prevention. Revascularization was achieved by CABG in 31% of patients and in 69% of patients with percutaneous interventions. A total of 709,000 open heart surgery procedures were recorded during the same year, with CABG procedures performed in 306,000 patients.[5] Despite progress in reducing the rate of target vessel restenosis, particularly with the advent of drug-eluting stents, reintervention rates remain higher and angina relief lower following PCI rather than CABG. Furthermore, CABG procedures can be carried out today with remarkably low periprocedural mortality and morbidity and excellent long-term results despite an increasing risk profile.[6] There are also mounting data to suggest a late mortality benefit with CABG over PCI,[7–9] although a complete discussion of this topic is beyond our scope here. It is sufficient to note that surgical revascularization will undoubtedly continue to play a significant role in the management of CAD for the foreseeable future.

There has been considerable interest of late in performing CABG without use of cardiopulmonary bypass as discussed in detail in a separate chapter. "Off-pump" CABG is technically demanding, however, and is likely not applicable to every patient. Excellent short- and mid-term results have been achieved by centers with special interest in this technique; however, concerns about graft patency with off-pump techniques still exist, and long-term outcomes as well as graft patency studies are eagerly awaited. Currently, 80% of surgical myocardial revascularizations (MRs) in the United States are performed with the aid of cardiopulmonary bypass.[4] At this time MR with cardiopulmonary bypass remains the gold standard against which newer techniques must be compared. In the foreseeable future MR with cardiopulmonary bypass will continue to be a cornerstone of the management of patients with CAD.

HISTORY OF CORONARY ARTERY BYPASS GRAFTING

Indirect methods to restore blood supply to the ischemic myocardium were pioneered by Claude Beck,[10] who reported in 1935 on the placement of a pedicled pectoralis muscle flap on the abraded pericardium. In 1951 Vineberg described direct implantation of the internal thoracic artery (ITA) into the myocardium,[11,12] and Sen described "myocardial acupuncture" in 1968.[13] Gibbon's development of the cardiopulmonary bypass machine and its successful clinical application by Kirklin at the Mayo Clinic and Lillehei at the University of Minnesota[14–16] made direct coronary revascularization technically feasible. Bailey

in 1957 reported the first successful coronary endarterectomy, and in 1958 Longmire reported a mammary-to-coronary anastomosis performed after a surgical misadventure with a coronary endarterectomy.[17,18] Goetz in 1960 performed the first successful planned coronary artery bypass operation, employing a metal cannula to connect the right ITA to the right coronary artery (RCA), with angiographic patency confirmed 2 weeks after operation.[19,20] The first reported use of a saphenous vein aorto-coronary bypass was reported by Sabiston in 1962; however, the postoperative death of the patient dissuaded repetition of the procedure.[21,22] The Russian surgeon Kolessov is credited with the first successful planned sutured internal mammary-to-coronary anastomosis in 1964.[23,24] Garrett and DeBakey reported a 7-year follow-up of a bypass with venous conduit performed also in 1964.[25]

It was, however, the development of coronary angiography by Mason Sones at the Cleveland Clinic in 1957 that opened the door to the elective treatment of coronary atherosclerosis by means of direct revascularization.[26] Initial studies by Rene Favaloro and Donald B. Effler with venous and arterial conduits, and their systematic application of these techniques to treat clinical events associated with stenotic lesions of the coronary arteries, culminated in the first large series of aorto-coronary grafts with venous conduits reported in 1968.[27–30] Simultaneously Dudley Johnson of Milwaukee published a series of 301 patients undergoing coronary bypass with venous conduits in 1969.[31] The success of these techniques was soon demonstrated in larger series,[32] initiating the modern era of coronary artery surgery.

One of the most striking features of the history of CABG is the extent to which the procedure was subjected virtually from the outset to prospectively randomized study. Surgical revascularization was demonstrated to provide excellent relief of symptoms as well as improved survival among patients with the most severe forms of atherosclerotic coronary involvement.[33–35] The subsequent establishment of large databases has allowed advances in risk stratification, mortality prediction, and long-term follow-up, making CABG arguably the most data-driven, evidence-based medical procedure performed today.

INDICATIONS FOR SURGICAL CORONARY REVASCULARIZATION

The indications for CABG are reviewed in detail in a separate chapter. In brief, the indications established by the American Heart Association and American College of Cardiology (AHA/ACC) consensus panel[36] are based predominantly on the results of trials comparing surgical revascularization with medical therapy for patients with chronic stable angina. Between 1972 and 1984 several randomized trials compared medical and surgical therapy for the treatment of atherosclerotic CAD. The three major trials, the Coronary Artery Surgery Study (CASS),[34,37] the Veterans Administration Coronary Artery Bypass Cooperative Study Group,[35] and the European Coronary Surgery Study (ECSS),[33] and three smaller randomized trials,[38–40] demonstrate the greatest survival benefit of revascularization to be among those patients at highest risk as defined by the severity of angina and/or ischemia, the number of diseased vessels, and the presence of left ventricular dysfunction.[35,41–43] It is widely accepted that there is a survival advantage for surgical revascularization over medical therapy in patients with left main disease,[44] and those with triple-vessel disease and left ventricular dysfunction.[45,46] There is also significant evidence supporting a survival advantage with CABG for those with two-vessel disease and proximal left anterior descending (LAD) disease,[33] and in patients with severe ischemia and multivessel disease.[47,48] More recent progress in both PCI and medical therapy, however, has raised intriguing questions as reviewed in the aforementioned chapter.

PREDICTION OF OPERATIVE RISK

The ultimate decision whether or not to proceed with CABG in an individual patient can only be made with an estimate of the individual's risk. Formal prediction of risk-adjusted outcomes permits both the surgeon and the patient to weigh the risks against potential benefits and realistic expectations, thereby permitting the patient to give a true informed consent prior to coronary surgery. Accurate risk-adjusted prediction of postoperative morbidity and mortality also provides an important quality improvement tool to understand and examine the variability in institutional and individual surgeon performance.

Operative Mortality

A number of large single-center and multicenter cardiac surgery databases have been used to develop risk models for predicting operative mortality in patients undergoing CABG.[36,49–51] The most accurate assessment of individual operative risk is likely that derived using the Society of Thoracic Surgeons (STS) database (Table 22-1). Database participants have access to a desktop program into which they are able to enter individual patient variables to obtain an actual percent of predicted risk. The precise STS risk algorithm is proprietary, however, and demands database participation as well as access to the computer program.[52–55]

A practical "seat of the pants" sense of risk can be more simply derived simply from an understanding of the core variables most predictive of risk in the aforementioned data sets. The strongest predictors of operative mortality include nonelective surgery, low ejection fraction, and prior heart surgery.[36] Jones and associates examined seven large datasets, with more than 172,000 patients undergoing isolated CABG, to assess the predictive power of certain preoperative values

Table 22–1.

Independent Variables Associated with Mortality After Isolated Coronary Artery Bypass Graft (CABG) Surgery

Variable	Odds ratio	95% Confidence interval
Multiple reoperations	4.19	3.61–4.86
First reoperation	2.76	2.62–2.91
Shock	2.04	1.90–2.19
Surgery status	1.96	1.88–2.05
Renal failure/dialysis	1.88	1.80–1.96
Immunosuppressants	1.75	1.57–1.95
Insulin-dependent diabetes mellitus	1.5	1.42–1.58
Intra-aortic balloon pump use	1.46	1.37–1.55
Chronic lung disease	1.41	1.35–1.48
Percutaneous transluminal coronary angioplasty, 6 hours	1.32	1.18–1.48)

Data were collected from 503,478 patients undergoing isolated CABG in the U.S. from 1997 to 1999 from Society of Thoracic Surgeons' database. Variables are listed in decreasing order of importance.
Source: Data from Shroyer AL, Coombs LP, Peterson ED, et al: The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. Ann Thorac Surg *2003;75:1856.*

on operative mortality. Seven variables were found to be predictive of mortality in all datasets. These seven core variables included urgency of operation, age, prior heart surgery, gender, left ventricular ejection fraction (LVEF), percentage of stenosis of the left main coronary artery, and number of major coronary arteries with >70% stenosis. The variables with the greatest predictive power related to urgency of operation, age, and reoperative surgery, while variables that described coronary anatomy had the least predictive power.[56] Chronic comorbidities have also been found to be associated with an increased operative mortality after coronary bypass, including treated diabetes,[57] peripheral vascular occlusive disease,[58] chronic renal insufficiency,[59] and chronic obstructive pulmonary disease (COPD).[53,60]

Operative Morbidity

Of nearly equal concern to patients and physicians alike are the risks of significant morbidity following CABG surgery. Perioperative morbidities are linked to increased operative mortality, reduced long-term survival, and increased cost of care.[61,62] Accordingly there has been considerable interest in the development of risk models to predict a variety of postoperative complications.[36,54] The Northern New England Cardiovascular Disease Study Group initially developed a scoring system to calculate the risk of cerebrovascular accident (CVA) and mediastinitis following isolated CABG. A score is assigned to each independent variable according to its strength of association. Variables used to predict CVA risk in decreasing order of importance included: emergency surgery, increasing age, chronic renal failure with or without dialysis dependence, previous CVA, peripheral vascular disease, diabetes, female gender, and LVEF <40%. Variables used to predict mediastinitis risk in decreasing order of importance included: severe obesity (body mass index >37 kg/m^2), dialysis dependence, obesity (body mass index 31 to 36 kg/m^2), COPD, emergent or urgent surgery, age >80 years, diabetes, LVEF <40%, and age >70 years. The reader is referred to the AHA/ACC consensus panel guidelines for a more detailed review of these scoring systems.[36]

More recent data have been provided by the STS. The STS risk model for postoperative complications is based on data collected from 503,478 patients undergoing isolated CABG in the United States from 1997 to 1999. The 30-day operative death and major complication rates for STS CABG procedures were 3.05 and 13.4%, respectively, including stroke (1.6%), renal failure (3.5%), reoperation (5.2%), prolonged ventilation (5.9%), and sternal infection (0.63%).

Table 22–2.

Variables Associated with Development of a Major Complication After Isolated Coronary Artery Bypass Graft Surgery (CABG)

Variable	Odds ratio	95% Confidence interval
Renal failure/dialysis	2.49	2.41–2.58
Multiple reoperations	2.13	1.92–2.36
Shock	1.86	1.78–1.95
Intra-aortic balloon pump use	1.78	1.72–1.84
First reoperation	1.75	1.70–1.81
Insulin-dependent diabetes mellitus	1.59	1.54–1.64
Surgery status	1.58	1.53–1.63
Chronic lung disease	1.41	1.38–1.45
Immunosuppressants	1.34	1.26–1.43
Percutaneous transluminal coronary angioplasty <6 hours	1.33	1.23–1.43

Any major complication is defined as the composite outcome of stroke, renal failure, prolonged ventilation, mediastinitis, or reoperation. Data collected from 503,478 patients undergoing isolated CABG in the U.S. from 1997 to 1999 from the Society of Thoracic Surgeons' database. Variables are listed in decreasing order of importance.

Source: Data from Shroyer AL, Coombs LP, Peterson ED, et al: The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. Ann Thorac Surg *2003;75:1856.*

Risk models were developed using multivariate analysis to stratify the strength of the association from among 30 potential preoperative risk factors for mortality and major complications as shown in Tables 22-2 and 22-3. Except for deep sternal wound infection, the development of any of these complications correlated with an increased risk-adjusted operative mortality.[54]

PREOPERATIVE ASSESSMENT

Patient Evaluation

Regardless of the risk model applied, there is no substitute for clinical evaluation of the patient. Particular attention should be paid to the history of the nature, duration, and severity of ischemic symptoms, as well as signs and symptoms of congestive heart failure (CHF). Evidence of coexisting cardiovascular disease, including cerebrovascular and peripheral vascular disease, will impact both formal risk models and the "foot-of-the-bed" estimate of operative risk, as will COPD disease, diabetes mellitus, and renal or hepatic insufficiency. Recent gastrointestinal hemorrhage may pose a particular risk perioperatively, given both the aggressive anticoagulation required intraoperatively and the general physiologic stress to which the patient will be subjected. The most accurate predictor of excessive perioperative bleeding is a history of prior bleeding disorders. Although universal precautions demand that all patients be treated as if they were carriers of blood-borne transmissible disease, knowledge of active hepatitis or human immunodeficiency virus infection may serve to reinforce to caregivers the importance of using caution in handling sharps and other materials contaminated with the patient's blood. Likewise, identification and treatment of acute medical issues may minimize postoperative morbidity. Review of current medications and dosages with special attention paid to antiplatelet agents such as clopidogrel or anticoagulation with warfarin may impact the technical aspects of surgery and the decision to use antifibrinolytic agents or aprotinin.

Particularly important aspects of the physical examination may be overlooked by our medical colleagues. These include: the adequacy of presternal soft tissues to permit adequate healing, particularly in patients with a history of mediastinal irradiation, cachectic elderly patients, and women who have undergone prior mastectomy. Evidence of venous varicosities, or even prior vein stripping, may alter

Table 22–3.

Variables Associated with Development of a Specific Postoperative Complication

Stroke	Renal failure	Prolonged ventilation	Mediastinitis	Reoperation
Variable, odds ratio (95% confidence interval)				
PVD/CVD, 1.5(1.44–1.56)	Renal failure/dialysis, 4.3 (4.09–4.52)	Multiple reoperations, 2.3 (2.01–2.64)	IDDM, 2.74 (2.47–3.03)	Multiple reoperations, 1.69 (1.49–1.97)
Renal failure/dialysis, 1.49 (1.37–1.62)	IDDM, 2.26 (2.16–2.37)	IABP, 2.26 (2.17–2.36)	Chronic lung disease, 1.62 (1.47–1.78)	Shock, 1.46 (1.37–1.56)
IDDM, 1.48 (1.37–1.59)	Shock, 1.6 (1.48–1.72)	First reoperation, 1.97 (1.89–2.05)	NIDDM, 1.53 (1.38–1.70)	First reoperation, 1.40 (1.33–1.47)
Previous CVA, 1.43 (1.33–1.53)	Multiple reoperations, 1.6 (1.33–1.92)	Renal failure/dialysis, 1.95 (1.86–2.04)	Immunosuppressants, 1.49 (1.18–1.89)	PTCA <6 hours, 1.42 (1.28–1.58)
Surgery status, 1.38 (1.29–1.48)	First reoperation, 1.55 (1.46–1.64)	Shock, 1.95 (1.85–2.06)	IABP, 1.43 (1.25–1.64)	Renal failure/dialysis, 1.38 (1.33–1.44)
Shock, 1.36 (1.21–1.52)	IABP, 1.54 (1.45–1.64)	Chronic lung disease, 1.67 (1.61–1.73)	Mitral insufficiency, 1.39 (1.17–1.65)	IABP, 1.36 (1.29–1.43)
NIDDM, 1.36 (1.28–1.45)	Immunosuppressants, 1.48 (1.33–1.64)	IDDM, 1.53 (1.47–1.59)	Obese female, 1.38 (1.35–1.42)	Chronic lung disease, 1.32 (1.27–1.37)
HTN, 1.30 (1.22–1.38)	PTCA <6 hours, 1.46 (1.29–1.66)	Surgery status, 1.46 (1.41–1.52)	Renal failure/dialysis, 1.27 (1.14–1.41)	Mitral insufficiency, 1.31 (1.23–1.40)

Data collected from 503,478 patients undergoing isolated CABG in the U.S. from 1997 to 1999 from the Society of Thoracic Surgeons' database. Variables are listed in decreasing order of importance.
CVA = cerebrovascular accident; HTN = history of hypertension; IABP = intra-aortic balloon pump use; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin-dependent diabetes mellitus; PTCA = percutaneous transluminal coronary angioplasty; PVD/CVD = peripheral vascular disease/cardiovascular disease.
Source: Data from Shroyer AL, Coombs LP, Peterson ED, et al: The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. Ann Thorac Surg *2003;75:1856.*

one's plans for conduit. An Allen test may be performed to determine the availability of a radial artery as an alternate conduit.

At a minimum, radiologic evaluation should include a recent chest x-ray to rule out concomitant neoplasm or active pulmonary infection. Coronary angiography must be reviewed and potential graft targets identified preoperatively. Hemodynamically significant lesions reduce coronary blood flow under conditions of increased demand, resulting in myocardial ischemia. A 75% reduction in cross-sectional area, which correlates with a 50% loss of arterial diameter, is sufficient to impair coronary blood flow reserve and distal coronary pressure, and is accepted as a significant stenosis by the AHA consensus and the Bypass Angioplasty Revascularization Investigation (BARI) study investigators.[36,63] In general, lesions with this magnitude of obstruction should be considered for bypass, provided that the distal vessel is of adequate size and quality. A loss of 90% of the luminal area, which correlates with a 75 to 80% loss in diameter, will result in reduced blood flow at rest.[64] It should be noted, however, that bypassing less-than-significantly stenotic lesions creates a state of competitive flow between the graft and the native vessel, predisposing to low flow in the bypass conduit and increasing the risk of graft occlusion regardless of the conduit used.[65–68]

Finally, it is critical that the surgeon discuss in detail the risks, benefits, and alternatives to surgery with the patient to permit the patient to make a truly informed decision. Ideally, this discussion is held in the presence of friends or family of the patient, since patients often have difficulty absorbing the details of the discussion at the time of first meeting a surgeon. The patient and family should be given the details of the planned operation, anticipated perioperative events, and estimate of the need for postoperative rehabilitation, as well as the tempo and time course of recovery. A clear understanding

of the expectations for the perioperative period will reduce the patient's anxiety about surgery, promote early recovery, and is the physician's best protection from litigation should untoward events occur.

BYPASS CONDUITS

Internal Thoracic Artery

The use of the left internal thoracic artery (ITA) as a bypass graft to the LAD artery has been proven to provide superior early and late survival, and better event-free survival after coronary artery bypass (CAB).[69–74] The superior biologic characteristics, unparalleled long-term patency, and better clinical outcomes associated with the use of the ITA make it the conduit of first choice for MI.

Characteristics

The ITA demonstrates remarkable resistance to development of atherosclerosis. This may be in part attributable to a greater resistance of its endothelium to harvest injury as compared with the saphenous vein; under electron microscopy thrombogenic intimal defects are essentially nonexistent in the ITA, but are commonly detected in venous grafts.[75] Perhaps more significantly, however, is the nonfenestrated internal elastic lamina of the ITA that may inhibit cellular migration, thereby preventing initiation of intimal hyperplasia. In addition, the medial layer of the ITA is thin, with fewer smooth muscle cells that exhibit a lesser proliferative response to known mitogens such as platelet-derived growth factor and pulsatile mechanical stretch.[76,77]

The endothelium of the ITA is itself unique as well. With a significantly higher basal production of the vasodilators nitric oxide and prostacyclin,[78–82] the ITA demonstrates a favorable response to pharmacologic agents commonly used in the postoperative period. The ITA vasodilates in response to milrinone and does not vasoconstrict in response to norepinephrine.[83] Nitroglycerin causes vasodilation in the ITA, but not in the saphenous vein.[84] The endogenous secretion of such vasodilators may also have a "downstream" effect on the coronary vasculature, explaining the common observation that the coronary target itself appears relatively protected distal to the anastomosis. Finally, the ITA exhibits remarkable remodeling over time, adapting to the demand for flow by often increasing in diameter over time as observed on late postoperative angiograms. The ITA increases its flow in the same way as normal coronary arteries, through an increase in velocity and caliber mediated by the endothelium.[85]

Surgical anatomy of the internal thoracic artery

The ITA arises from the undersurface of the first portion of the subclavian artery opposite the thyrocervical trunk. The left ITA (LITA) originates as a single artery in 70% of the time and as a common trunk with other arteries in 30%, in contrast the right ITA (RITA), which originates as a single artery in 95% of cases.[86] At the level of the clavicle and the first rib, the ITA passes at first downward and medially behind the subclavian vein and lateral to the innominate vein. In this area the phrenic nerve crosses the ITA, from its lateral to its medial side, before contacting the pericardium. The distance between the origin of the ITA and the intersection with the phrenic nerve is 1.9 $\pm$ 0.7 cm on the left and 1.5 $\pm$ 0.7 cm on the right side. The phrenic nerve crosses anterior to the ITA 66% of the time on the left and 74% of the time on the right.[86] It is important to keep these relations in mind to avoid phrenic nerve injury during ITA harvest, especially when dissecting the most proximal 3 cm of the vessel.

Below the first costal cartilage the ITA descends almost vertically and slightly laterally at a short distance from the margin of the sternum. The ITA lies posterior to the cartilages of the upper six ribs and the intervening internal intercostal muscles. In the upper chest there is a bare area of variable length where the ITA is covered only by the endothoracic fascia and parietal pleura. Below this level the transversus thoracis muscle covers the posterior surface of the ITA. The mean distance of the LITA from the sternal margin at the level of the first intercostal space is 10.5 $\pm$ 3.2 mm, whereas at the level of the sixth intercostal space the distance increases to 20.0 $\pm$ 6.7 mm. The RITA is slightly closer to the sternal margin than the LITA. At the level of the sixth rib the ITA bifurcates into its terminal branches: the musculophrenic and superior epigastric arteries. The length of the ITA ranges from 15 to 26 cm, with a mean of 20.4 $\pm$ 2.1 cm; the LITA is slightly longer than the right.[86] A pair of internal mammary veins accompanies the ITA, at the most superior portion these veins form a single vessel, which runs medial to the artery and drains into the innominate vein.

The ITA supplies blood to the pericardium, phrenic nerve, sternum, anterior chest wall, the pectoralis major, the mammary gland, the anterior abdominal wall, and the diaphragm. The pericardiophrenic artery arises from the ITA in 90% of individuals. It runs parallel to the phrenic nerve, and its division may cause devascularization of the nerve. A large lateral costal artery branches from the ITA in 15% of cases, and some have argued that if left undivided it may create a steal phenomenon following CABG, although this remains unproven and seems unlikely in the absence of a proximal ITA stenosis.[86] The smaller parietal branches of the ITA can arise as single vessels or as a trunk from the ITA. The sternal, intercostal, and perforating arteries typically arise respectively from the medial, lateral, and anterior aspects of the ITA at the superior and inferior margin of the costal cartilages.[87] The sternal/intercostal branches and sternal/perforating branches arise by a common trunk and then divide at a variable distance from the ITA. Theoretically, division of a common trunk close to its ITA origin would allow collateral circulation to the sternum from intercostal and thoracoacromial sources. These potential sources of collateral blood flow are not as common as vessels with a single origin (ratio of 2:5), and only a few of them (14%) are encountered in the distal two-thirds of the sternum.[87]

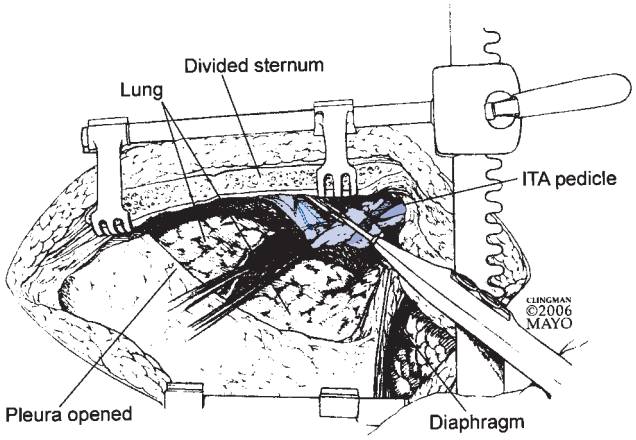

Figure 22-1. Internal thoracic artery (ITA) harvest. A self-retaining mammary retractor is used for exposure of the ITA bed. The left pleura is dissected away from the mammary pedicle and opened along the course of the ITA. The endothoracic fascia is incised medial and lateral to the ITA pedicle. The pedicle is carefully separated with blunt dissection from the underside of the rib. Gentle traction on the pedicle exposes arterial and venous branches at the level of the intercostal spaces; vessels are clipped on the ITA side and cauterized or clipped on the chest wall side. The proximal dissection is carried to the inferior border of the subclavian vein; the distal dissection is then carried to the level of the ITA bifurcation. The transversus thoracis muscle must be divided to expose the ITA bifurcation. The ITA is divided after full heparinization, either at the end of harvest or just prior to grafting of the left anterior descending (LAD) artery.

Pedicled harvest technique

After the sternum is divided, the LITA is harvested (Fig. 22-1). A self-retaining internal mammary retractor is utilized for exposure of the internal mammary bed. A variety of retractors are available including table-mounted models providing a combination of upward and lateral retraction, as well as modified sternal retractors providing simultaneous upward pull on the left and downward push on the right hemisternum. Excessive retraction can cause costal fractures or dislocation of the costosternal joints, resulting in severe postoperative pain as well as brachial plexus injury. The parietal pleura and loose connective tissue with accompanying fat is pushed away from the chest wall. The left pleural space can be entered or left intact at the surgeon's discretion. Opening the pleural space allows easier exposure of the ITA, especially in its most proximal aspect, and permits the ITA to fall into a more lateral and posterior path on its way to the heart. Slightly rotating the operating table to the patient's left and decreasing the patient's tidal volume can aid in the visualization of the mammary bed. The ITA is identified lateral to the border of the sternum by inspection of the bare area or by palpation in the area of artery covered by muscle. The ITA can then be harvested using either a pedicled, semiskeletonized, or a skeletonized technique.

In the pedicled technique the dissection plane is started in the bare area of the ITA at the level of the third or fourth rib; the intercostal space is avoided since it contains branches of the vessel. The endothoracic fascia is incised medial and lateral to a 1 cm pedicle that includes the ITA and accompanying veins. The first portion of the pedicle is carefully separated with blunt dissection from the rib. Exposure can be obtained by pushing the pedicle away with closed forceps or by gently grasping the fascia; the conduit must never be grasped with the forceps. Gentle traction on the pedicle allows exposure of arterial and venous branches; larger vessels should be clipped on the ITA side and cauterized or clipped on the chest wall side; cauterizing vessels close to the ITA must be avoided since thermal injury may occur. After the pedicle is partially developed, the dissection is continued proximally and distally. The transverse thoracic muscle must be divided in order to identify the distal pedicle and the dissection is then carried to the level of the ITA bifurcation. The proximal dissection is carried to the inferior border of the subclavian vein; special attention should be given to avoid injury to the phrenic nerve in this location. Once the pedicle is completed, the patient is heparinized and the pedicle is divided distally just proximal to the bifurcation. The distal vessel is ligated with a 2-0 silk suture and reinforced with a metal clip. A small plastic bulldog clamp is applied to the distal end of the artery and the pedicle is sprayed with papaverine solution or wrapped in a papaverine-soaked sponge. Alternatively the pedicle may be left in situ and transsected just prior to using the conduit.

Skeletonization of the internal thoracic artery

Sternal ischemia is a consequence of ITA harvest. Sternal blood flow decreases significantly after pedicled ITA harvest.[87,88] Skeletonization of the ITA reduces the degree of sternal ischemia produced by ITA harvest. Two small prospective randomized studies have assessed sternal blood supply using bone scan with single photon emission computed tomography after skeletonized and pedicled ITA harvest. Pedicled ITA harvest resulted in a steep decrease in sternal vascularity, while skeletonization of the ITA resulted in minimal change in sternal blood supply, and multivariate analysis found the harvesting technique to be the only factor responsible for postoperative sternal ischemia.[89,90]

Excellent results have been reported using skeletonization in the setting of bilateral ITA harvesting. Matsa and associates reported a deep sternal wound infection rate of 1.7% in 765 patients using bilateral skeletonized ITAs. Sternal complications occurred in only 2.6% of 231 diabetic patients in this study, and the incidence was not significantly different from that of the nondiabetic patients.[91] In Calafiore and coworkers' review of 842 patients undergoing skeletonized bilateral ITA grafting compared with a historical nonskeletonized bilateral ITA control group, skeletonization was associated with a reduced incidence of sternal wound complications (4.5 versus 1.7%). The diabetic patients in this study derived the greatest benefit from skeletonization of the ITAs (10 versus 2.2%).[92]

Using the skeletonization technique of ITA harvest, only the artery itself is mobilized, leaving the internal thoracic venous plexus intact. In the semiskeletonization technique, both the ITA and the two adjacent veins are mobilized with no other surrounding tissue. Skeletonization of the ITA offers multiple advantages: It increases luminal diameter and free flow compared to a pedicled graft, and also provides a longer conduit which allows a greater number of sequential anastomoses, maximizing the targets for arterial revascularization.[92] Skeletonization of the ITA is a technically more demanding and time-consuming procedure. Some surgeons have expressed concerns regarding functional integrity, vasoreactive profile, and early and long-term patency. Noera and colleagues, however, found no difference in endothelial damage assessed by light microscopy between pedicled or skeletonized ITAs in a retrospective analysis.[93] In prospective randomized studies, Gaudino and associates found no difference in endothelial integrity by light and electron microscopy, and no difference in regard to endothelial-dependent or neurogenic-dependent vasoreactivity between skeletonized and pedicled ITAs.[94,95] Unfortunately, there are as yet no randomized studies comparing long-term patency differences between skeletonized and pedicled grafts, although review of current evidence suggests that early and mid-term patency is similar to those of pedicled grafts.[96,97]

Patency

The superior late patency of an ITA graft to the LAD coronary artery compared to a saphenous vein graft (SVG) was initially demonstrated by Barner and colleagues in the 1980s.[98] Superior patency translates into improved 10-year survival (LITA-to-LAD artery 82.6% versus saphenous vein graft-to-LAD artery 71%), and less incidence of myocardial infarction (MI), hospitalization for cardiac events, and cardiac reoperations.[73] The superior performance of ITA grafts appears to persist in the current era despite the use of agents to improve vein graft performance; in the BARI trial the patency rate of ITA grafts was 98% at 1-year, while that of vein grafts was 87%. At 4 years the patency rate for ITA grafts was 91% and 83% for venous grafts.[99,100] The superior patency of the ITA becomes even more prominent with longer follow-up. In a recent angiographic study of 1408 symptomatic post-CABG patients, patency rates for the LITA at 10 and 15 years were 95 and 88%, respectively, while SVG patencies were 61 and 32% at the same time intervals.[101]

Radial Artery

The use of the radial artery (RA) as a conduit for coronary bypass was originally described by Carpentier and associates in the early 1970s.[102] Spasm of the artery was common during surgery and was managed by mechanical dilation. The initial results were disappointing, with 32% of grafts occluded at 2 years.[103] Accordingly, the RA was abandoned as a conduit for CABG. Acar and colleagues revived the use of the RA after a number of grafts, angiographically demonstrated to be "occluded" early postoperatively, but that were found to be fully patent 15 years later. Acar postulated that harvest injury was responsible for the spasm/graft occlusion.[103,104] Proponents of the RA have demonstrated encouraging mid- and long-term results with a pedicled harvesting technique and pharmacologic manipulation to prevent radial artery vasospasm.[105–107] As a result, this conduit has enjoyed a remarkable resurgence of interest as a supplementary arterial conduit for coronary revascularization. Randomized data on comparison with other conduits are scarce, and an undeniable superiority to the saphenous vein remains unproven.

Characteristics

Histologically, the RA has a fenestrated internal elastic lamina, and a thicker wall than the ITA with a higher density of myocytes in its media.[108] The RA is also more likely to have atherosclerotic changes at the time of harvest than the ITA, with 28% of RAs having some degree of demonstrable atherosclerosis, as compared with only 6% of ITAs. Whether these differences indicate that the RA will prove more susceptible to graft atherosclerosis remains unknown.[109]

Physiologically, the RA is equally sensitive to norepinephrine as the ITA; however, given its greater muscle mass it generates a higher force of contraction, accounting for its well recognized propensity for spasm.[110] Fortunately, the RA also readily responds to a variety of vasodilators including calcium channel blockers, papaverine, nitrates, and milrinone.[111–114] In vitro, nitroglycerine appears to be the most effective agent for inhibiting and reversing RA spasm.[115] Additionally, nitroglycerin has been shown to be better tolerated clinically, equally effective, and less expensive than diltiazem in prophylaxis of RA spasm after CABG in a prospective randomized trial.[116]

Surgical anatomy of the radial artery

The RA originates from the brachial artery just proximal to the biceps tendon. In the proximal forearm the RA courses underneath the brachioradialis muscle. As it courses distally, it emerges from the lower surface of the muscle, becoming more superficial, and runs beneath the antebrachial fascia between the tendon of the brachioradialis muscle and the flexor carpi radialis muscle and anterior to the radius and pronator quadratus muscle. The radial recurrent artery originates from the lateral aspect of the RA soon after its origin from the brachial artery. Multiple small muscular branches emerge from the deep and lateral surfaces of the artery. At the wrist the RA gives rise to the palmar carpal branch, the dorsal carpal branch, the superficial palmar branch, and the deep palmar branch, that join similar branches from the ulnar artery to form the palmar arches.[113] Throughout its course the RA is accompanied by a rich plexus of venae comitantes. The average length of the RA ranges between 18 and 22 cm with an inner diameter of 2 to 3 mm.[117]

Harvest technique

It is most common to consider the patient's nondominant arm for harvest, partially out of concern for the impact of even subtle neurologic changes, and partially given the convenience of harvesting the left radial artery simultaneously with the LITA. The extremity of interest must have adequate ulnar collateral circulation to ensure viability of the hand. Assessment of collateral circulation is performed clinically with an Allen test. Patients with positive or equivocal results may undergo noninvasive duplex ultrasonography.[118,119] The RA of the dominant hand can also be harvested. Tatoulis and associates reported 261 patients undergoing bilateral RA harvesting with safe functional outcomes of both extremities.[120]

The arm is prepped circumferentially and the hand wrapped in a sterile fashion. The upper extremity is place on an arm board perpendicular to the long axis of the operating table. As shown in Fig. 22-2, a medially curved incision is made on the skin overlying the RA from a point 2 cm proximal to the styloid process of the radius to a point 2 cm distal to the elbow crease and 1 cm medial to the biceps tendon. The subcutaneous tissue is divided with the cautery. The dissection can be initiated at either end depending on the surgeons' preference, although most surgeons would start the dissection at the distal end. The deep fascia of the forearm is incised directly over the RA. The RA is harvested as a pedicle with minimal manipulation using sharp dissection, diathermy, or the harmonic scalpel. There are some data to suggest that early graft flow is superior when the harmonic scalpel is used.[121] On the proximal half of the forearm lateral gentle retraction of the brachioradialis muscle aids in the exposure. At the distal end of the dissection the satellite veins are identified and clipped individually. The proximal end of the dissection is marked by the radial recurrent branch and a large venous plexus in the medial aspect of the RA. It is our routine to leave the recurrent radial branch intact. Once the pedicle is free and systemic heparin has been administered, the artery is divided proximally and distally and stored in a solution of 1% papaverine in heparinized arterial blood at room temperature. An alternative approach is division of the artery distally during the dissection and injection of 5 mL of 1% papaverine in heparinized arterial blood intraluminally with a 1-mm blunt-tipped cannula. The distal end is occluded with a clip, allowing the radial artery to distend under arterial pressure while the more proximal dissection is completed. After the RA is removed from the forearm, hemostasis of the operative field is obtained and the arm is closed in multiple layers. A closed suction drain may be placed to prevent seroma/hematoma formation. The arm is then abducted and secured to the table. Reports of endoscopic RA harvest are beginning to emerge with good functional and cosmetic results; nonetheless the impact of the technique on graft patency is unknown.[122,123]

Two nerves must be protected during RA dissection. The lateral antebrachial cutaneous nerve lies superficial to the belly of the brachioradialis muscle and runs close to its medial border. Placing the skin incision medial to the edge of the brachioradialis prevents potential injury. Damage to this nerve will produce paresthesias and numbness of the radial

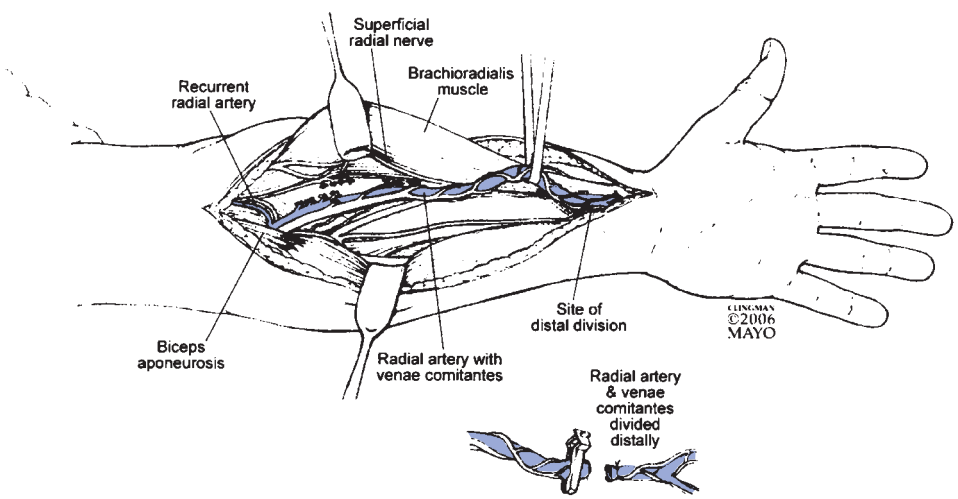

Figure 22-2. Radial artery harvest. A medially curved incision is made on the forearm over the artery. The deep fascia of the forearm is incised directly over the artery. The brachioradialis muscle is retracted laterally. Dissection is begun at the distal end and the satellite veins are divided. The RA is harvested as a pedicle with minimal manipulation. The proximal end of the dissection is marked by the radial recurrent branch which is left intact. After the pedicle is free and heparin has been given, the artery is divided proximally and distally and stored in a solution of 1% papaverine in heparinized arterial blood at room temperature. Hemostasis of the operative field is obtained and the arm is closed in multiple layers. A closed suction drain may be placed.

aspect of the volar forearm. The superficial branch of the radial nerve lies under the brachioradialis muscle and in the proximal two-thirds of the forearm runs parallel to the RA. Injury to this nerve will result in paresthesias and numbness of the thumb and the dorsum of the hand. This nerve can best be protected by avoiding excessive lateral retraction on the brachioradialis muscle.[113,124] Transient paresthesias, numbness, and thumb weakness are reported by almost a third of patients after RA harvest; however, they gradually resolve with time so that after 1 year only 10% of patients still have residual symptoms, and only 1% report their symptoms as severe.[125–127]

Patency

Acar and associates in 1992 reported on 122 radial grafts with a 100% patency rate at 2 weeks and 93% patency at 9 months.[111] A number of authors since then have also reported satisfactory mid- and long-term patency for RA grafts. The reported 5-year patency ranges from 83 to 95%; lower patency rates were found in series in which angiograms were performed only on symptomatic patients, and higher patency rates in series with protocol-directed angiography.[104–107,128] The RA patency appears not to be affected by the site of the proximal anastomosis,[105] but its performance seems to be very susceptible to competitive flow. The graft failure rate is higher if the target vessel stenosis is less than severe, and on the right coronary system.[66,106,129]

The most solid data we have on the performance of the RA comes from the Radial Artery Patency Study, a prospective randomized trial comparing the patency rate of the RA compared to the SVG at 1 year.[130] In this study, complete graft occlusion occurred less frequently with RA grafts than with SVGs (8.2 versus 13.6%); however, string signs occur more commonly with RA grafts than with SVGs (7 versus 0.9%). More severe target coronary lesions were associated with a lower rate of occlusion (>90% obstruction 5.9% versus 70 to 89% obstruction 11.8%), and string sign in the RA grafts (>90% obstruction 3.7% versus 70 to 89% obstruction 12.4%). A second important study, the Radial Artery Patency and Clinical Outcomes study, reported interim results on the 5-year patency and cardiac event-free survival of the RA graft as a second graft with that of the free RITA in younger patients (<70 years), and that of the SVG in older patients (>70 years).[131] Unfortunately, only a quarter of the patients enrolled in the study (114/396) underwent protocol-directed angiography regardless of symptoms. The 5-year RA graft patency was 95% compared to 100% for the RITA in the younger group, and the 5-year graft patency was 86% for RA and 95% for SVG in the older group. These differences were not statistically significant.

Gastroepiploic artery

The use of the right gastroepiploic artery (RGEA) as a pedicled coronary graft conduit was described in the early eighties by Pym and Suma and their coworkers.[132,133] The gastroepiploic artery (GEA) may be utilized in reoperative surgery in the absence of other suitable conduits,[134,135] or as a secondary or tertiary arterial conduit in an attempt to provide all-arterial revascularization.[136–140] Despite the enthusiastic support of a small cohort of surgeons, the widespread use of the GEA as a coronary conduit has been limited by increased operative time required to harvest the conduit, the potential for perioperative and long-term abdominal complications, and the lack of consensus on the long-term benefit for total arterial revascularization.

Characteristics

The GEA is a muscular artery with a thin intima and a fenestrated internal elastic lamina. The medial layer is less developed than that of the RA and has similar thickness to the ITA.[141,142] Compared to the ITA, the media of the GEA generates a greater contractile force; however, the GEA demonstrates endothelial-dependent relaxation, prostacyclin production, and response to clinically used vasoconstrictors similar to that of the ITA.[143–145] The GEA may not be suitable for use in all patients. Its use is contraindicated in patients with previous gastric resection, prior endovascular instrumentation of the artery, or documented mesenteric vascular insufficiency. Any patient suspected of having preoperative mesenteric vascular insufficiency must have angiographic evaluation of the celiac axis and GEA patency before harvest of the conduit.

Surgical anatomy of the gastroepiploic artery

The gastroduodenal artery, a branch of the common hepatic artery, gives rise to the superior pancreaticoduodenal artery and the RGEA. This division occurs soon after the gastroduodenal emerges from behind the first portion of the duodenum. The RGEA then runs superiorly and laterally, following the greater curvature of the stomach approximately 2 cm from the gastric wall accompanied by small satellite veins running its entire course between the layers of the gastro-colic omentum. Proximally the RGEA gives several small branches to the head of the pancreas, duodenum, and pylorus. The RGEA gives off inferior branches to the greater omentum and superior branches then run into the body of the stomach at 1 to 2 cm intervals. On its distal portion the RGEA fans out into multiple small gastric branches and finally anastomoses with the left gastroepiploic artery at approximately the junction of the proximal and distal half of the greater curvature. In an anatomic study of the RGEA, the mean internal diameter at the anastomotic sites was 2.20 mm (range 1.5 to 4.0 mm) with a mean pedicle length of 19.2 cm (range 16 to 26 cm).[146]

Harvest technique

The GEA is usually harvested after the ITA dissection is completed. The median sternotomy incision is extended inferiorly to a limited upper midline laparotomy. Nasogastric decompression is established. The greater curvature of

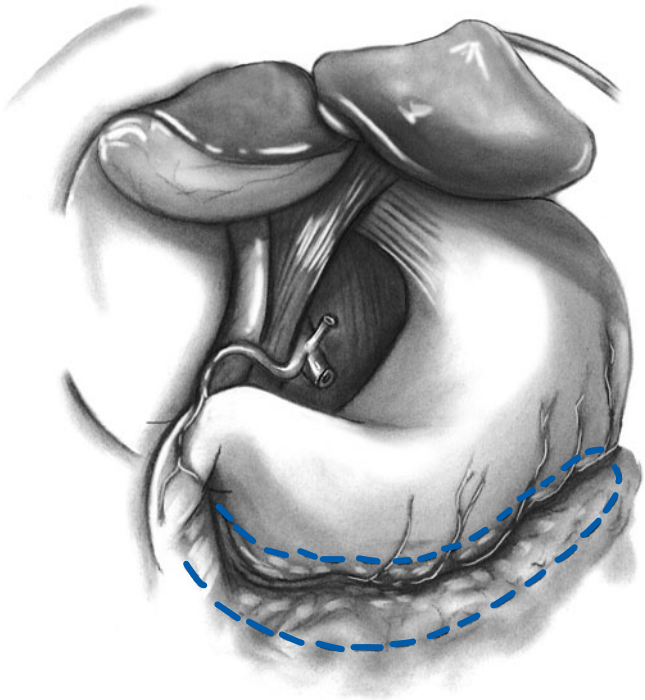

Figure 22-3. Right gastroepiploic artery (RGEA) harvest. The greater omentum outside the gastroepiploic arcade is divided with careful preservation of the artery. The GEA is palpated to assess patency. A pedicle of the RGEA and associated veins is circumferentially dissected free of the greater omentum and of the wall of the stomach. All side branches should be carefully ligated. Avoid leaving any uncontrolled branches since large mesenteric hematomas may develop. Proximally the dissection is carried to the level of the pylorus. Distally the dissection is carried along the greater curvature toward the spleen until the left gastroepiploic artery is encountered. After systemic heparinization, the artery is transsected and flow is assessed. A soft vascular bulldog clamp is applied to its distal end. Placement of the pedicle anterior to the stomach and duodenum minimizes tension on the conduit if gastric distention should occur, but places the conduit at risk if a future laparotomy is necessary; placement posterior to the stomach provides the opposite trade-off.

the stomach is exposed by division of the greater omentum outside the gastroepiploic arcade with careful preservation of the artery (Fig. 22-3). The GEA is palpated to assess patency. A pedicle of the RGEA and associated veins is circumferentially dissected free of the greater omentum and of the wall of the stomach. Electrocautery, surgical clips, or a harmonic scalpel can be used to divide small lateral branches. Great care should be taken to avoid leaving any uncontrolled branches since large mesenteric hematomas may develop. Proximally the dissection is carried to the level of the pylorus. Distally the dissection is carried along the greater curvature toward the spleen until the left gastroepiploic artery is encountered.[147] After systemic heparinization, the RGEA is transsected and adequacy of flow is assessed. A small soft vascular bulldog clamp is applied to its distal end. Topical anti-spasm measures similar to those described for RA harvesting should be used. Placement of the pedicle anterior to the stomach and duodenum minimizes tension on the conduit if gastric distention should occur, but places the conduit at risk if a future laparotomy is necessary; placement posterior to the stomach provides the opposite trade-off.[148] The best route prior to entry into the pericardium will depend on the length of the pedicle, the coronary target, and the size of the left lateral segment of the liver. The pedicle can be placed anterior or posterior to the liver in order to provide the best anatomic positioning. Several centimeters of conduit should be left inside the pericardium to provide a tension-free anastomosis and allow cardiac mobility. The GEA has been used to supply the RCA, the LAD artery, and the distal circumflex system.[134,149–151] If there is lack of conduit or inability to reach the target vessel, the GEA can be used as a free graft.

Patency

Suma and colleagues have reported a patency rate for GEA grafts of 96, 91, 80, and 62% at 1 month, 1 year, 5 years, and 10 years, respectively. The patency of the GEA is influenced by competitive flow, as is the case for other arterial grafts.[152] The perioperative risk after CABG with the use of the GEA is similar to that of other primary coronary operations, with a reported 30-day mortality ranging from 1.5 to 3.3% in large series.[136,138,149,151,153] Reported long-term clinical outcomes include actuarial survival of 88 to 92% at 5 years and 84% at 10 years, and freedom from any cardiac event of 85% at 5 years and 70 to 80% at 10 years.[140,151,152]

Other Arterial Conduits

A variety of arterial conduits have been used in patients in whom no other conduits are available. Anecdotal use of the ulnar, left gastric, splenic, thoracodorsal, and lateral femoral circumflex arteries as coronary graft conduits has been reported in the literature.[154–157] There has been interest in the past in the use of the inferior epigastric artery as well, and several series have demonstrated encouraging early clinical results with good early patencies.[158–161] The popularity of the RA, however, has in large measure superseded these options.

Greater Saphenous Vein

In spite of its shortcomings the saphenous vein continues to be one of the most commonly used conduits in coronary bypass grafting. Characteristics that have solidified the greater saphenous vein as a coronary conduit include its ease of harvest, ready availability, versatility, resistance to spasm, and thoroughly studied long-term results.

The loss of clinical benefit after CABG due to the time-related attrition of venous grafts has generated interest in pharmacologic strategies to maximize early and late venous graft patency. Prospective randomized trials have shown that early aspirin administration reduces vein graft occlusion in the first year after CABG.[162,163] Administration of aspirin within

48 hours after CABG also reduces early postoperative complications including mortality, MI, stroke, renal failure, and bowel infarction.[164] More recently it has been recognized that lipid-lowering agents reduce the progression of both native coronary artery and graft atherosclerosis, as well as subsequent cardiovascular events.[165–167] Aggressive use of statins to achieve a low-density lipoprotein cholesterol <100 mg/dL decreased by one-third the number of grafts affected with atherosclerosis at angiographic follow-up, and also decreased the need for repeat revascularization in The Post Coronary Artery Bypass Graft Trial Investigation.[165] Despite clear documentation of improved outcomes with these two pharmacologic strategies, there is evidence of underutilization of these therapies after CABG.[168,169] Systemic approaches to ensure their universal application are needed.[36] Finally, in the future gene therapy may allow modification of the venous vascular endothelium to avert development of intimal hyperplasia.[170,171] Unfortunately, the PREVENT IV trial, testing whether short-term angiographic vein graft failure could be diminished with treatment of saphenous vein prior to grafting with edifoligide (an oligonucleotide decoy that binds to and inhibits E2F transcription factors) demonstrated no impact of the treatment.[172] The concept remains a valid one, however, and gene therapy will continue to be an exciting area of investigation in the future.

Harvest technique

Some surgeons prefer to harvest vein from the lower leg because of a more appropriate caliber and wall thickness, as well as greater distance from the perineum (a potential source of infection). Others prefer to harvest vein from the thigh, arguing improved wound healing, particularly among patients with distal peripheral arterial occlusive disease. In patients with a history of previous vein stripping it is important to perform a complete duplex examination of the venous system of the lower extremities to assess remaining suitable greater and lesser saphenous veins.

Saphenous vein harvest can be performed with a completely open, bridged, or endoscopic technique. More extensive skin incisions allow harvest with the least amount of surgical trauma to the conduit at the risk of a higher rate of wound complications and postoperative pain, while bridged incisions may decrease pain and wound complications but increase surgical manipulation of the conduit. Open dissection can be started either in the upper thigh, above the knee, or at the ankle (Fig. 22-4). Identification of the vein is easiest at the ankle, just above the medial malleolus. An incision overlying the vein and extended directly over the trajectory of the vein is made, taking care not to create skin flaps. Sharp dissection is then used to free the vein from the surrounding tissue with all side branches ligated and divided in situ. Side branches on the vein should be

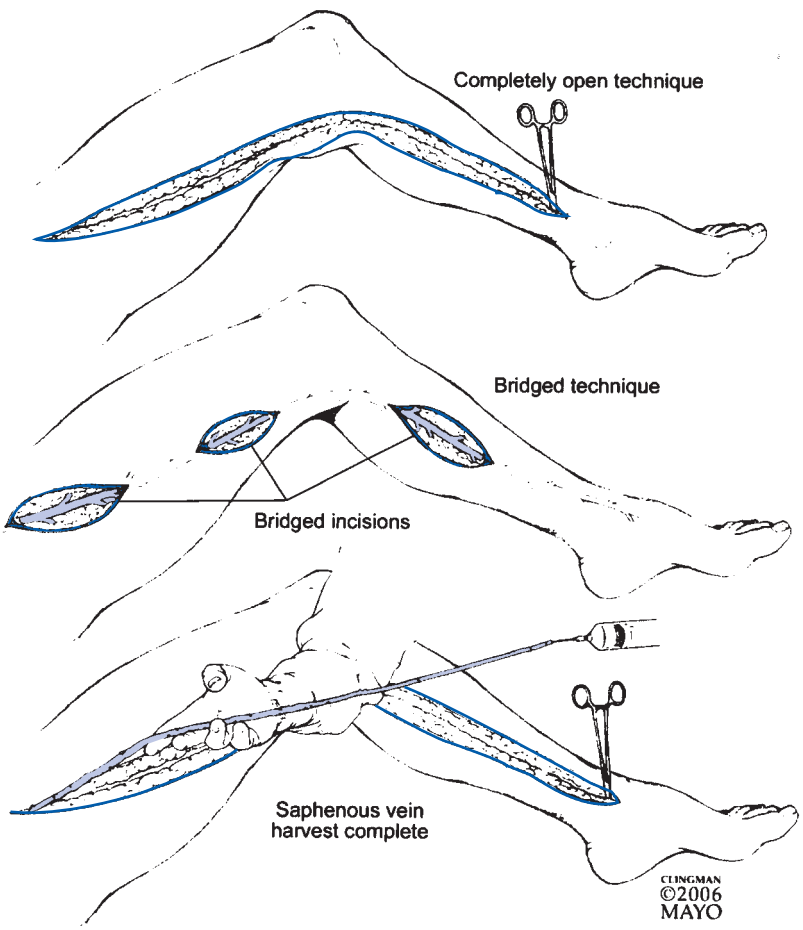

Figure 22-4. Saphenous vein harvest: open and bridged technique. Open technique (top): Dissection can be started in the upper thigh, above the knee, or at the ankle. Identification of the vein is easiest at the ankle, just above the medial malleolus. An incision is made overlying the vein and extended directly over its trajectory. The vein is dissected and all venous tributaries are ligated and divided in situ. Bridged technique (middle): Two- or three- step incisions are performed over the course of the vein. Dissection of the vein is carried in a similar fashion as the opened technique except that branches are divided in situ and ligated once the vein is explanted. Completed dissection (bottom): Once dissection is completed, the vein is ligated and divided proximally and distally. Stumps of side branches on the vein are left long and then are ligated flush with the vein, avoiding narrowing of the conduit. The vein is then gently flushed and stored in heparinized blood solution. The skin incisions are closed and the leg is wrapped with an elastic bandage.

left long and should be ligated flush with the vein, taking care to avoid narrowing of the conduit. In the lower leg, care should be taken to avoid trauma to the saphenous nerve, which is in close proximity to the vein. Once dissection is completed the vein is ligated and divided proximally and distally. The vein is then gently flushed with heparinized blood solution. A blunt-tipped cannula is placed in the distal end and the conduit stored in heparinized blood solution. The vein should not be grasped with forceps, stretched, or overdistended, since patency rates may be related to endothelial damage induced during harvest and preparation.[173–180] When using a bridged technique, two or three step incisions are performed over the course of the vein (see Fig. 22-4). Dissection of the vein is carried out in a similar fashion except that branches are divided in situ and ligated once the vein is explanted.

Minimally invasive harvest of the saphenous vein using an endoscopic technique is gaining popularity.[181] Compared to traditional harvest there appears to be no detrimental effects on vein morphology, endothelial structure, or function.[182–185] Endoscopic harvest decreases wound complication rates and produces an improved cosmetic result, although the operative time devoted to harvest is increased. The reported rate of conversion to open harvest ranges from 5 to 7%.[186–189] Despite an increased number of defects requiring suture repair with endoscopic techniques, the 3- and 6-month patency rates appeared similar to those of open harvest in two prospective randomized studies.[190,191] A 1.5 to 2.0 cm skin incision is made in the medial aspect of the extremity above or below the knee, depending on the length of vein required (Fig. 22-5). CO_2 insufflation for visualization and dissection is established. Harvesting is directed toward the groin region as far proximally as possible. Side branches are divided by using bipolar cauterizing scissors or clips. Once dissection is completed, a small puncture is made in the groin directly over the saphenous vein and the vein is exteriorized under endoscopic guidance. After removing the vein from the leg, side branches are ligated with 4-0 silk ties. If any branches have been avulsed, the vein is repaired with interrupted 6-0 polypropylene sutures. The skin incisions are closed with absorbable subcutaneous and subcuticular sutures and the leg is wrapped with an elastic bandage.

Other Venous Conduits

Alternative venous conduits such as the lesser saphenous and cephalic veins may be used in the setting of reoperative surgery when no other conduits are available. The lesser saphenous vein can be harvested in a supine position through a lateral approach by flexing the hip and medially rotating the knee or by an inferior approach with straight elevation of the extremity. A skin incision is usually started midway between the Achilles tendon and the lateral malleolus. Dissection is carried proximally along the leg. Attention should be paid to avoid injuring the sural nerve. The vein is otherwise managed similarly to the greater saphenous vein. The patency rate for arm veins is significantly lower than that of saphenous veins and they should be considered essentially conduits of last resort.[192,193] For cephalic vein harvest, the arm is prepared and positioned as during radial artery harvest. Incisions are placed along the medial and superior aspect of the arm. The vein is identified and harvested similarly to the

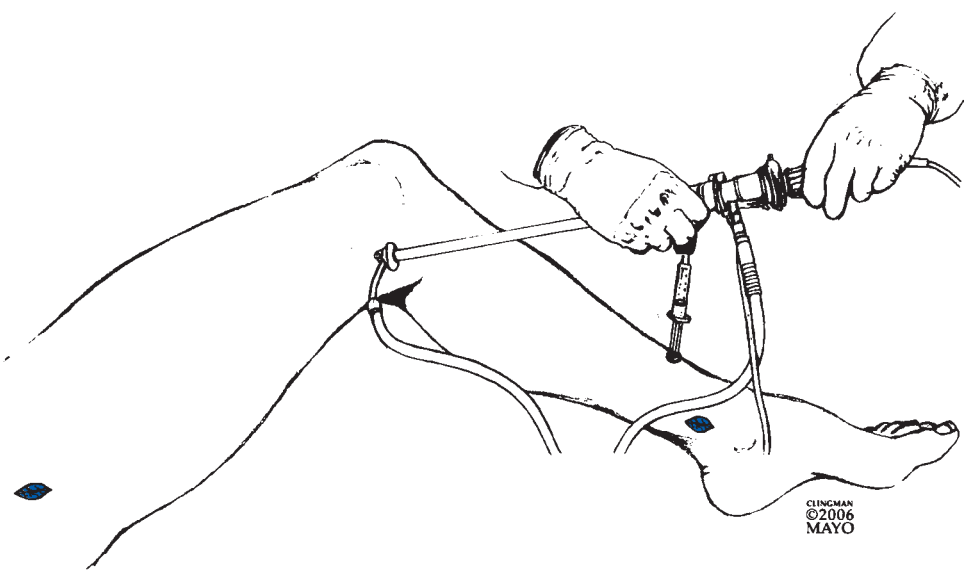

Figure 22-5. Endoscopic saphenous vein harvest. A 2.0 cm skin incision is made in the medial aspect of the knee. CO_2 insufflation is established. Harvesting is directed toward the groin region as far proximally as possible. Side branches are divided by using bipolar cauterizing scissors. Once dissection is completed a small puncture is made in the groin directly over the vein and the vein is exteriorized under endoscopic guidance. After removing the vein from the leg, side branches are ligated with 4-0 silk ties. If any branches have been avulsed, the vein is repaired with interrupted 6-0 polypropylene sutures.

greater saphenous vein. The cephalic vein is relatively thin-walled in comparison to the greater saphenous vein and extra care should be taken during harvest. The cephalic vein is also predisposed to aneurysmal dilatation.

CONDUCT OF THE OPERATION

Intravenous access is established through two large-bore peripheral venous lines and central venous access is via an internal jugular approach prior to the induction of general anesthesia. Monitoring lines typically include one or more arterial lines, including a femoral arterial line in patients for whom one anticipates that a perioperative intra-aortic balloon pump (IABP) may be required. Pulmonary artery catheters with or without oximetric capability are commonly used. There has been increasing use of intraoperative transesophageal echocardiography (TEE) as a routine adjunct,[194] although complications of intraoperative TEE have been reported.[195] The patient is positioned in the decubitus supine position with arms tucked at the side. Care should be taken to avoid peripheral nerve complications due to pressure injury. The lower extremities are positioned with a slight internal rotation and flexion of the knees. The operative field is prepped to include the lower neck, the chest, and abdomen between the anterior axillary lines and the lower extremities circumferentially.

Incisions

In most instances a midline sternotomy incision is performed, with the skin incision extending from a point midway between the angle of Louis and the sternal notch, to just below the tip of the xiphoid process. Either the scalpel or electrocautery is used to extend the incision through the subcutaneous tissues down to the sternum. Special attention should be devoted to identifying the middle of the sternum. In thin individuals this can be easily accomplished by palpating the sternal borders, in obese patients a pointed instrument may be used to identify the sternal edges. The middle of the sternal periosteum is marked with the electrocautery. Attention is then turned to the sternal notch where the interclavicular ligament is divided, allowing palpation of the posterior aspect of the sternal manubrium. The xiphoid process is identified and divided in the midline with heavy scissors or electrocautery. The sternum is divided in the midline either from the top down or bottom up depending on the surgeon's preference. Bleeding points in the sternal periosteum are selectively cauterized with care not to strip all of the periosteum away from the edges one hopes will heal after the operation. Harvest of the saphenous vein or the RA is initiated simultaneous with the sternotomy. Once the sternum has been divided, the ITA is harvested as previously described.

Cannulation and Establishment of Cardiopulmonary Bypass

The pericardium is divided vertically down to the diaphragm and the inferior attachment of the pericardium to the diaphragm is divided transversely. The remnant of thymic tissue and pericardial fat is divided in the midline until the inferior aspect of the left innominate vein is identified. Placement of pericardial retraction sutures to create a pericardial cradle improves exposure of the ascending aorta and right atrium. The distal ascending aorta is inspected and manually palpated for soft nonatherosclerotic areas suitable for cannulation and cross-clamping (Fig. 22-6). Systemic anticoagulation is achieved prior to arterial cannulation with intravenous administration of 300 to 400 U/kg of unfractionated heparin. Prior to aortic cannulation the systolic blood pressure should be reduced below100 mm Hg to minimize the risk of aortic dissection. Two partial-thickness concentric diamond-shaped purse-string sutures using 3-0 Tevdek or polypropylene suture are placed in the distal ascending aorta just proximal and to the left of the innominate artery origin; the size of the purse strings should be one-third greater than the aortic cannula tip. The ends of the sutures are passed through rubber tourniquets that will be used for tightening the purse strings. The aortic adventitia within the purse strings is divided in preparation for aortotomy. The adventitia just superior to the planned aortotomy is grasped with a forceps and an aortotomy equal in size to the cannula tip is created with a no. 11 blade. Bleeding is easily controlled with slight inferior traction of the forceps on the adventitia. The aortic cannula is inserted and properly

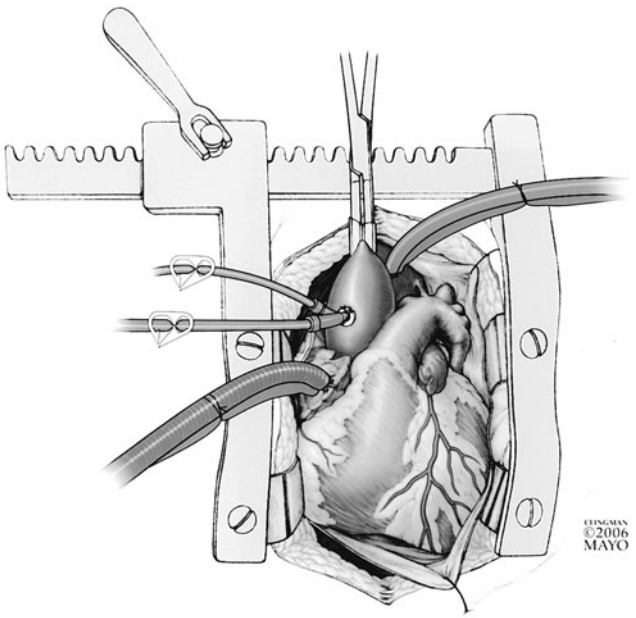

Figure 22-6. Cannulation. After full systemic heparinization, cannulation of the distal ascending aorta is performed with an appropriately sized curved or straight tip aortic cannula. A two-stage venous cannula is used for access to the right atrium, usually through the right atrial appendage. An aortic root cardioplegia/vent is placed. A retrograde cardioplegia cannula may be placed at the discretion of the surgeon. Patients with aortic regurgitation benefit from placement of a right superior pulmonary vent to avoid distention of the left ventricle from infusion of cardioplegia into the aortic root.

positioned, and the purse strings are tightened. The rubber tourniquet is secured to the aortic cannula with a heavy silk tie and then the cannula is secured to the skin. The aortic cannula is then de-aired and connected to the arterial end of the pump tubing. Intraluminal positioning of the cannula is confirmed by watching for the cannula to fill with arterial blood and by confirming a pulsatile waveform with the perfusionist.

Venous cannulation is accomplished with a two-stage venous cannula inserted in the right atrial appendage. A 2-0 Tevdek or polypropylene purse-string suture is placed around the tip of the right atrial appendage. The purse string should be wide enough for easy access of the selected venous cannula. An atriotomy is made with scissors at the tip of the appendage, both edges of the atrial appendage are grasped with forceps, and the incision is extended superiorly and inferiorly to a size appropriate for the venous cannula. Small bridging fibers of muscle are divided with scissors to permit easy entry of the cannula and the venous cannula is inserted. Some surgeons place a partial occlusion clamp on the right atrial appendage at the level of the purse-string suture to simplify preparation of the cannulation site, and once this is accomplished the clamp is removed and the cannula is inserted. The purse-string suture is tightened and the rubber tourniquet is secured to the venous cannula with a heavy silk tie. The tip of the venous cannula should be in the inferior vena cava. The venous line is then connected to the pump tubing. After ensuring that the appropriate activated clotting time target has been reached, cardiopulmonary bypass is initiated. An aortic root cannula for administration of cardioplegia and venting is placed in the ascending aorta. Some surgeons place this at the site of a planned proximal anastomosis. Retrograde cardioplegia may be used, particularly if there is aortic regurgitation, left main disease, severe proximal multivessel disease, or poor left ventricular function (LVF). Patients with aortic insufficiency that is not to be surgically addressed may benefit from the placement of a left ventricular vent catheter via the right superior pulmonary vein to avoid left ventricular distention.

Target vessels may be easier to identify before cardioplegic arrest while they are fully distended in their native state. Target locations are usually confirmed by visual inspection and epicardial examination with the location of planned distal anastomoses marked with a scalpel. Systemic cooling to between 28 and 34°C is preferred by many surgeons, although it is our practice to perfuse patients normothermically. Cardioplegia may be administered warm, tepid (25°C), or cold via antegrade or retrograde routes. Some surgeons even administer cardioplegia simultaneously both antegrade and retrograde. Adequacy of myocardial protection may be assessed with intraoperative monitoring of myocardial temperature or pH.[196,197] A substudy of the CABG Patch Trial investigated the effect of cardioplegia type, temperature, and delivery route in 885 CAD patients with low ejection fraction (EF) (<36%). Patients receiving crystalloid cardioplegia versus those receiving blood cardioplegia were found to have significantly more operative deaths (2 versus 0.3%), postoperative MIs (10 versus 2%), shock (13% versus 7%), and postoperative conduction defects (21.6 versus 12.4%). Despite a higher operative morbidity no significant difference was demonstrated in early or late mortality between crystalloid or blood cardioplegia. Furthermore, patients receiving normothermic blood cardioplegia had less postoperative right ventricular dysfunction (10%) than those receiving cold blood (25%), or cold blood with warm reperfusion (30%). There was also no significant difference in early or late mortality with regard to temperature of blood cardioplegia. Finally, combined antegrade and retrograde cardioplegia delivery was associated with significantly less inotrope use (71 versus 84%), right ventricular dysfunction (23 versus 41%), and postoperative balloon pump use (12 versus 19%) than antegrade cardioplegia delivery alone.[198]

DISTAL ANASTOMOSES

Location of Targets and Sequence of Anastomoses

Arteriotomy sites should be chosen proximal enough to offer the largest-sized coronary target and just distal enough to avoid the area of obstruction. Arteriotomies at bifurcations should be avoided. Diseased vessels with an intramyocardial course can often be localized by noting epicardial indentation, accompanying epicardial veins, or a whitish streak within the myocardium. Sharp dissection of overlying tissue is then required to identify the desired target site. The LAD coronary artery can be particularly difficult when it has an intramyocardial course, since one may inadvertently enter the right ventricular cavity while dissecting in the interventricular fat plane. Such a ventriculotomy can be closed with fine 6-0 polypropylene sutures, keeping in mind that the right ventricle is a low-pressure chamber and deep bites of myocardium are not necessary. If extreme difficulty is encountered in identifying an LAD artery, a fine probe may be passed retrograde via a small transverse arteriotomy into the LAD artery at the apex of the heart. One can then palpate the proximal target and cut down appropriately. The arteriotomy is then closed with an 8-0 polypropylene suture.

The distribution of cardioplegia is usually relatively uniform; however, the sequence of anastomoses may be planned based on ischemic regions if myocardial protection is a particular concern. Grafting the most ischemic area first will permit early antegrade delivery of cardioplegia through the graft. Alternatively, the sequence of anastomoses may be dictated by the quality of the conduit itself, matching the best conduit to the most important territories. It is customary to perform the left internal thoracic artery-to-LAD artery anastomosis last to avoid tension and potential disruption of the anastomosis.

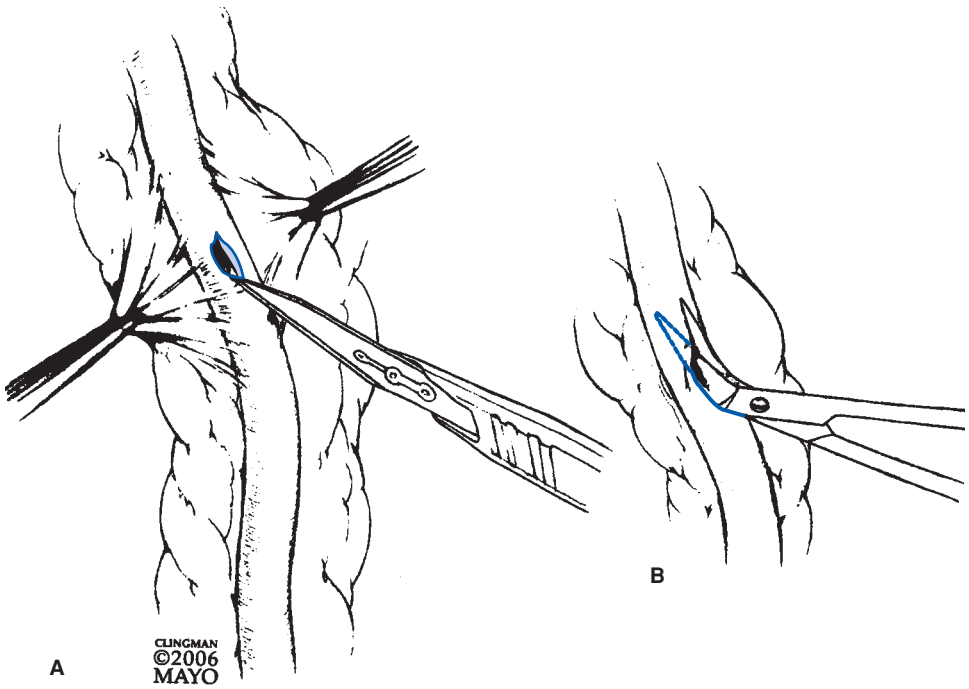

Figure 22-7. Distal anastomosis: Arteriotomy. (A) Arteriotomy sites should be proximal enough to offer the largest-sized coronary target, and just distal enough to avoid the area of obstruction. Intramyocardial vessels can often be localized by noting epicardial indentation, accompanying epicardial veins, or a whitish streak within the myocardium. Sharp dissection of overlying tissue is then required to identify the desired target site. The arteriotomy is then performed with a no. 11 blade. (B) The arteriotomy is extended with fine Pott's scissors proximally and distally. The arteriotomy should match the conduit diameter, and should be at least 1.5 times the diameter of the distal coronary.

Arteriotomy

The choice of the site of arteriotomy is critical. Opening into a plaque may force endarterectomy, while injury to the posterior wall with the knife transforms a straightforward anastomosis into a complex repair. Silastic tapes placed proximally and distally around the coronary artery may help to stabilize the vessel, although only a minority of surgeons employ this technique. The arteriotomy can be performed with a no. 11 or 15 blade and extended with fine Pott's scissors proximally and distally. The arteriotomy should match the conduit diameter, and should be at least 1.5 times the diameter of the distal coronary (Fig. 22-7).

Anastomotic Technique

The goal of the anastomosis is to join the conduit and the target vessel with precise endothelial approximation with minimal resistance to flow. The wall of the vessel should be handled with care, avoiding endothelial injury to prevent thrombotic complications. Coronary anastomoses are typically constructed with 7-0 polypropylene suture. Sutures should be evenly spaced to prevent leaks at the conclusion of the anastomosis. In order to increase anastomotic area we prefer to bevel the conduits at approximately 30° and notch them at the heel. Anastomoses may be performed either with a continuous running suture or in an interrupted fashion. We prefer a continuous, parachuting technique initiated at the lateral midpoint for virtually all anastomoses. We will describe an end-to-side anastomosis and a side-to-side sequential anastomosis.

The conduit is brought onto the field with a mosquito clamp on the adventitia at the toe of the conduit. An end-to-side anastomosis is accomplished with 12 sutures (Fig. 22-8). Starting at 3 o'clock on the right side of the vessel, the suture is passed outside-in on the conduit and then inside-out at the corresponding location of the target coronary vessel. Two more stitches are taken before the heel, one directly in the heel, and then two more on the left side of the anastomosis before parachuting the conduit down to the target vessel. The anastomosis is then completed by placing another six stitches evenly spaced in the same manner around the toe until the other thread is encountered. This technique encourages one to move out of the heel and toe of the anastomosis, minimizing the risk of narrowing the outflow. Care must be taken to prevent suturing the back wall of the coronary, and the proper amount of tension on the follow-through must be provided to avoid both leakage and a purse-string effect. To prevent anastomotic tension and torsion, pedicled conduits can be suture-fixated to the adjacent epicardium. This is particularly relevant when further manipulation of the heart is anticipated due to the need for concomitant procedures.

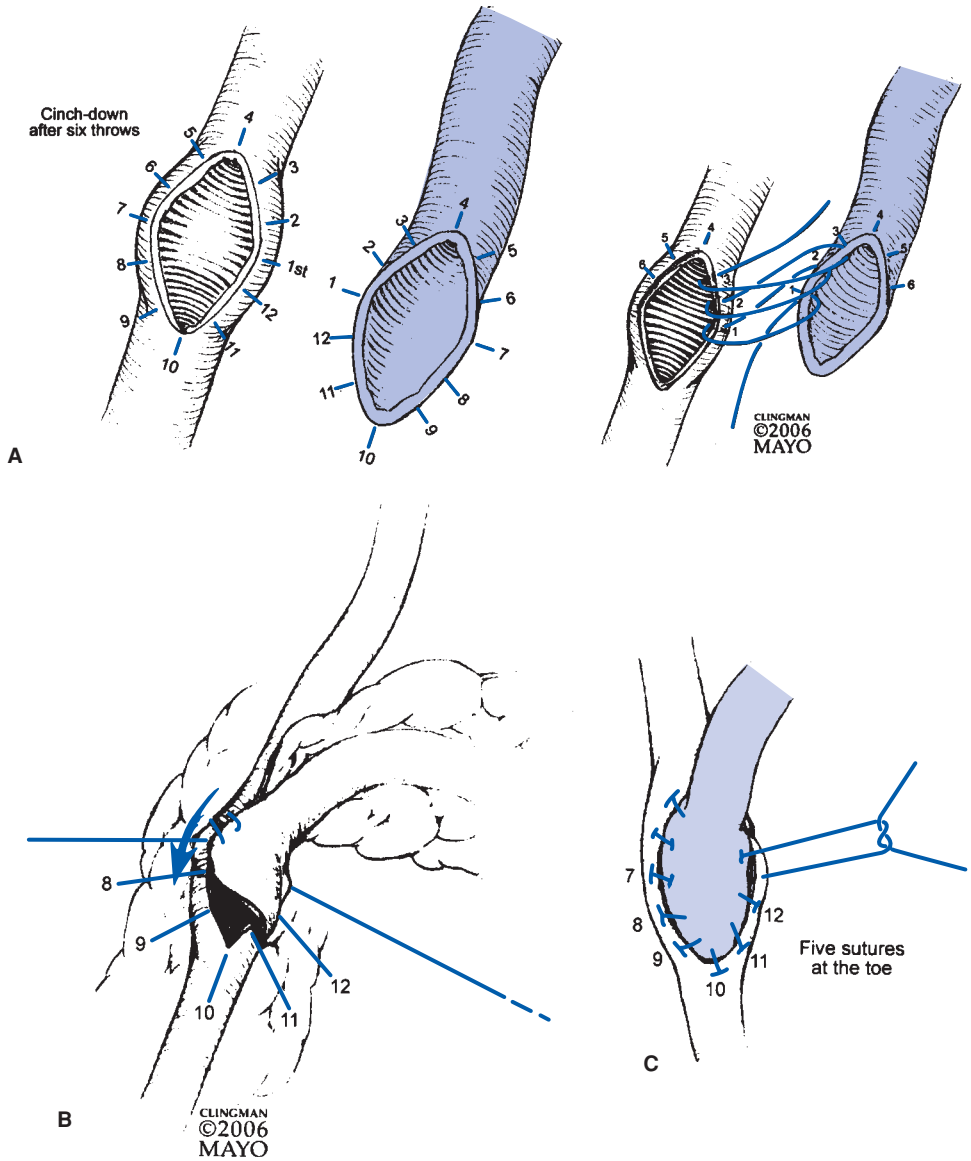

Figure 22-8. Distal anastomosis suture technique. (A) The conduit is beveled at 30° and notched at the heel. We use a continuous, parachuting technique with 7-0 or 8-0 polypropylene suture. The conduit is brought onto the field with a mosquito clamp on the adventitia at the toe of the conduit. An end-to-side anastomosis is accomplished with 12 sutures. Starting at 3 o'clock on the right side of the vessel, the suture is passed outside-in on the conduit and then inside-out at the corresponding location of the target vessel. (B) Two more stitches are taken before the heel, one directly in the heel, and then two more on the left side of the anastomosis before parachuting the conduit down to the target vessel. (C) The anastomosis is then completed by placing another six stitches evenly spaced in the same manner for the toe.

Sequential grafting permits efficient use of conduit, and when target vessels are small, increased flow in the conduit. When planning sequential anastomoses, the most distal anastomosis should be to the largest target vessel with the greatest outflow potential. If the reverse situation is created, the most distal anastomosis is at increased risk for failure, given the likelihood of preferential flow to the larger more proximal anastomosis.[199,200] A clear disadvantage of sequential grafting is the reliance of two or more distal targets upon a single conduit and proximal anastomosis, placing a potentially larger region of myocardium at jeopardy.[200] Although some surgeons avoid using the LITA for sequential grafting or as a donor for composite Y-grafting of other conduits because of concerns of compromising critical LITA-to-LAD flow, several series have demonstrated successful use of the ITA for sequential grafting of stenotic diagonal coronary arteries with excellent results.[201,202] The LITA has also been used for multiple sequential anastomoses to the circumflex territory

with grafting of the RITA to the LAD artery.[203] Sequential grafting has also been performed with the RGEA[204] as well as the RA.[205]

When constructing a sequential anastomosis, it is our preference in most instances to complete the distal anastomosis first and move proximally (Fig. 22-9). This facilitates determination of optimal intergraft spacing. In the case of the LAD-diagonal graft, however, it is easier to move from proximal to distal, performing the diagonal anastomosis first. Sequential side-to-side anastomoses may be perpendicular or longitudinal. When constructing perpendicular anastomoses, care must be taken not to make the arteriotomies too long, as there is risk of creating a "gull-wing" deformity and placing the graft at jeopardy. Arteriotomies in both the conduit and target are made in the direction of the long axis of the vessel. The two incisions are then aligned perpendicular to one another and an eight-stitch anastomosis is completed, creating a diamond-shaped anastomosis. The arteriotomy for longitudinal anastomosis may be made as long as necessary without risk of distorting the conduit. Typically the longitudinal anastomosis is begun at the heel and the far wall is completed open. It is then parachuted down and the front wall is completed.

CORONARY ENDARTERECTOMY

Coronary endarterectomy predated CABG as a direct surgical approach to relieving coronary occlusive disease.[17,18,206,207] Coronary endarterectomy has been relegated to a position of secondary importance, however, thanks to the reliable and reproducible results obtained with CABG. Recently there has been increased interest in endarterectomy techniques, as the patient population coming to CABG has a greater atherosclerotic burden due to diabetes, hyperlipidemia, and advanced age.[208] Most commonly the need for endarterectomy arises intraoperatively when no soft site can be identified for arteriotomy or a vessel has been inadvertently opened in an extensively diseased area not amenable to grafting. Occasionally, endarterectomy is undertaken electively in patients with diffuse and extensive coronary disease with no other choices except transplantation.

The perioperative risk of CABG with endarterectomy is higher than that for CABG alone in most studies.[209–211] Reported mortality rates range from 2 to 6% with perioperative MI rates of 5 to 10%.[212–215] There appears to be higher perioperative risk when multiple vessels require endarterectomy.[210,212,216] There has been controversy regarding the risk of endarterectomy of the LAD, with some studies showing increased risk[210] while others demonstrate no such increased risk.[215,217,218]

The late results of endarterectomy are inferior to those of routine CABG, with reported 3-year patency for ITA grafts to endarterectomized LAD targets ranging from 74 to 80%.[213,219] Despite this, angina relief is remarkably good initially. Unfortunately, the rate of recurrent angina is somewhat higher than after uncomplicated CABG; reported recurrence of angina varies from 9 to 35% at 5 years.[215,218–220] The reported 5-year survival following coronary endarterectomy ranges from 70 to 87%.[212–215] Among patients in whom bypass to more distal nondiseased segments is not possible, coronary endarterectomy with subsequent bypass offers a viable alternative to leaving a territory ungrafted.

The technique of endarterectomy requires that the central core be extracted adequately in order to relieve obstruction of the branch vessels. Patency of a graft to the endarterectomized vessel depends upon the adequacy of run-off, therefore the distal endpoints of the endarterectomy core must be smoothly tapered. If the core fractures leaving behind disease in side branches, distal counter-incisions may be needed to obtain a satisfactory result.

The RCA is the vessel most often endarterectomized, usually at the level of its bifurcation. A manual eversion endarterectomy is performed after entering at the vessel approximately 1 cm proximal to the crux. A circumferential plane of dissection between the core and the adventitia is developed with a fine coronary spatula. The core is transsected proximally and gently grasped with DeBakey forceps while the spatula is used to tease the adventitia away from the core. The core is regrasped hand over hand as distally as possible to avoid fracture. When the crux is reached, the posterior descending artery and the left ventricular branch are endarterectomized separately. If endarterectomy of the proximal segment of the RCA is needed, we prefer to use an open technique since it is difficult to obtain a nice tapering of the core at the take-off of the acute marginal branches with a retrograde eversion endarterectomy. The vessel wall is then reconstructed with a long hood created with the bypass conduit of choice.

We prefer open extended technique when the LAD is endarterectomized (Fig. 22-10). The vessel is opened as far proximal as possible if endarterectomy is anticipated. If the vessel has been opened in its mid-portion before it is apparent that endarterectomy is necessary, we extend the incision in the adventitia proximally before developing the endarterectomy plane. Retrograde eversion endarterectomy is dangerous because branch vessels will not be opened. Once the core is separated from the adventitia it is transsected proximally at the heel and the vessel is opened beyond the takeoff of the major diagonals to permit individual eversion endarterectomy of each of the branches. The segment is reconstructed with a long hood of the conduit of choice or a vein patch into which the ITA is anastomosed. The circumflex artery is the most infrequently endarterectomized vessel. Its rapid branching pattern makes satisfactory endarterectomy difficult. We tend to begin with an eversion technique focusing our efforts on opening the largest distal branches as much as possible.

PROXIMAL ANASTOMOSES

Proximal anastomoses of saphenous vein or RA to the aorta can be performed before or after the distal anastomoses. Construction of proximal anastomoses prior to the institution of cardiopulmonary bypass will minimize pump time but risks

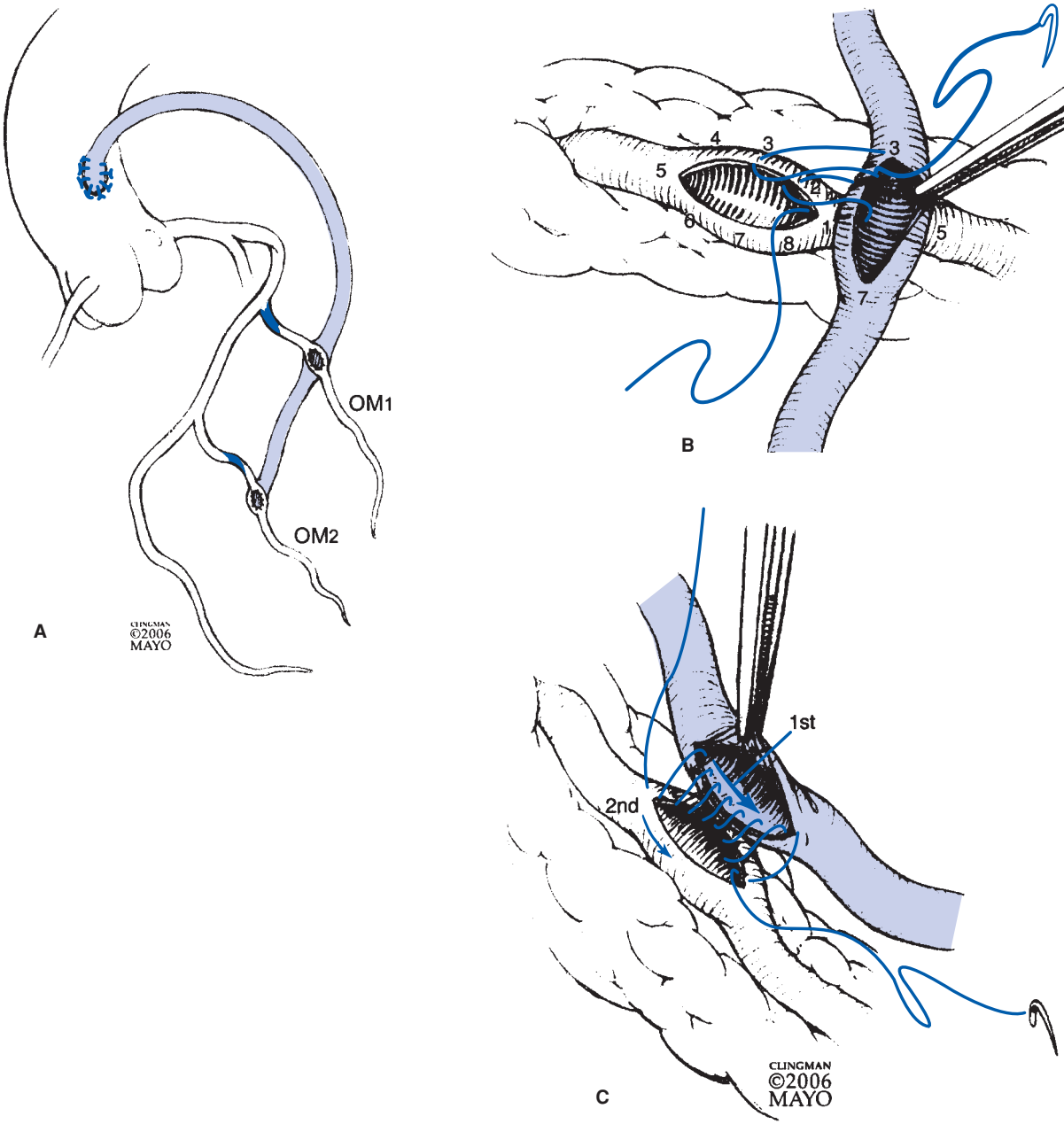

Figure 22-9. Sequential anastomosis. (A) Order of anastomoses: The order in which sequential anastomoses are performed is important to facilitate optimal intergraft spacing and avoid kinking. The distal anastomosis is completed first and the more proximal sequential anastomosis is performed second, except for an LAD-diagonal graft, in which the diagonal is performed first followed by the LAD. (B) Perpendicular sequential side-to-side anastomosis: Arteriotomies are made in the direction of the long axis of the coronary and the conduit. Care must be taken not to make the arteriotomies too long, since there is risk of creating a "gull-wing" deformity. The two incisions are aligned perpendicular to one another. The suture is passed starting inside-out at the apex of the target coronary and then outside-in at the mid-portion the conduit. An eight-stitch anastomosis is completed creating a diamond-shaped anastomosis. (C) Longitudinal sequential side-to-side anastomosis: The arteriotomy for longitudinal anastomosis may be made as long as necessary without risk of distorting the conduit. The anastomosis is begun at the heel and the far wall is completed open. It is then parachuted down and the front wall completed.

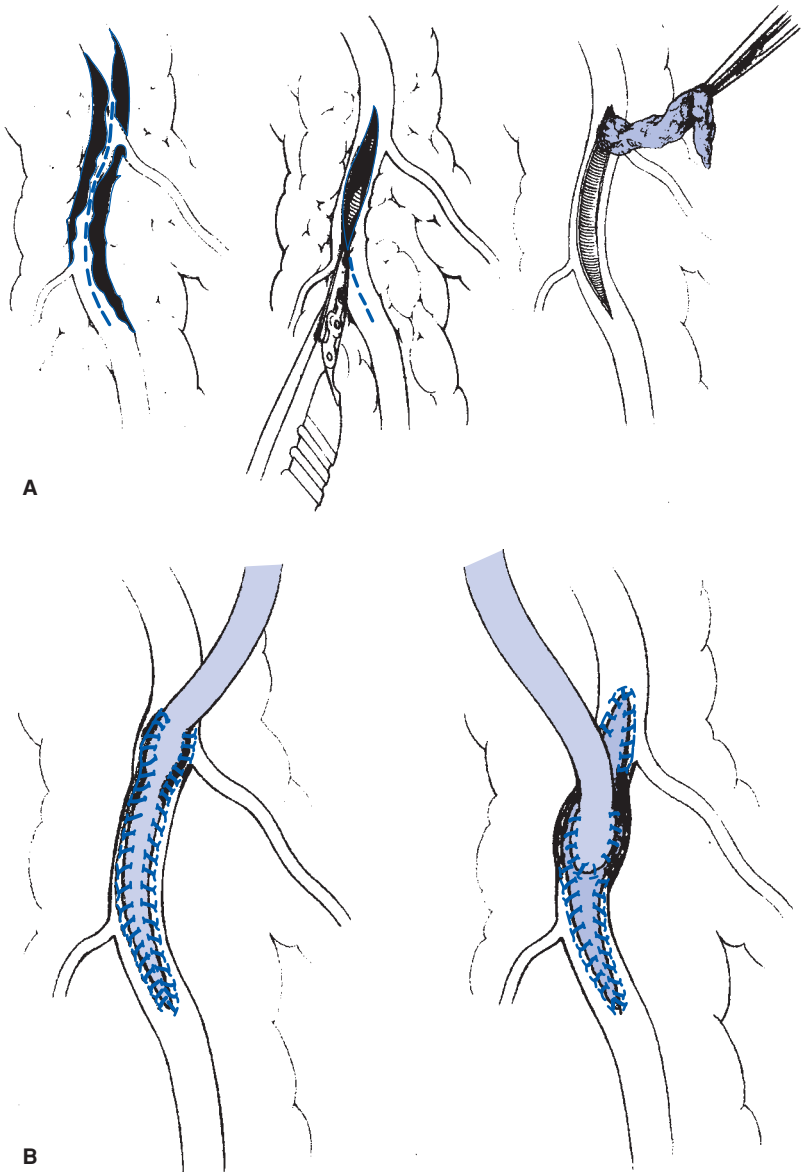

Figure 22-10. Coronary endarterectomy: Open extended technique. (A) The extent of disease is evaluated to plan the length of the arteriotomy and endarterectomy. The arteriotomy is performed and extended as proximal as needed before the circumferential plane of dissection between the core and the adventitia is developed with a fine coronary spatula. Once the core is separated from the adventitia it is transsected proximally at the heel and the vessel is opened beyond the takeoff of the major branches to permit individual eversion endarterectomy of each of the branches. (B) The segment is reconstructed with a long hood of the conduit of choice. The segment may be reconstructed with vein patch into which the ITA is anastomosed.

damage to the aorta due to application of the partial occlusion clamp to the pulsatile, pressurized aorta. Alternatively, proximal anastomoses may be constructed on bypass but before application of the cross-clamp with subsequent completion of distal anastomoses. If performed after the distal anastomoses, they may be constructed after completion of each distal anastomosis, or after all distals. The proximal anastomoses may be constructed under the same cross-clamp or with a partial aortic occlusion clamp. Use of a partial occlusion clamp limits ischemic cross-clamp time, but does require a greater degree of aortic manipulation and has been associated with a higher risk of stroke as compared with the single-clamp technique.[221]

Anastomotic Technique

Once an appropriate site for aortotomy is identified, the fatty tissue overlying the aorta is removed (Fig. 22-11). An arteriotomy is created with a no. 11 blade, and a 4 to 5 mm punch is used to create a circular aortotomy. The size of the punch will vary depending on the size of the conduit graft. The proximal aspect of the conduit is beveled and then notched at the heel. A running 5-0 polypropylene suture is used for a venous graft and a 6-0 polypropylene suture for an arterial conduit. The long axis of the graft is aligned at an appropriate angle to the ascending aorta. The anastomosis can be completed with eight stitches in most cases; symmetry in the spacing of sutures is paramount to obtain a hemostatic anastomosis. The site of anastomosis can be marked to facilitate future cardiac catheterization.[222] Free arterial grafts may be anastomosed directly to the aorta, or to the hood of a vein graft.

Composite Grafts

As an alternative to proximal anastomosis to the aorta, a free graft can be anastomosed proximally to the pedicled ITA

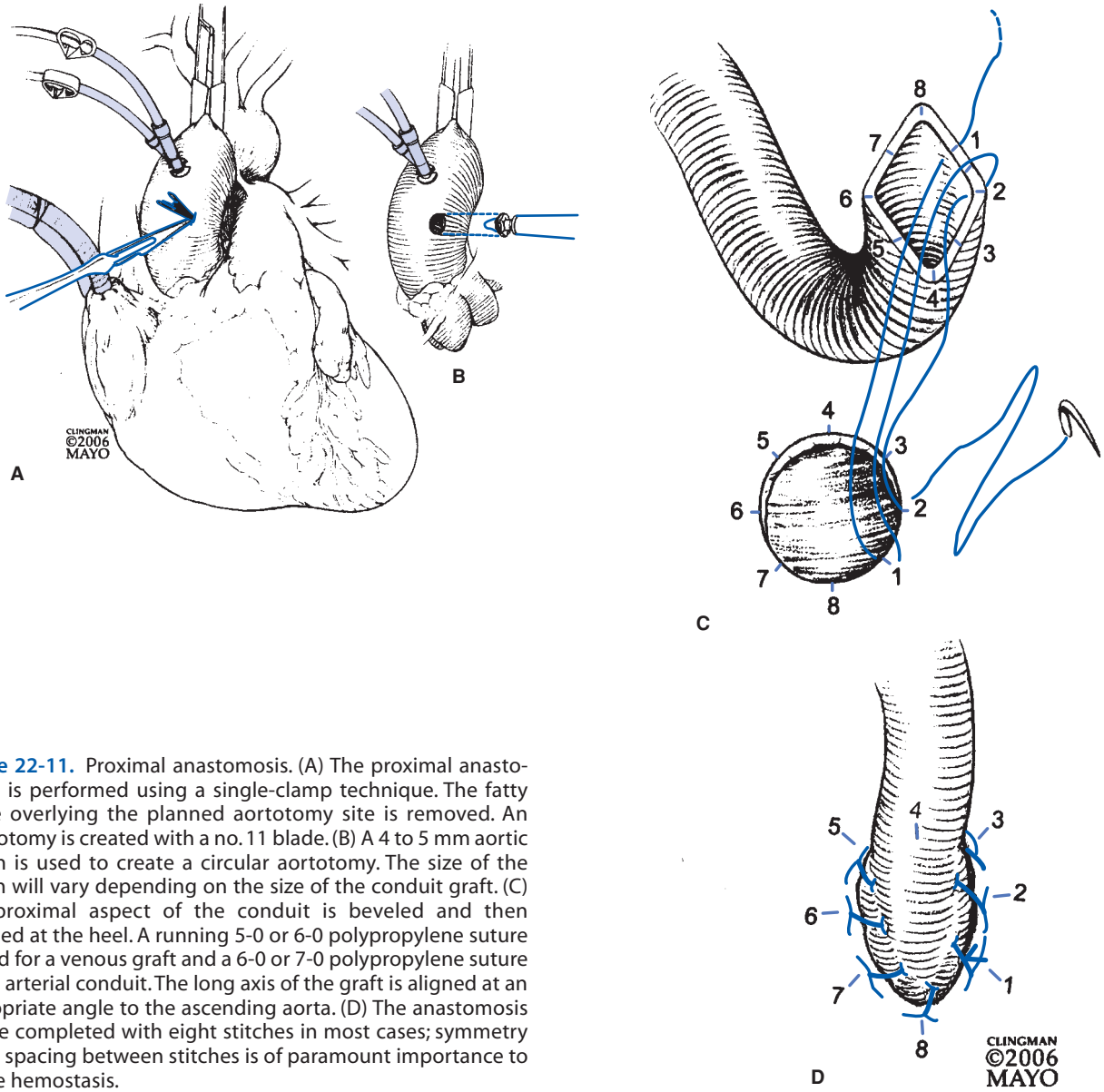

Figure 22-11. Proximal anastomosis. (A) The proximal anastomosis is performed using a single-clamp technique. The fatty tissue overlying the planned aortotomy site is removed. An arteriotomy is created with a no. 11 blade. (B) A 4 to 5 mm aortic punch is used to create a circular aortotomy. The size of the punch will vary depending on the size of the conduit graft. (C) The proximal aspect of the conduit is beveled and then notched at the heel. A running 5-0 or 6-0 polypropylene suture is used for a venous graft and a 6-0 or 7-0 polypropylene suture for an arterial conduit. The long axis of the graft is aligned at an appropriate angle to the ascending aorta. (D) The anastomosis can be completed with eight stitches in most cases; symmetry in the spacing between stitches is of paramount importance to assure hemostasis.

(Fig. 22-12). This technique has the theoretical advantage of providing a more physiologic arterial pressure waveform by attaching the conduit to a third-order vessel rather than to the aorta. Composite grafting is also a useful tool for the hostile, calcified ascending aorta or when there is a limited length of conduit available. It is also advantageous when there is a marked mismatch between aortic wall thickness and arterial conduit size.[223]

A combination of composite and sequential grafting allows the opportunity to perform complete arterial revascularization with only ITAs[224,225] or with a LITA and other arterial conduits.[226–229] Multiple configurations of Y- and T-grafts can be devised to best suit the anatomic characteristics of each patient.[230] The LITA has been shown to have more than sufficient flow reserve to supply flow to the entire coronary circulation.[231] The free right ITA, the RA, or other arterial conduit can be based in this manner.[159,232,233]

All-arterial Y-grafts are usually planned in advance and constructed prior to the initiation of cardiopulmonary bypass. Special care must be taken during construction of composite grafts to avoid tension, rotational torsion, or narrowing of the inflow anastomosis. Disadvantages include technical difficulty and reliance upon a single inflow source for two or more distal targets.

MANAGEMENT OF THE ATHEROSCLEROTIC ASCENDING AORTA

Ascending aortic atherosclerosis has been consistently identified as a very important risk factor for stroke in multiple series. Epiaortic ultrasound can be performed to define the extent of atherosclerosis of the ascending aorta and its likelihood of embolization.[234] Patients with severe atherosclerosis

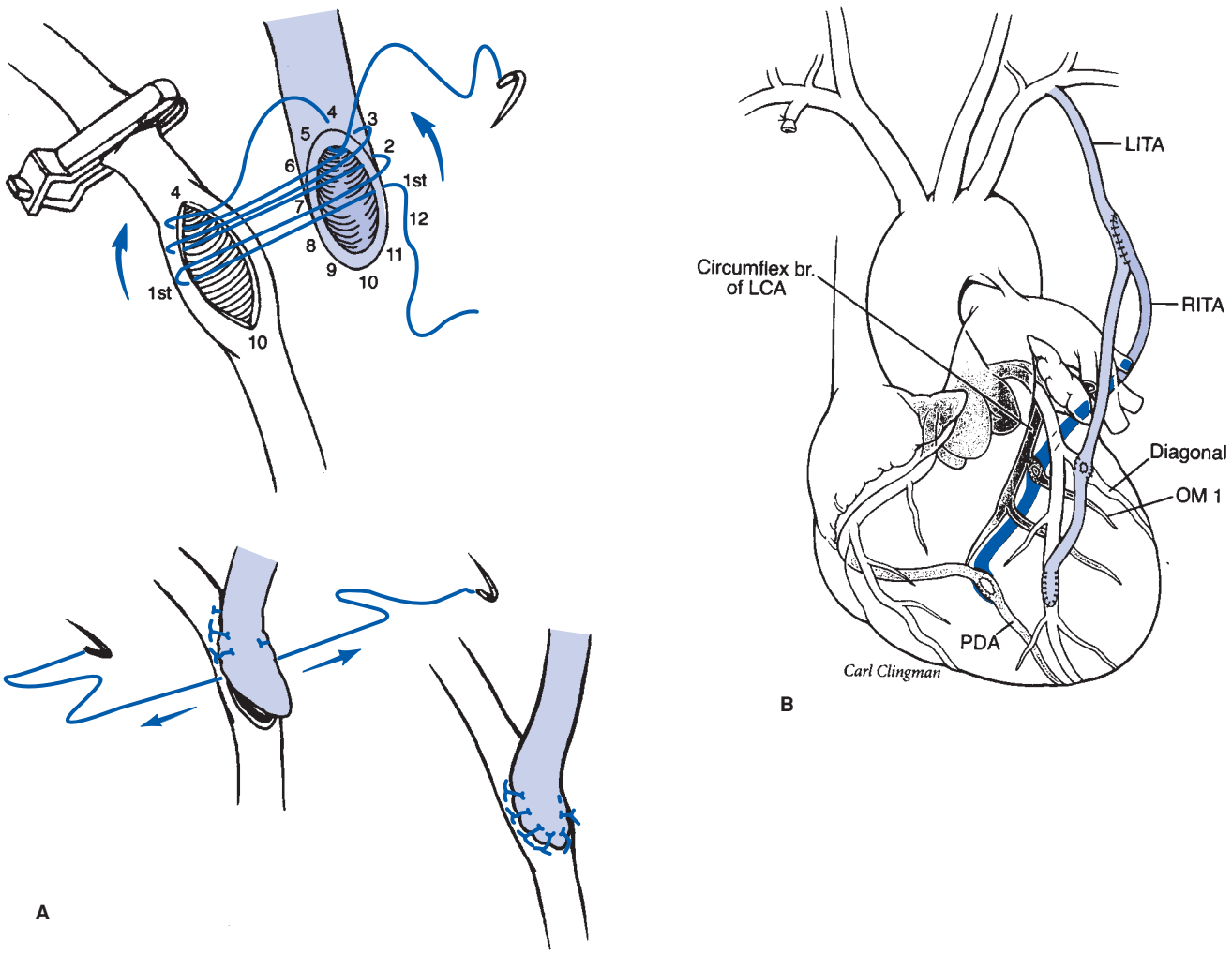

Figure 22-12. Composite Y graft. (A) Y-graft anastomotic technique: A coronary artery bypass graft (CABG) is used as a donor site for the proximal anastomosis of another conduit. An incision is created in the donor conduit. The proximal end of the recipient conduit is then anastomosed to the donor site in an end-to-side fashion as previously described for a distal anastomosis. The recipient conduit is then gently parachuted down onto the donor conduit. (B) Total arterial revascularization: As shown, arterial revascularization can be performed using the right internal thoracic artery (RITA) off the left internal thoracic artery (LITA) as a Y graft and liberal use of sequential grafting.

of the ascending aorta may require alternative strategies to prevent embolization of aortic atheroma. If the ascending aorta is hostile, cannulation can be performed at the aortic arch, innominate artery, axillary artery, femoral artery, or external iliac artery. Distal arch or innominate artery cannulation should be avoided if there are atherosclerotic changes in those regions. Femoral arterial cannulation avoids manipulation of a diseased ascending aorta, but will reverse the direction of flow in the descending thoracic aorta and arch toward the head, potentially embolizing atherosclerotic debris, especially in patients with atheromatous descending aortas or abdominal aortic aneurysms. Also, severe atherosclerotic changes may render the femoral or external iliac vessels unusable for cannulation. The axillary artery is a good option to achieve arterial inflow, either by direct cannulation or by using a chimney side graft, as dictated by the size of the artery. If needed, aortic clamping may be performed in areas free of atheroma, usually in the more proximal ascending aorta.

Coronary revascularization can be achieved with a variety of methods. Using a "no touch" technique, revascularization can be done using only pedicled arterial conduits, and if proximal anastomoses are required they can be based off pedicled conduits or brachiocephalic vessels. Distal anastomoses can be performed under cold fibrillatory arrest without aortic cross-clamping, and they also can be accomplished using off-pump techniques.[234–237] Proximal anastomoses can be performed under deep hypothermic circulatory arrest or after graft replacement of the ascending aorta if there are large mobile atheromas.[237,238]

Weaning from Cardiopulmonary Bypass

Upon completion of all anastomoses, the patient is prepared for transition from supported circulation to native circulation. Prior to separation from cardiopulmonary bypass, hemostasis of all possible surgical sites and appropriate de-airing is confirmed. The patient must be rewarmed to normothermia if cooled and the acid-base status and electrolyte abnormalities corrected. Weaning from bypass is otherwise the same as for other cardiac surgical cases. Issues particular to CABG include attention to avoid overdistention of the heart, which may place grafts on tension and disrupt anastomoses. If air has entered the heart, bubbles may pass into the aorta and down the bypass grafts. This may cause arrhythmias and regional wall motion abnormalities in the distributions supplied by the grafts.

OUTCOMES

Operative Mortality

The risk profile of patients requiring isolated CABG in the United States has changed significantly in the past decade. CABG patients are now older, with a greater number of comorbidities, decreased LVEF, and a higher burden of atherosclerotic disease; however, early outcomes after coronary artery bypass continue to improve. The STS database demonstrates that despite an increase in expected mortality from 2.6 to 3.4% (relative increase 30%) in the decade of the 1990s, the observed mortality has actually decreased from 3.9 to 3.0% (relative decrease 23%).[6] Similar observations have been made using the Veterans Affairs mandatory national database. The unadjusted mortality rate for isolated CABG in the Veterans Affairs database fell from 4.3% in 1989 to 2.7% in the year 2000.[239] In the private sector similar trends have been observed. In an analysis of outcomes of patients undergoing isolated CABG in the HCA system, a nationwide for-profit health care system involving 200 hospitals in 23 states, Mack and associates reported an ongoing decrease in unadjusted operative mortality among 51,353 patients, 80% of whom were operated on with cardiopulmonary bypass. In this study the operative mortality for on-pump CABG fell from 2.88% in 1999 to 2.24% in 2002.[4]

Causes of Death

In a multicenter prospective study performed by the Northern New England Cardiovascular Disease Study Group, 384 deaths in 8641 consecutive patients undergoing isolated CABG between 1990 and 1995 were analyzed with respect to the mode of death. The mode of death was defined as the seminal event that precipitated clinical deterioration and ultimately resulted in the patient's demise. Heart failure was judged to be the primary mode of death for 65% of the patients, followed in frequency by neurologic causes (7.3%), hemorrhage (7%), respiratory failure (5.5%), and dysrhythmia (5.5%). The greatest variability in mortality rates observed across surgeons in the study was attributable to differences in rates of heart failure.[240] Cardiac causes were also identified by Sergeant and colleagues as the most common causes of death in a series 5880 patients undergoing CABG at the Katholieke Universiteit Leuven, Belgium between 1983 and 1988.[72]

Operative Morbidity

Myocardial dysfunction

Postischemic myocardial dysfunction and cardiac failure after CABG may be related to preoperative ischemic injury, inadequate myocardial protection, incomplete revascularization, or postoperative graft failure. The spectrum of myocardial injury varies from subtle degrees of global myocardial ischemia to transmural infarction. The incidence of myocardial injury varies with the sensitivity of the method used for detection. Development of segmental transmural MI with development of new Q waves occurs in 1 to 5% of patients undergoing isolated CABG, and it results in a decrement in operative and long-term survival after coronary surgery.[241–245] Elevations of cardiac specific enzymes are ubiquitous after CABG,[246] and elevations in creatinine kinase-myocardial bound (CK-MB) greater than five times the upper limit of normal (ULN) value are considered significant.[247,248] In a prospective study of 2918 patients undergoing CABG, 38% of patients had a CK-MB >5 ULN and 17% had a CK-MB >10 ULN with an incidence of new Q-wave MI of 4.7%.[248] Troponin may be a more sensitive marker than CK-MB, but its role in large populations of CABG patients is still to be defined.[249–252] Prominent elevations of CK-MB and troponin have been associated with global ischemia, MI, low cardiac output, and increased operative mortality, as well as increased mid-term and long-term mortality.[247,248,250,253]

Postoperative myocardial dysfunction may be manifest clinically as low cardiac output syndrome as defined by the need for postoperative inotropic support or aortic counterpulsation to maintain a systolic blood pressure >90 mm Hg or a cardiac index >2.2 L/min. Transient myocardial dysfunction necessitating low-dose inotropic support for a short period of time is common after CABG. The reported incidence of low output syndrome, therefore, will vary depending on the defining criteria. For example, in one study in which low output syndrome was defined as the need for intra-aortic balloon (IAB) pulsation or inotropic support for >30 minutes, the incidence of low output was 9%, whereas in another series defining low output as the need of IAB pulsation or inotropic support for >8 hours, the incidence was 4.3%.[254,255] Low output syndrome has been shown to be a marker for increased operative mortality by 10- to 15-fold.[254,255] Independent predictors of low output syndrome in order of importance include: LVEF <20%, reoperation, emergency operation, female gender, diabetes, age older than 70, left main disease, recent MI, and triple vessel disease.

Adverse neurologic outcomes

Neurologic deficits after coronary surgery are divided into two types: type 1 deficits include major neurologic deficits, stupor, and coma; type 2 deficits are characterized by deterioration of intellectual function and memory. In a prospective multicenter study conducted by the Multicenter Study of Perioperative Ischemia Research Group, 2108 patients from 24 U.S. institutions were evaluated with regard to adverse cerebral outcomes after CABG: the incidence of type 1 deficits was 3.1% and type 2 deficits was 3%. The associated mortality rates were 21 and 10%, respectively, while the operative mortality in patients with no neurologic dysfunction was 2%.[256] Predictors of both types of deficits included advanced age (≥70 years of age), and history or presence of severe hypertension. Independent predictors of type 1 deficits included proximal aortic atherosclerosis, history of prior neurologic disease, use of IABP, diabetes, unstable angina, and perioperative hypotension. Predictors of type 2 deficits included history of alcohol consumption, dysrhythmias, prior CABG, peripheral vascular disease, congestive heart failure (CHF), and perioperative hypotension. Similar predictors of adverse neurologic outcomes have been observed in other studies.[256–258]

Deep sternal wound infection

Deep sternal wound infection occurs in 1 to 4% of CABG patients and carries a mortality rate of 25%.[259] Proven methods to reduce postoperative wound complications include the use of preoperative showers with chlorhexidine gluconate on the evening and morning before the procedure,[260] prophylactic intranasal application of mupirocin given on the evening and the morning before the procedure and twice daily for 5 days postoperatively,[261–263] hair clipping the morning of surgery,[264] and administration of intravenous prophylactic antibiotics prior to skin incision.[265–269]

Obesity and diabetes are strong independent predictors of mediastinitis. Insulin-dependent diabetics are especially susceptible to deep sternal wound infection.[270–272] Recent data suggest that tight glycemic control in the postoperative period decreases the risk of mediastinitis in the diabetic population.[273,274] Other preoperative variables independently associated with an increased incidence of deep sternal wound infection include reoperations, longer operative times, re-exploration for bleeding, and blood transfusions.[271,272,275]

The use of bilateral ITAs had been implicated as a risk factor for mediastinitis, especially in diabetics;[271,276] however, this risk appears to be mitigated in part by using a skeletonized ITA harvesting technique.[91,277–279] Bilateral ITA harvest must be avoided in obese diabetic women since they exhibit a prohibitively high risk of deep sternal wound infection, even with skeletonization of the IMAs.[91]

Acute renal failure

Acute renal failure ensuing after CABG with cardiopulmonary bypass is an ominous event. In a prospective observational study conducted at 24 university centers in the United States, 2222 CABG patients were evaluated with regard to postoperative renal dysfunction. Renal dysfunction not requiring dialysis occurred in 6.3%, and renal dysfunction requiring hemodialysis developed in 1.4%. Mortality was directly related to postoperative renal function. Patients with no renal dysfunction had 0.9% mortality, and postoperative renal dysfunction increased mortality to 19% if no dialysis was needed and to 63% if hemodialysis was required. Independent predictors of postoperative renal dysfunction included increasing age, CHF, reoperation, diabetes mellitus, chronic renal insufficiency, prolonged cardiopulmonary bypass time, and low cardiac output.[280] These findings were confirmed by a series of 42,733 patients with similar incidence and mortality associated with postoperative renal dysfunction.[281] One in four patients with preoperative chronic renal insufficiency (creatinine >1.6 mg/dL) will require renal replacement therapy post-CABG, and patients at highest risk are older than 70 years and have a baseline creatinine >2.5 mg/dl.[59]

Long-Term Outcomes

The long-term outcomes of surgical MR depend on the complex interaction of patient-related and procedure-related factors. Important patient-related factors include anatomic distribution of the CAD, the extent and severity of coronary atherosclerosis, the physiologic impact of ischemia on ventricular function at the time of the original operation, age, gender, overall health status, severity of atherosclerotic burden throughout the body, the presence and severity of associated comorbidities, development of operative complications such as stroke, and a need for permanent hemodialysis. The progression rate of native coronary atherosclerosis after surgery and the development of coronary bypass graft failure are of extreme importance in the development of post-CABG angina recurrence, MI, need for reintervention, and cardiac-related mortality. Procedure-related factors that influence long-term outcomes include completeness of revascularization, myocardial protection, and selection of bypass conduits.

Sergeant and colleagues at the Gasthuiberg University Hospital of the Katholieke Universiteit (KU) Leuven, Belgium have provided us with the most complete data set on clinical outcomes after MR. From 1971 to 1993, 9600 consecutive CABG patients were prospectively followed with special attention to clinical outcomes after surgical MR; the investigators achieved a 99.9% complete follow-up in this cohort. Clinical outcomes prospectively followed at the KU Leuven included mortality, return of angina, MI, and coronary reintervention.[282]

Sergeant defined return of angina as the first recurrence of angina of any intensity or duration unless it was associated on the same day with MI or death. The severity of this event was also recorded. At the KU Leuven the overall nonrisk adjusted freedom from return of angina was 95% at

1 year, 82% at 5 years, 61% at 10 years, 38% at 15 years, and 21% at 20 years. The data suggest that if followed long enough after CABG, the return of angina is almost inevitable, and at 12 years one-half of operated patients had return of angina. The initial episode of recurrent angina was rated as mild in 59% of patients.[283] In the Bypass Angioplasty Revascularization Investigation (BARI) trial of 914 patients with symptomatic multivessel disease randomly assigned to receive CABG, freedom from angina was 89% at 1 year and 82% at 5 years.[284]

The overall nonrisk adjusted freedom from MI after CABG at the KU Leuven was 97% at 30 days, 94% at 5 years, 86% at 10 years, 73% at 15 years, and 56% at 20 years.[285] The overall nonrisk adjusted freedom from a coronary reintervention, either PCI or reoperative CABG, was 99.7% at 30 days, 97% at 5 years, 89% at 10 years, 72% at 15 years, and 48% at 20 years.[286] In the BARI trial, freedom from subsequent coronary reintervention intervention at 7 years was 86.9%.[284]

Overall risk-unadjusted survival after CABG in the KU Leuven experience was 98% at 30 days, 92% at 5 years, 81% at 10 years, 66% at 15 years, and 51% at 20 years. Mortality after CABG was characterized by an initial period of high risk in the first month after surgery, then risk declined to its lowest at 1 year after the operation, and thereafter the mortality risk rose slowly and steadily for as long as the patient was followed. This slow and steady rise in the risk of death over time paralleled that of the general population when matched for sex, age, and ethnicity.[286] The occurrence of ischemic clinical events after CABG negatively influenced survival. Overall survival was lessened by return of angina, with an observed survival of 83% at 5 years and 54% at 15 years, the more intense the severity of angina at its return, the greater its influence on survival.[283] The occurrence of MI after CABG has a greater negative effect on survival. Observed long-term survival after post-CABG infarction at the KU Leuven was 80% at 30 days, 65% at 5 years, 52% at 10 years, and 41% at 15 years.[285]

Progression of disease in native coronary arteries

Progression of atherosclerosis in the native coronary arteries continues after CABG. Bourassa and associates studied the progression of atherosclerosis in the native circulation 10 years after surgery and found that progression of CAD occurs in approximately 50% of nongrafted arteries. The rate of progression of disease in nongrafted arteries was no different from that of grafted arteries with patent grafts; however, progression was more frequent in grafted arteries with occluded grafts. Progression of pre-existing stenoses in native coronaries was more frequent than appearance of new stenoses, and it was related to the severity of the pre-existing stenosis only in nongrafted arteries. Progression of native CAD was associated with deterioration in LVF. Native coronary atherosclerosis progressed at a similar rate to that of equally diseased arteries in nonoperated patients.[287] Low levels of high-density lipoprotein cholesterol and elevated levels of plasma low-density lipoprotein cholesterol correlated with native disease progression and development of new atherosclerotic lesions.[288,289] These findings underline the need for aggressive secondary prevention to diminish the progression of native coronary atherosclerosis.

Graft failure

Although the use of the saphenous vein helped popularize coronary bypass grafting, the propensity of the saphenous vein to occlude over time has been the Achilles' heel of the procedure. Three entities are responsible for saphenous vein graft failure: thrombosis, intimal hyperplasia, and graft atherosclerosis.[290]

Thrombosis accounts for graft failure within the first month after CABG, and graft occlusion is found on angiography in 3 to 12% of all venous grafts. Thrombosis of the graft may be related to endothelial injury and technical errors. Injury during conduit harvest may cause disruption of the intimal and even medial layers of the vessel. Endothelial injury can also occur with forceful distention of the conduit and nonphysiologic pH of the distending fluid. Endothelial damage creates a prothrombotic milieu in the conduit. Technical errors include poorly constructed anastomoses, graft kinking, and insufficient graft length that causes tension at the anastomosis. Graft-target size mismatch, poor vessel run-off, and competitive flow will produce low flow through the graft conduit and may also lead to early thrombosis.[77,290,291]

Intimal hyperplasia defined as the accumulation of smooth muscle cells and extracellular matrix in the intimal compartment, is the major disease process in venous grafts between 1 month and 1 year after implantation. Nearly all veins implanted into the arterial circulation develop further intimal thickening within 4 to 6 weeks, which may reduce the lumen by up to 25%. Intimal hyperplasia rarely produces significant stenosis per se. More importantly, however, it will provide the foundation for later development of graft atheroma. Progression of atherosclerosis in aortocoronary saphenous vein grafts is frequent and is the predominant cause of late graft closure after CABG. Vein graft atherosclerosis may begin as early as the first year, but is fully developed only after about 5 years. Ten years after surgery 50 to 60% of SVGs will be occluded and one-half of still patent grafts will show angiographic evidence of atherosclerosis; two-thirds of these lesions will have a luminal diameter reduction of 50% or greater.[287] Vein graft atherosclerosis is the leading cause for reoperation following CABG, more so than progression of disease in native coronary arteries.[292–295]

Extended use of arterial grafting

BILATERAL ITA: In contrast to the easily demonstrated survival benefit conferred by an ITA graft to the LAD artery, it was more difficult to demonstrate a survival benefit to a second arterial graft. Buxton and colleagues studied 1243 patients undergoing primary CABG with bilateral ITA grafts compared with 1583 patients with single ITA grafts.

This group demonstrated a 15% absolute improvement in actuarial survival rates 10 years after CABG with the use of bilateral ITA grafts, as compared with the use of a single ITA graft (10-year survival for bilateral ITA was 86 ± 3% versus 71 ± 5% for a single ITA).[296] Lytle and colleagues demonstrated an improvement in survival at 12 years (79 versus 71%), as well as superior reoperation-free survival (77 versus 62%) among 2001 bilateral and 8123 single ITA graft patients.[297]

COMPLETE ARTERIAL REVASCULARIZATION: The better long-term results achieved with the use of bilateral ITAs and the well-known time-related attrition in patency of venous conduits encouraged the exclusive use of arterial conduits for MR. Complete arterial revascularization can be achieved by a variety of strategies including composite grafting using exclusively ITAs or secondary arterial conduits such as the RA and the GEA. The use of sequential anastomotic techniques maximizes the utilization of arterial conduits. Although technically demanding, sequential grafting can be performed safely and with excellent long-term results. Dion and colleagues reported a 96% patency rate at 7.5 years of follow-up on1150 sequential ITA anastomoses.[298]

Tector has championed complete arterial revascularization using bilateral ITAs in a T configuration with end-to-side anastomosis of one ITA as a free graft to the side of the second ITA which is left as a pedicled graft, combined with liberal use of sequential anastomoses. In his series of 897 patients overall survival was 75%, and freedom from reintervention was 92% 8 years after revascularization.[225] Barner has reported similar encouraging results with composite grafting using one ITA and one RA.[232]

Data from randomized studies are beginning to emerge supporting improvement in early outcomes with complete arterial revascularization compared to conventional CABG. Muneretto and associates randomized 200 patients to complete arterial revascularization (left ITA to the LAD artery and composite grafts with the right ITA, RA, or both) versus conventional CABG (left ITA to the LAD artery and SVGs). In mid-term follow-up (20 months) superior event-free survival (freedom from nonfatal MI, angina recurrence, graft occlusion, need for percutaneous transluminal coronary angioplasty, and late death) was demonstrable in the complete arterial revascularization patients compared to conventional CABG.[299] The same group conducted a second randomized trial comparing complete arterial revascularization to conventional CABG (ITA to LAD artery and SVG) in 160 patients older than 70 years of age undergoing first time nonemergent CABG. Early mortality was similar, but at 16 ± 3 months, there were significantly fewer graft occlusions and recurrences of angina among the complete arterial revascularization group. Independent predictors of graft occlusion and angina recurrence were use of SVGs, diabetes, and dyslipidemia.[228] The result of longer follow-up of these trials is eagerly awaited.

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CHAPTER 23

Myocardial Revascularization without Cardiopulmonary Bypass

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Coronary artery bypass grafting (CABG), while declining in overall numbers, continues to comprise the majority of open-heart procedures performed on a yearly basis in the United States. The efficacy of this procedure for survival, symptom improvement, and quality of life has been well documented in specific patient subgroups. Additionally, it has been a technique that can be performed reproducibly by a wide variety of operators with varying degrees of technical skill and acumen with generally good results. However, conventional bypass grafting using cardioplegic arrest continues to be associated with singular complications that may negate an otherwise successful procedure. Renewed interest in off-pump bypass grafting (OPCABG) in the mid-1990s presented surgeons with the option of revascularization without the potential complications of extracorporeal support. However, widespread acceptance and use of this technique remain sporadic. While this approach has been adopted as the primary mode of coronary revascularization by some, most surgeons still prefer to operate on an arrested heart. This is evidenced by the fact that off-pump surgery still only accounts for approximately 20 to 25% of all coronary artery bypass procedures performed in the United States.[1] For most surgeons, the transformation of this technique from compelling idea to standard therapy relies on scientifically demonstrating the following: (1) graft patency rates that are at least equivalent to conventional techniques, (2) reduced morbidity and mortality, especially in high-risk groups, (3) a rapid return to usual functional capacity, and (4) an economic benefit. Unfortunately, many of the results reported in the literature concerning outcomes with off-pump bypass grafting have been inconclusive as to the overall benefit of the technique. Most studies have suffered from the fact that they have been retrospective reviews with perceived patient selection bias, despite many times including sophisticated statistical risk adjustment. And while newer prospective studies continue to be published, questions regarding the ultimate benefit of this technique remain unanswered in the minds of many surgeons. Ultimately, it will be up to individual surgeons to decide whether to include this useful technique in their surgical repertoire.

PATIENT SELECTION

Patient selection for off-pump bypass grafting depends largely on the interaction between the experience level and technical skill of the operating surgeon and the angiographic coronary anatomy identified at the time of cardiac catheterization. Many decisions regarding a patient's suitability for an off-pump approach can be made prior to the patient going to the operating theater. Surgeons with little off-pump experience should concentrate on patients with less demanding revascularization requirements (Table 23-1). These would include patients with good-sized epicardial target vessels (>1.25 mm), coronary arteries with focal stenosis rather than diffuse disease, target vessels away from the atrioventricular groove, and vessels in which an endarterectomy is not required. Additionally, these procedures should be performed in nonemergent situations in which the patients are hemodynamically stable and have relatively well-preserved left ventricular function. These operations also should be primary revascularization procedures and not reoperations.

With experience, higher-risk and technically more challenging procedures can be undertaken. These include procedures on patients with marginal hemodynamics but who are otherwise stable, those requiring multiple grafts to the posterior and lateral walls or the atrioventricular groove, and those with enlarged right or left ventricles[2–6] (Table 23-2). Difficult patients most likely to benefit from off-pump surgery include those with severe left ventricular dysfunction, renal insufficiency, atherosclerotic disease of the ascending aorta, severe chronic obstructive

Table 23–1.

OPCAB Patient Selection in Early Experience

Anterior vessels
Limited number of bypasses (1–3)
Normal LV function
Epicardial location of targets
Large vessels not diffusely diseased
Hemodynamically stable
Primary revascularization
First case of the day

LV = left ventricular; OPCAB = off-pump coronary artery bypass.

pulmonary disease, and those grafted emergently after an acute myocardial infarction.[6–9] Patients presenting the most significant challenge include those requiring reoperations and those with small and diffusely diseased vessels.[10,11]

Patients who are unstable, either hemodynamically or electrically, may not tolerate the manipulation required for off-pump bypass grafting and therefore represent a population generally not considered candidates for OPCABG. Additionally, patients with moderate or greater aortic or mitral insufficiency may not tolerate extremes of positioning for revascularization. Excessive manipulation of the heart can worsen valvular incompetence, leading to ventricular distension and ultimately ventricular fibrillation. Close attention to hemodynamic parameters such as the pulmonary artery pressures, mixed venous oxygen saturation, and systemic blood pressure can give an early indication of impending problems and allow time for cardiac repositioning. Patients clearly not amendable to an off-pump approach can be revascularized safely by performing pump-supported beating-heart surgery. Patients are supported by the extracorporeal circuit to maintain hemodynamic stability, but global ischemia is avoided by performing the anastomosis using beating-heart techniques. The ability to apply these techniques when needed augments the armamentarium of the practicing surgeon.

Table 23–2.

Patients Most Likely to Benefit from OPCAB

Age >70 years
Low ejection fraction
Reoperative surgery
Patients with significant comorbidities Cerebral vascular disease Peripheral vascular disease Hepatic disease Bleeding disorders COPD Renal dysfunction
Atheromatous or calcified aorta
Patients who refuse blood products

COPD = chronic obstructive pulmonary disease; OPCAB = off-pump coronary artery bypass.

ANESTHESIA FOR OPCABG

The avoidance of extracorporeal circulation in association with off-pump revascularization requires modifying not only the anesthetic technique used in these patients but also the level of participation of the anesthesiologist, especially during construction of the distal anastomoses. Close collaboration with a familiar and involved anesthesiologist is vital to the performance of off-pump bypass grafting. Lines of communication between the surgeon and the anesthesiologist should be clearly established in order to provide appropriate responses to rapidly changing clinical situations.

The anesthetic technique for off-pump bypass grafting is tailored to provide hemodynamic stability during displacement of the heart, reduce the sequelae of regional myocardial ischemia, and allow early recovery of consciousness and extubation (Table 23-3). These techniques are predicated on the avoidance of long-acting agents and the use of short- and intermediate-acting narcotics.

Without the heat exchanger of the bypass circuit to control the patient's body temperature, maintenance of body heat by ancillary methods becomes necessary. The patient's temperature is maintained using warming mattresses, infusion of warmed fluids, warmed oxygen and anesthetic gases, and keeping the room temperature elevated. Immediate extubation of patients at the conclusion of the procedure should be the goal in the majority of off-pump cases. Several reports have confirmed the safety of immediate extubation after off-pump bypass grafting, provided that certain criteria are met, namely, (1) patients should be stable hemodynamically, (2) oxygenation and ventilation parameters should be satisfactory, (3) patients should have adequate return of muscular strength, (4) patients should have a

Table 23–3.

Essentials of Anesthetic Management in OPCAB

Use intermediate- or short-acting agents
Warming mattresses, warmed fluids and gases
Elevated room temperature
Oximetric pulmonary artery catheters
Transesophageal echocardiography
Trendelenburg position to increase preload
Volume loading
Nitroglycerine for ischemia prophylaxis
Judicious use of positive inotropes
Avoidance of negative inotropes

OPCAB = off-pump coronary artery bypass.

level of consciousness sufficient to respond to simple commands, and (5) surgical bleeding should be controlled.[12] In one series, 514 patients of 548 (94%) undergoing off-pump bypass grafting were extubated successfully in the operating room, with a minimal number of patients requiring reintubation.[13]

All patients receive continuous oximetric pulmonary artery catheters and transesophageal echocardiography probes. These provide continuous hemodynamic monitoring and allow treatment to be directed toward specific alterations in the patient's cardiac function. Additionally, undiagnosed intracardiac abnormalities are identified intermittently that may require treatment and alteration of the operative plan. Nitroglycerine infusion for ischemic prophylaxis and volume loading are instituted at the beginning of the case. Patients are preload-sensitive during the manipulation that occurs when setting up the anastomoses, especially of the posterior circulation vessels. Cardiac displacement leads to right ventricular deformation and decreased pump function without valvular incompetence; this occurs secondary to inflow occlusion or outflow obstruction.[14–19] Volume loading and the use of Trendelenburg positioning increase preload, thereby augmenting right ventricular filling pressures and allowing patients to tolerate the distortion in anatomy and maintain adequate cardiac output and systemic blood pressure. Antiarrhythmics are instituted as needed but are seldom required. Pacing wires and intraluminal shunts are placed often when grafting poorly collateralized large right coronary arteries because hypotension and bradycardia are seen frequently with occlusion of these vessels.

Most surgeons believe that negative inotropic or chronotropic agents are to be avoided in off-pump surgery. They provide little in facilitating construction of the anastomoses while reducing cardiac performance enough to make some areas of the heart ungraftable. Use of positive inotropes can increase the force of myocardial contraction, accentuating cardiac motion and making target stabilization more difficult. During manipulation and positioning of the heart, volume infusion and small aliquots of pressor agents are used to support blood pressure and optimize cardiac output.

Anticoagulation is produced using 1.5 to 2.0 mg/kg of heparin in order to maintain an activated clotting time (ACT) of greater than 300 seconds. At the end of the procedure, the anticoagulation is reversed to varying degrees, depending on surgeon preference, with protamine sulfate. A bypass circuit is available routinely in the operative suite in the event that conversion to cardiopulmonary support is indicated. Conversion rates vary with surgeon experience but generally are less than 4%.[20]

SURGICAL TECHNIQUE

Incision

A median sternotomy is the most frequently used route for cardiac access when performing multivessel grafting. Isolated grafting of specific individual vessels can be performed using a variation of thoracotomy, anterior for the left anterior descending artery or lateral for access to the marginal vessels. The use of thoracotomy for multivessel grafting also has been reported. A median sternotomy allows the surgeon to visualize the operative field from an orientation that is familiar and similar to on-pump procedures. This facilitates target-vessel identification as well as harvesting of the internal mammary arteries for use as conduit. Additionally, should conversion to conventional bypass become necessary, a median sternotomy allows easy access for cannulation of the heart.

Once conduit is obtained, the retractor is positioned inferiorly in the sternal incision. This placement reduces traction on the brachial plexus and generally facilitates mobilization of the heart for positioning. Current retractors used for beating-heart surgery come with attachable devices to aid in positioning the heart as well as stabilizing the target artery (Fig. 23-1). The pericardium is opened in an inverted T-shaped incision. The lateral extensions are exaggerated to facilitate mobilization of the apex of the heart and to create increased space for the right ventricle during positioning. When dealing with hypertrophic hearts, it is often helpful to displace the heart into the right side of the chest to aid in exposure of the lateral wall vessels. This is accomplished by incising the right pleura parallel to and along the entire length of the sternotomy. Additionally, the pericardial incision is extended posteriorly toward the inferior vena cava along the right diaphragm (Fig. 23-2). This incision is stopped just prior to reaching the phrenic nerve to avoid

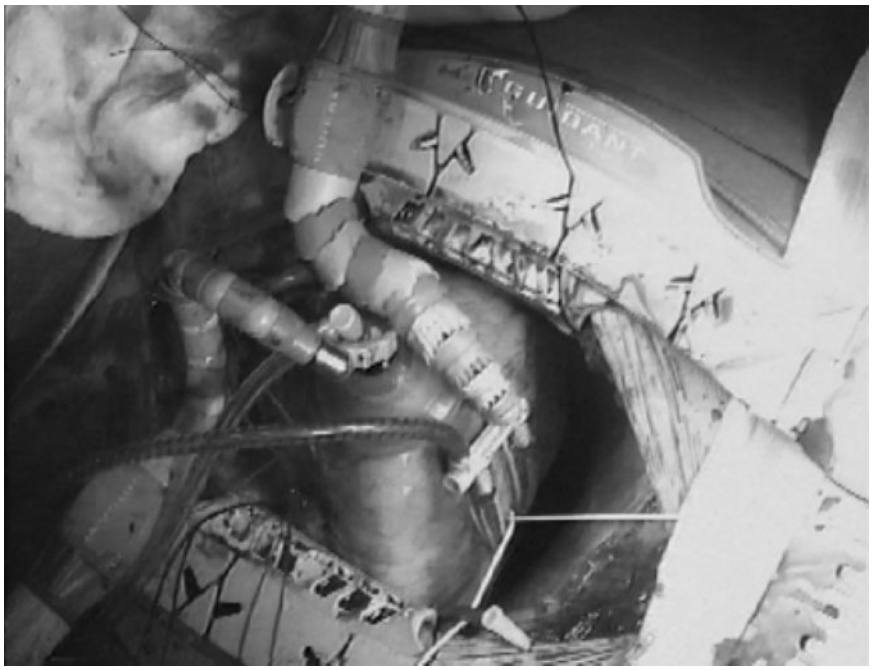


Figure 23-1. Custom off-pump sternotomy retractor. Note the suture holders and tracts for attachment of stabilizer and suction exposure device.

injury. Graft preparation is performed prior to manipulating the heart in order to reduce the amount of time spent with the heart in a nonanatomic position. All varieties of conduit used in conventional bypass grafting likewise can be used in beating-heart surgery.[21]

Patient Positioning

Standard positioning for OPCABG is to place the patient in a slight Trendelenburg position and also mildly rotated toward the operating surgeon. This position helps to maintain hemodynamic stability by augmenting cardiac output by increasing venous return to the heart. Additionally, rightward rotation enlists gravity to facilitate mobilization of the heart, thereby simplifying visualization of the coronary arteries of the lateral, posterior, and inferior walls. Extreme degrees of rotation may be necessary to obtain hemodynamically tolerable positions for some difficult anastomoses.

Target-Vessel Exposure and Stabilization

Optimal target-vessel exposure and three-dimensional stabilization are essential for successful off-pump bypass surgery. The most common technique used to manipulate the heart

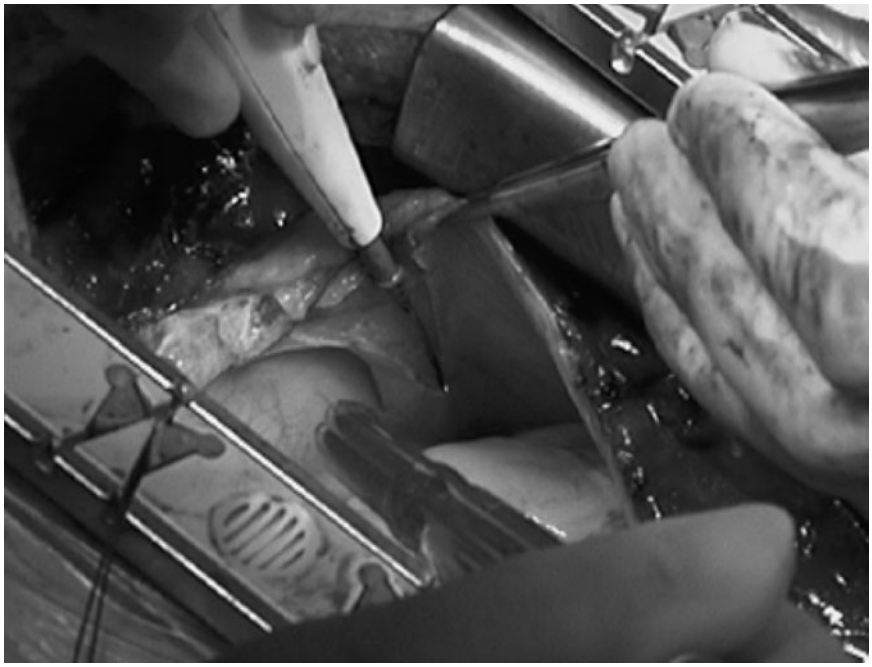


Figure 23-2. Extension of the pericardial incision along the right diaphragmatic reflection to create room for the right ventricle during displacement.

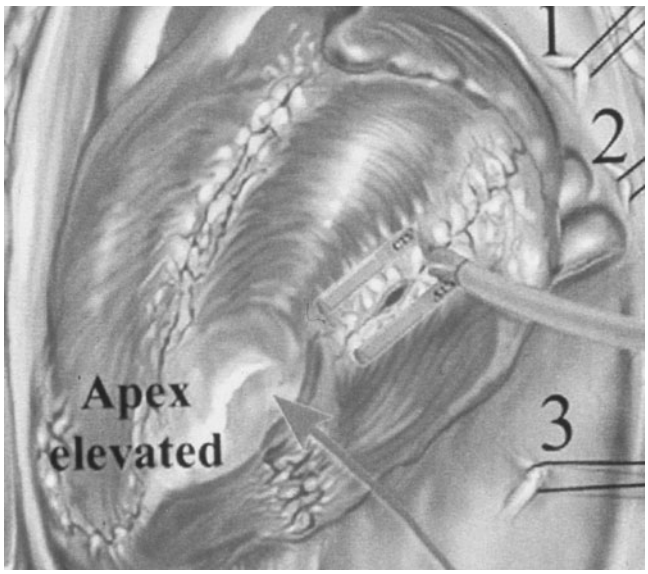


Figure 23-3. Placement of deep pericardial sutures for cardiac displacement during exposure of the posterior circulation.

and expose the coronary arteries is the use of deep pericardial sutures for cardiac distraction and exposure (Fig. 23-3) or, more commonly, apical suction devices. Apical suction devices allow distraction and manipulation of the heart by creating a vacuum-type seal to the epicardial surface (Fig. 23-4). These devices extend from reticulating arms that attach to the sternal retractor and allow the heart to be positioned for optimal vessel exposure. By applying suction and moving the apex of the heart toward the right sternum, the anterior descending, diagonal, and obtuse marginal vessels are presented. Suction applied to the acute margin of the heart with retraction toward the left shoulder exposes the distal right coronary artery and its branch vessels.

The advantage of these devices is that they maintain the normal geometry of the heart and avoid compression of the right ventricle. This improves hemodynamic stability when grafting difficult arteries, especially in patients with reduced ejection fractions, and allows the surgeon to be meticulous during construction of the anastomoses instead of hurried.

Stabilization of the target vessel for the anastomoses is obtained by using a two-armed suction stabilizer.[22] These stabilizers consist of pods of suction cups within the prongs of the stabilizer that immobilize the target area by creating a vacuum between the epicardial surface and the stabilizer arm (Fig. 23-5). This allows for construction of the anastomoses to take place in a motionless field, recreating the same visual image seen in an arrested heart.

Grafting Strategy

The sequence of graft construction is crucial to the success of the procedure (Table 23-4). In general, collateralized vessels should be grafted before collateralizing vessels. Additionally, a bloodless field is necessary to perform a precise distal anastomosis. Proximal control of the vessel selected for grafting is obtained with a soft Silastic tape mounted on a blunt needle (Quest Medical, Allen, TX) (see Fig. 23-5). This tape is placed circumferentially just proximal to the site of the anastomosis. Tension applied to the suture restricts blood flow by inflow occlusion and facilitates the anastomosis. A distal snare can be placed if backbleeding from collateralizing vessels is problematic. However, most surgeons avoid distal loops because of potential damage to the intima of the outflow portion

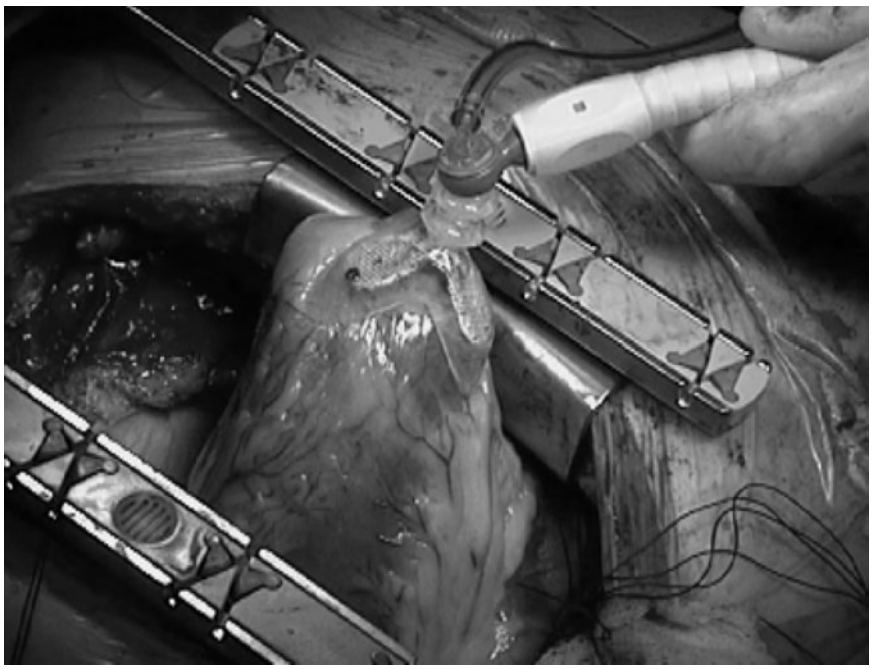


Figure 23-4. Attachment of an apical suction device to the epicardial surface to facilitate exposure of the posterior circulation without compression or distortion of the right ventricle.

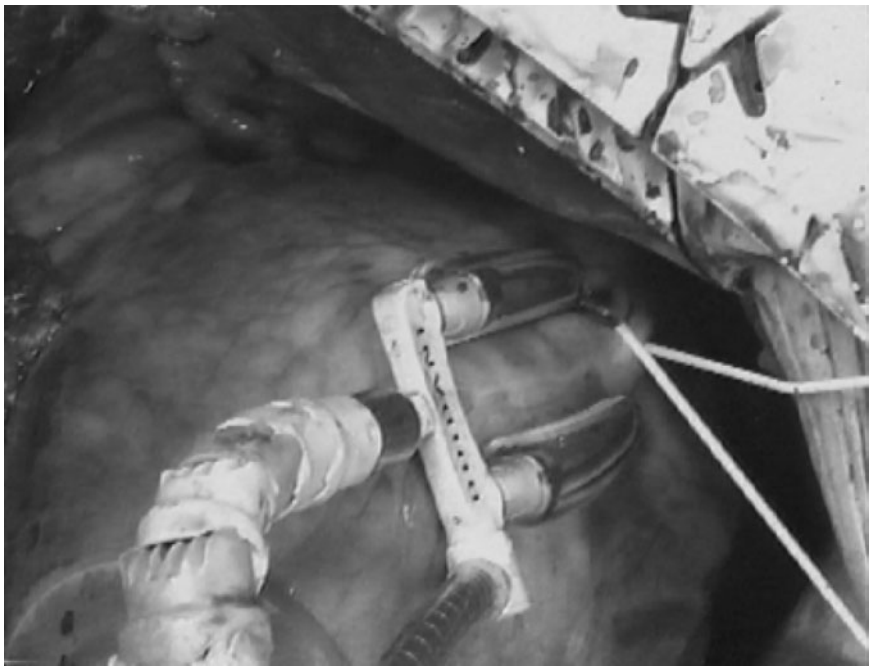


Figure 23-5. Suction stabilizer device placed adjacent to the obtuse marginal circumflex branch for local immobilization. Note the Silastic snare around the proximal vessel.

of the grafted artery.[23] A misted carbon dioxide blower also is employed to clear blood from the field and to open the arteriotomy during the anastomosis (Fig. 23-6). A heparinized, pH-balanced solution should be used in the blower.[24] The flow rate of carbon dioxide from the blower should be limited to the minimal level needed to perform the anastomosis because excessive gas jet velocity can injure the target coronary endothelium or the conduits.[24] Intracoronary shunts may be employed to provide distal vessel perfusion during the construction of the anastomosis if ischemia is a concern. Patience is rewarded when positioning the heart to expose the target vessels. Small changes in positioning can have profound hemodynamic effects. Avoidance of overreacting to pressure changes and close collaboration with the anesthesiologist generally allow the heart to be positioned with acceptable hemodynamics and exposure for the anastomoses.

Table 23–4.

Grafting Strategy for OPCAB—Easiest to Hardest

Collateralized vessels before collateralizing
Left anterior descending with LIMA
Proximal anastomosis before distals
Diagonal artery
Main right coronary artery
Posterior descending artery
Distal circumflex, second, third obtuse marginal vessels
Posterior lateral artery
Proximal obtuse marginal artery
Ramus intermedius artery

OPCAB = off-pump coronary artery bypass; LIMA = left internal mammary artery.

The left anterior descending (LAD) artery typically is the first anastomosis performed using the internal mammary artery. This vessel is the easiest to expose and access and allows revascularization of the septum and anterior wall prior to other provocative maneuvers. Exposure usually is obtained by placing a moist laparotomy pad behind the heart to bring the vessel to the midline. An exception to this strategy might occur if the LAD artery collateralizes a completely occluded right coronary artery (RCA), thereby providing the sole blood supply to the septum and anterior and inferior walls. In this circumstance, initial grafting of the RCA to limit the amount of myocardium made ischemic during occlusion of the LAD artery would be a reasonable approach. A stabilizer then is placed straddling the target area, and the vessel is exposed. An intramyocardially located LAD artery can be particularly challenging. This situation can be addressed successfully by careful attention to the details of exposure. The dissection is not initiated until the stabilizing foot is in place. A misted carbon dioxide blower is used to maintain a bloodless field. Exposure of the LAD artery begins distally, where it emerges onto the epicardial surface near the apex of the heart. Dissection then proceeds proximally by relocating the stabilizer until a segment of artery suitable for grafting is identified. Alternatively, one can locate the anterior descending artery by tracing a

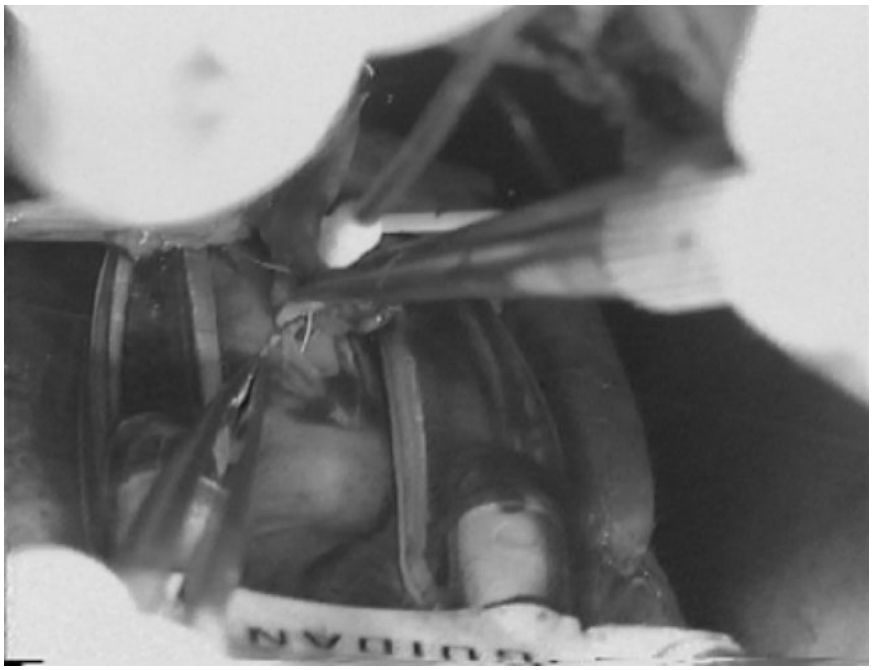


Figure 23-6. Creation of a motionless, bloodless operative field for a distal anastomosis to the left anterior descending coronary artery by use of a suction exposure device, a proximal Silastic snare, and a misted CO_2 blower (*arrow*).

diagonal artery back to its branch point with the LAD artery. Shed blood is scavenged using a Cell Saver (Haemonetics Corp, Braintree, MA). Intracoronary shunts can be used if the arteriotomy is centered over a septal perforator to reduce blood loss and aid in visualization or if preserved distal perfusion is required to maintain hemodynamic stability. After completion of the LAD anastomosis, a tacking suture is placed to secure the pedicle to the epicardium to eliminate torsion and tension on the anastomosis.

Grafting then is continued by performing the easier anastomoses prior to the more difficult ones. The diagonal arteries on the anterior surface of the heart are relatively straightforward to graft and can be exposed either by using a posteriorly placed laparotomy pad or by putting a suction device on the apex of the heart and moving the vessel to the midline. This position is well tolerated hemodynamically in most patients. Grafting then commences in standard fashion by placing the Silastic suture for inflow occlusion and stabilizing the target site.

The main RCA, while generally easy to demonstrate, can be problematic to graft. Problems occur most frequently when a large dominant, moderately stenotic RCA is to be bypassed proximal to the crux. Proximal occlusion causes ischemia to the atrioventricular node, thereby manifesting as bradycardia and heart block that can lead to ventricular distension and cardiovascular collapse. Helpful maneuvers, as noted previously, include placing atrial and ventricular pacing wires prior to making the arteriotomy, as well as placing an intracoronary shunt to preserve distal perfusion to the atrioventricular node. Trendelenburg positioning and suction distraction cephalad on the acute margin provide excellent exposure of the middle to distal RCA.

The posterior descending artery follows in degree of difficulty to expose and graft. A similar approach is used to that of exposing the distal RCA but with the angle of distraction oriented more toward the left shoulder of the patient. This positioning simplifies the anastomosis by placing the posterior descending artery on a level plane, thereby maintaining a consistent focal length for the surgeon. Bradyarrhythmias and hemodynamic problems are seen infrequently with occlusion of this vessel as opposed to the RCA.

The next most accessible vessels would include the middle to distal obtuse marginal branches and the posterior ventricular artery. The heart is positioned with the apex pointing toward the right midsternum using a suction device. The patient is placed in mild Trendelenburg position and also rotated to the right toward the surgeon to achieve adequate visualization of the target vessel. Release of right-sided pericardial stay sutures and/or opening of the pleura on the right side can help to avoid compression of the right ventricle and maintain acceptable hemodynamics during the anastomoses.

The ramus intermedius artery is challenging to expose owing to compression on the right ventricular outflow tract and pulmonary artery. The introduction of suction devices to position the heart has decreased the hemodynamic alterations associated with exposing this difficult part of the heart. The apex of the heart is retracted toward the patient's right hip, and the table is rotated toward the surgeon. This area of the heart tends to be tethered by the nearby pericardial reflection, reducing its mobility and making exposure difficult. Additionally, a large left atrial appendage can present visualization problems when grafting near the atrioventricular groove.

Rapid recovery of regional myocardial function prior to subsequent occlusion of other target arteries is essential for successful multivessel off-pump bypass grafting. Some

surgeons argue in favor of constructing the proximal anastomoses prior to performance of the distal anastomoses in order to provide immediate perfusion to the grafted artery and thereby decreasing regional ischemic impairment and promoting recovery of the grafted region. Other surgeons follow a sequence of grafting similar to an arrested-heart procedure, in that the distal anastomoses are completed prior to performing the proximal anastomoses. A third alternative is to provide perfusion-assisted blood flow down the grafts at the conclusion of the distal anastomoses.[25] This is done by attaching each completed vein graft to a perfusion pump that receives oxygenated blood from an aortic root cannula and delivers it to a standard multiperfusion catheter. This perfusion-assisted direct coronary artery bypass (PADCAB) technique (1) allows immediate blood flow to regionally ischemic myocardium, (2) provides the potential for including vasoactive substances or substrate-enhanced blood in the perfusate, and (3) can provide increased hemodynamic stability during multivessel grafting, particularly in patients with marginal hemodynamics or reduced left ventricular function. The saphenous vein grafts remain perfused until each is individually anastomosed to the ascending aorta. Excellent outcomes have been reported using each of the various techniques.[25]

The proximal anastomoses generally are constructed by using a partial occlusion clamp on a depressurized aorta. Many surgeons routinely use epiaortic scanning to survey the aorta for atheromatous disease that can escape even careful palpation.[26] Recent introduction of the HEARTSTRING Proximal Seal System (Guidant, Cupertino, CA) obviates the need for a partial occlusion clamp, thereby reducing the risk of atheromatous embolization or aortic dissection with placement of the clamp[27] (Fig. 23-7). This device creates a hemostatic seal with the inner surface of the ascending aorta that allows the creation of a hand-sewn angled take-off of the proximal vein graft.

On completion of the grafts, an assessment of the hemodynamic stability, the electrocardiogram (ECG), and the ventricular function of the patient is performed. Many surgeons do not routinely measure intraoperative graft flows but rely instead on ECG changes or wall motion abnormalities detected by transesophageal echo. Small drainage tubes (19 French Blake or Jackson-Pratt) are placed to facilitate immediate extubation. Pacing wires are placed according to the surgeon's discretion. The sternotomy is closed in standard fashion, and Cell Saver blood is returned to the patient.

PUMP-SUPPORTED BEATING-HEART SURGERY

The use of extracorporeal circulation for hemodynamic support while allowing the heart to beat remains a helpful tool in a surgeon's armamentarium. Patients taken to the operating suite who are unstable secondary to an acute myocardial infarction, severely reduced left ventricular ejection fraction, acute coronary artery closure or dissection, or other catheterization lab misadventure represent a difficult population for traditional beating-heart surgery. In these situations, standard positioning of the heart to achieve adequate exposure may worsen already marginal hemodynamics, leading to cardiovascular collapse and emergent conversion to cardiopulmonary bypass. Several studies have shown that emergent conversion to cardiopulmonary bypass after attempting off-pump grafting is associated with significantly higher rates of mortality, stroke, renal failure, respiratory failure, and postoperative bleeding.[20,28]

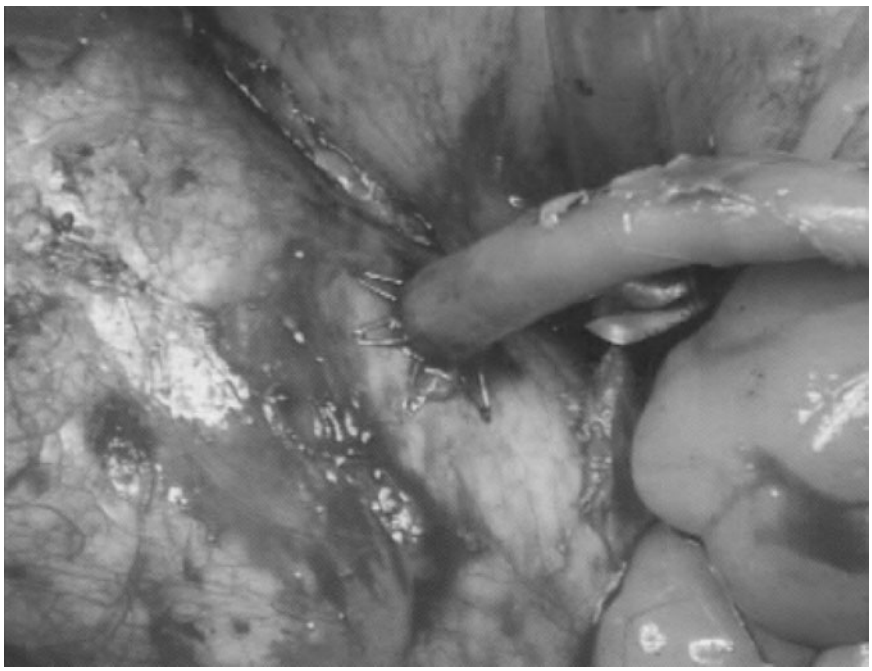


Figure 23-7. Aortosaphenous vein anastomosis performed in a "clampless" fashion with an anastomotic connector.

One approach is to initiate cardiopulmonary bypass with standard aortic and venous cannulas and to perform the grafts with the heart beating but supported.[29,30] The patients are moderately cooled during the procedure, and perfusion pressures are maintained in the 60– to 80–mm Hg range. Grafting then proceeds in similar fashion to off-pump beating-heart surgery. This technique not only supplies hemodynamic stability but also avoids the global myocardial ischemia seen with cardioplegic arrest. In one small study, the use of extracorporeal circulation and beating-heart grafting was associated with significant elevation of inflammatory markers such as interleukin 6 (IL-6), IL-8, IL-10, and tumor necrosis factor alpha (TNF-α).[31] The clinical significance of the elevation of these biochemical markers is yet to be determined; theoretically, however, they may be associated with increased capillary leak, myocardial injury, increased risk of bleeding, and a predisposition to wound infection. Aortic clamping and manipulation also can be avoided by using sealing-type devices such as the HEARTSTRING to perform the proximal anastomoses while on bypass.

THORACOTOMY FOR BEATING-HEART BYPASS GRAFTING

A thoracotomy incision has long been used to provide access to the heart for isolated valvular procedures, repair of atrial septal defects, and aortic arch and descending aortic aneurysm repair. Coronary reoperations also represent a patient cohort in which this technique has been used effectively.[32,33] Patients undergoing reoperative CABG owing to progression of native-vessel disease or attrition of previous bypass grafts have an increased operative mortality and morbidity compared with patients undergoing primary revascularization. Various strategies have evolved to minimize the risks of reoperative revascularization. These include avoiding repeat sternotomy, where the potential exists to injure patent grafts; reducing manipulation of the aorta or previous grafts to decrease the potential for embolization; and changes in approach to myocardial protection. Furthermore, a median sternotomy can be complicated by poor wound healing, sternal dehiscence, mediastinitis, and prolonged pain that may delay return to normal activities. In addition to reoperations, some surgical groups advocate primary multivessel CABG by thoracotomy as an alternative technique to standard off-pump bypass grafting by median sternotomy.

After induction of general anesthesia and insertion of a double-lumen endotracheal tube, patients either are placed in a right lateral decubitus position or are positioned such that the left side is elevated approximately 45 degrees. In reoperative patients, harvesting of the bypass conduit (e.g., radial artery or saphenous vein) occurs prior to positioning. The left internal mammary artery (LIMA) also can be used if not harvested previously. A left posterolateral thoracotomy incision is performed in the fourth or fifth intercostal space depending on the target vessel selected for revascularization. The left lung is collapsed, and the inferior pulmonary ligament is divided. This allows mobilization of the lung superiorly to the level of the inferior pulmonary vein. Patients with previous LIMA grafts generally have adhesions between the lung and the mammary bed that must be taken down in order to fully mobilize the lung and expose the pericardium. The pericardium is opened longitudinally posterior to the phrenic nerve. Lysis of existing adhesions and target-vessel identification then are performed. A Silastic suture is placed proximally around the target vessel to achieve vascular control. A stabilizer is positioned straddling the anastomotic area, and a misted CO_2 blower is used to keep the anastomotic site clear of blood and the edges of the artery separated. Senile grafts can be used as markers to identify the target vessels. The anastomosis is performed in a continuous fashion with a 7-0 Prolene suture. The proximal anastomosis then is performed by means of a side-biting clamp on the descending aorta or the left subclavian artery with a running 6-0 polypropylene. Proximal anastomotic connectors can facilitate the conduct of the operation and reduce the technical obstacles associated with operating deep within the chest. The graft then is positioned inferiorly to the hilum of the lung in a gentle curve if the inflow is the descending aorta or anterior to the hilum if the inflow is the subclavian artery (Fig. 23-8). Several reports describing the reoperative revascularization of the circumflex distribution using off-pump techniques via left thoracotomy have been published.[34,35] These series demonstrated no mortality, minimal morbidity, and symptomatic improvement from angina.

In patients undergoing primary revascularization via a thoracotomy, the internal mammary arteries are the conduits of choice. Both the right and left internal mammary arteries can be harvested for use either under direct vision or using robotically assisted techniques.[36,37] When the saphenous vein is used for conduit, the proximal vein graft anastomoses are performed prior to the distal anastomoses by means of a partial occluding clamp on the ascending aorta. The systemic blood pressure is maintained at 70 to 90 mm Hg using vasodilators during the proximal anastomoses. The distal anastomoses then are performed by using a suction device to position the heart and expose the target vessels. Stabilization of the target artery is achieved using standard suction-type stabilizers. A recent series reported excellent operative outcomes with an average of 2.9 grafts per patient and bypass grafts to all regions of the heart.[38] Patients with morbid obesity, ventricular hypertrophy with reduced ejection fraction, or a severely dilated cardiomyopathy that require grafts to the RCA circulation are poor candidates for this approach. Patients with reduced cardiac function and/or ventricular enlargement who require only revascularization to the LAD and circumflex distributions still can be grafted using this technique. Beating-heart bypass via thoracotomy provides a safe and effective alternative approach to median sternotomy for patients requiring limited redo CABG or even selected first-time procedures.

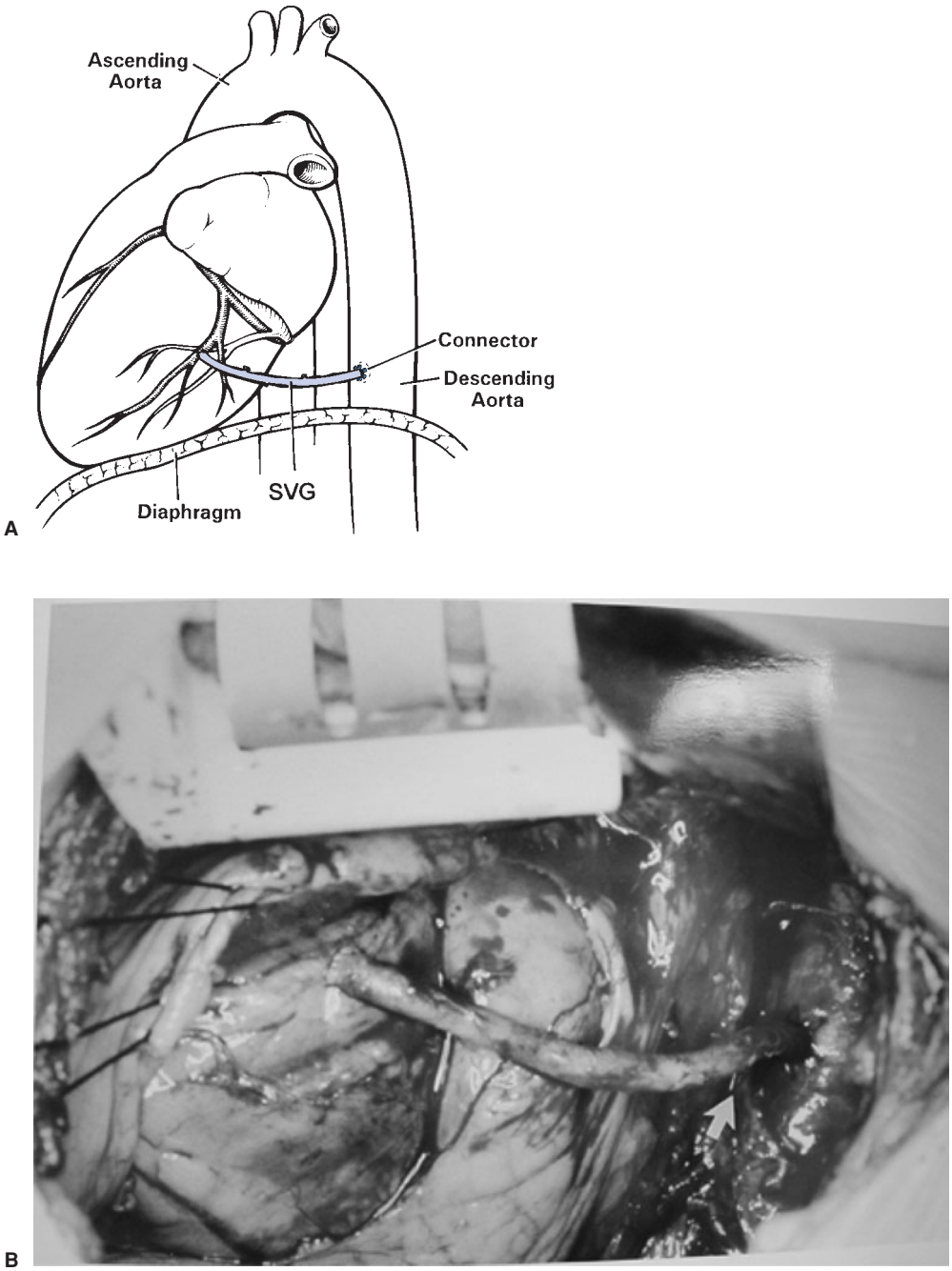


Figure 23-8. Saphenous vein graft (SVG) between descending aorta and an obtuse marginal branch of the circumflex coronary artery with a gentle curve beneath the inferior pulmonary vein.

RESULTS

Conventional CABG clearly has been demonstrated to prolong life and reduce symptoms. However, this comes at a price of significant risk, including mortality (2 to 5%), stroke (2%), transfusion (30 to 90%), atrial fibrillation (30%), and neurocognitive dysfunction (50 to 75%).[39–42] Although off-pump bypass surgery eliminates cardiopulmonary bypass and hypothermic cardiac arrest, manipulation of the ascending aorta by partial clamping is for the most part not eliminated. Whether elimination of bypass leads to superior outcomes is far from clear and may be somewhat mitigated by a small but real incidence of increased adverse outcomes associated with conversion from off-pump to on-pump bypass surgery.

Since the previous edition of this book, a large amount of new information has been published regarding the efficacy of OPCABG compared with conventional on-pump CABG. Even with data from the highest levels of evidenced-based medicine available, the question of the superiority of one surgical technique over the other has not been

answered clearly. Despite a significant number of randomized, controlled trials and seemingly almost as many meta-analyses of these trials, the issue is far from resolved. The debate continues to be a passionately argued one in the medical literature, at major meetings, and in the lay press. There have now been 37 randomized clinical trials published in 53 papers that have enrolled 3369 patients comparing OPCABG versus conventional CABG.[43–95] Three meta-analyses of not only these randomized trials but also major observational studies also have been published recently.[96–98] The American Heart Association has published a scientific statement, and the International Society for Minimally Invasive Cardiac Surgery (ISMICS) has published a consensus statement.[99,100]

Most of the early trials comparing OPCABG versus conventional CABG were nonrandomized comparisons of low-risk patients undergoing single- or double-vessel bypass with significant patient selection bias. More recently, nonrandomized comparisons of high-risk patients and randomized comparisons of mixed-risk patients have been published. Some trials focused on clinical endpoints, and some used surrogate endpoints such as inflammatory mediators and enzyme elevation. Because of the large number of patients required to adequately power important clinical outcomes such as death, stroke, and myocardial infarction, none of the randomized trials, even when analyzed by meta-analysis, are adequately powered to be able to define benefit. For these endpoints to be powered adequately to demonstrate a benefit in a randomized trial in the current clinical population would require approximately 85,000 patients to demonstrate a difference in death, 6000 patients to analyze any difference in stroke, and 12,000 patients to analyze any difference in myocardial infarction.[96] Thus, even though a large peer-reviewed published literature including randomized trials exists, all are underpowered to be able to adequately assess a potential benefit to off-pump techniques compared with on-pump surgery.

Operative Mortality

In randomized trials, there has been no difference in mortality at 30 days (Table 23-5). Pooled analyses of these randomized trials also has found no difference in 30-day mortality [odds ratio (OR) 1.02, 95% confidence interval (CI) 0.58–1.80, $p = .9$, $n = 3082$ patients in 29 randomized, controlled trials (RCTs)].[100] The pooled mortality risk was 1.2% for OPCABG and 1.0% for conventional CABG. Since the mortality in these studies is significantly lower than the Society of Thoracic Surgeons (STS) operative mortality in 2004 (2.4%), it is clear that these studies represent mostly low-risk patients. As mentioned earlier, to find a mortality difference of 0.2%, 85,000 patients would be required. Two meta-analyses of mixed-risk groups that included nonrandomized data did find that there was a reduced risk of mortality at 30 days with OPCABG of 36%. This analysis was in 39,647 patients in 43 combined studies. A second meta-analysis by Beattie found a 21% reduction in mortality in 159,845 patients in seven studies.[97]

Late Mortality

No difference has been found in mortality from 1 to 3 years in six randomized, controlled trials of 1135 patients. A meta-analysis of these trials also has found no difference in mortality at 1 to 3 years (OR 0.88, 95% CI 0.41–1.88, $p = .8$).[96]

Mortality in Patients Converted from Off-Pump to On-Pump CABG

Twenty randomized trials have reported conversion rates ranging from 0% to over 20% with an average rate of 8% of patients whose surgery was initiated off-pump.[96] There are five studies that quote a mortality specifically for converted patients ranging from 6 to 15%.[102–106] Criticisms of early OPCABG versus conventional CABG studies were that they were not analyzed on an intent-to-treat basis. Most studies now published report on an intent-to-treat basis, with converted patients being analyzed as off-pump patients. Suffice it to say that it has become clear that there is an increased incidence in mortality and morbidity when patients are converted *urgently* (i.e., owing to ventricular fibrillation or cardiopulmonary resuscitation) from off-pump to on-pump CABG. However, there does not appear to be an increased risk of complications in patients who are *electively* converted owing to an inability to access appropriate vessels.

Perioperative Morbidity

Most randomized trials have shown a significant reduction in the need for red blood cell transfusion, inotropic support, respiratory infections, and atrial fibrillation with OPCABG versus conventional CABG[98,107] (see Table 23-5). A meta-analysis of the randomized trials in mixed-risk populations shows a reduced incidence in the need for red blood cell transfusion (OR 0.43, 95% CI 0.29–0.65, $p < .0001$, $n = 2412$ patients in 17 RCTs), inotrope requirements (OR 0.48, 95% CI 0.32–0.73, $p < .0001$, $n = 1655$ in 16 RCTs), respiratory infection (OR 0.41, 95% CI 0.23–0.74, $p < .0001$, $n = 896$ patients in 7 RCTs), and atrial fibrillation (OR 0.58, 95% CI 0.44–077, $p = .0001$, $n = 2425$ patients in 17 RCTs).[100] No randomized trials have shown a significant reduction in stroke, myocardial infarction, acute renal failure, intra-aortic balloon pump (IABP) requirement, mediastinitis or wound infection, recurrence of angina, or need for reintervention within 30 days of OPCABG compared with conventional CABG.[97,98] Meta-analyses of these randomized trials also showed that OPCABG had a similar incidence of stroke, myocardial infarction, acute renal failure, IABP requirement, mediastinitis or wound infection, angina recurrence, and need for reintervention within 30 days. Similar results also were shown in these endpoints at 1 to 3 years. Retrospective studies and two meta-analyses of those retrospective studies have shown a reduced stroke risk of OPCABG versus conventional CABG.[97,98] The aforementioned studies also

Table 23–5.

Meta-Analysis of Randomized Trials in OPCABG (Level A)

Clinical Outcomes

Outcome	*n* (*N*)	OPCABG, %	Conventional CABG, %	OR (95% CI)	NNT (95% CI)	Heterogeneity		*P* for Overall Effect
						p Value	I^2	
Death, 30 days	3082 (29)	1.2	1.0	1.02 (0.58–1.80)	—	1.0	0	.9
Death, 1–2 years	1135 (6)	2.3	2.6	0.88 (0.41–1.88)	—	.9	0	.8
Atrial fibrillation, 30 days	2425 (17)	17.6	26.8	0.58 (0.44–0.77)	11 (8–17)	.07	36	<.0001
Transfused patients, 30 days	2412 (17)	28.4	42.5	0.43 (0.29–0.65)	7 (6–10)	<.0001	46	<.0001
Respiratory infections, 30 days	896 (7)	4.6	9.9	0.41 (0.23–0.74)	19 (12–52)	.3	21	<.0001
Inotropes, in hospital	1655 (16)	15.1	23.6	0.48 (0.32–0.73)	12 (8–21)	.04	43	<.0001
Cognitive dysfunction, 2–6 mo	393 (3)	20.3	31.8	0.56 (0.35–0.89)	10 (6–11)	.19	39	.01

Resource Untilization

Outcome	*N*	WMD (95% CI)	Heterogeneity		*P* for Overall Effect
			p Value	I^2	
Hospital LOS, days	1384 (17)	–1.0 days (–1.5 to –0.5)	<.0001	66	<.0001
ICU LOS, days	1266 (15)	–0.3 days (–0.6 to –0.1)	<.0001	78	.003
Ventilation time, hours	1425 (20)	–3.4 hrs (–5.1 to –1.7)	<.0001	97	<.0001

LOS = Length of stay; NNT = number needed to treat; WMD = weighted mean difference.

showed a 40% and 45% reduction in the risk of stroke. The same two studies also showed a significant reduction in myocardial infarction (OR 0.58, 95% CI 0.44–076, $p = .00009$, $n = 24{,}322$ patients in 26 studies), atrial fibrillation (OR 0.69, 95% CI 0.58–081, $p = .00001$, $n = 22{,}092$ patients in 28 studies), renal failure (OR 0.62, 95% CI 0.58–0.78, $p = .00003$, $n = 20{,}845$ patients in 17 studies), reoperation for bleeding (OR 0.54, 95% CI 0.44–0.67, $p < .0001$, $n = 33{,}000$ patients in 24 studies), wound infection (OR 0.155, 95% CI 0.37–0.83, $p = .004$, $n = 16{,}039$ patients in 17 studies), and need for reintervention (OR 3.63, CI 1.91–6.78, $p = .0001$, $n = 2823$ patients in 7 studies).[97,98]

Neurocognitive Outcomes

One of the early reasons for the introduction of OPCABG was to attempt to improve neurocognitive outcomes after coronary bypass surgery or to avoid "pump head." Whether any improvement has been achieved continues to remain controversial. Two randomized trials showed a significant reduction in early cognitive decline, whereas one randomized trial did not show any difference at 1 month.[68,86,94] There are also three randomized trials that show improved cognitive outcomes with OPCABG at 2 to 6 months and one that shows no difference.[95] Pooled analysis of these trials shows a 46% reduction in the number of patients with cognitive dysfunction with OPCABG.[68,72,86,95] Four randomized trials have looked at neurocognitive outcomes at 1 year and found no difference in OPCABG versus conventional CABG. A meta-analysis of these trials again shows no difference at 1 year.

Resource Utilization

Various studies have shown a significant reduction in the duration of ventilation, ICU stay, hospital stay, and in-hospital costs with OPCABG. These results have been confirmed in a meta-analysis of randomized trials.[96] The reduction appears to be due to a reduction in the ICU length of stay, hospital length of stay, and need for blood transfusion, and a lower incidence of postoperative complications.

High-Risk Patients

Advocates of off-pump surgery feel that the greatest benefit is in high-risk patients who are most likely to have complications. In addition, because of the higher incidence of complications in these patients, studies would be more likely to demonstrate a benefit if present. There have been no randomized trials of only high-risk patients. However, 42 nonrandomized trials of high-risk patients have been identified that do demonstrate a significant reduction in mortality with OPCABG (Table 23-6). Specific patient subgroups that appear to benefit in different studies include a Euroscore of greater than 5, left ventricular dysfunction, and the presence of atheromata in the ascending aorta.[100] No benefit has been found in patients specifically with older age, left main disease, diabetes, renal dysfunction, and chronic obstructive pulmonary disease. Morbidity appears to be less in a meta-analysis of high-risk patients in specific subgroups in nonrandomized trials. Specific endpoints that appeared to be reduced include stroke, myocardial infarction, atrial fibrillation, renal dysfunction, transfusion, inotrope requirements, need for IABP placement, and reoperation for bleeding (Tables 23-7 through 23-9). No significant difference has been found in postoperative wound infection or pulmonary complications. Specific patient risk subgroups that appear to have lower morbidity with OPCABG include those who have a Euroscore of greater than 5, a recent acute myocardial infarction, age over 75 years, or a history of stroke, atrial fibrillation, diabetes, renal failure, left ventricular dysfunction, left main disease, redo CABG, and chronic obstructive pulmonary disease.[62]

Completeness of Revascularization and Graft Patency

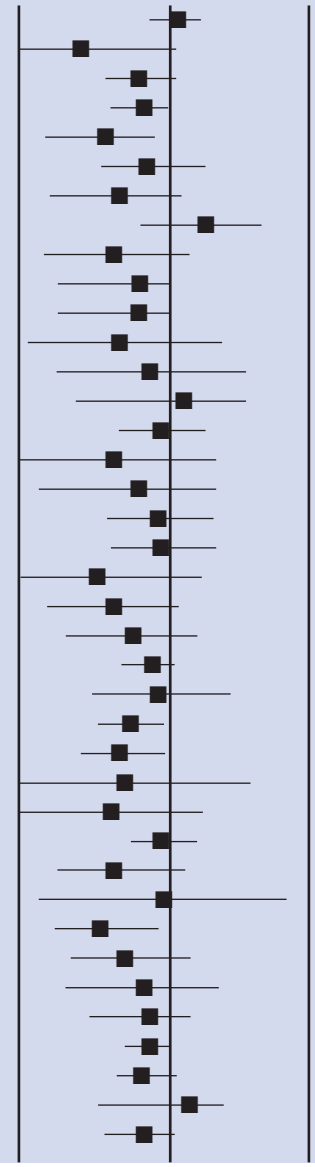
Specific concern has been raised as to whether potential benefits of OPCABG have come at a cost of less complete revascularization and lower graft patency compared with conventional CABG. These concerns specifically were raised by one highly publicized study by Khan.[66] Although that study had significant shortcomings, it did raise the profile of this issue. A meta-analysis of randomized trials has consistently shown a lower number of grafts per patient in off-pump versus on-pump CABG (2.6 versus 2.8, $p < .0001$).[100] Even analysis of later trials in which surgeon experience is greater still shows less complete revascularization performed off-pump versus on-pump (2.7 versus 2.9 grafts). It still has not been clarified whether this represents patient selection or incompleteness of revascularization. Completeness of revascularization has been reported only in randomized trials, and two studies have demonstrated a decrease in completeness of revascularization,[53,56] whereas five other trials have shown no difference.[54,66,69,76,79] Nonrandomized trials suggest that completeness of revascularization may be similar or decreased with OPCABG. Graft patency has been evaluated in four randomized trials from in-hospital to 1 year postoperatively. Puskas demonstrated no difference in graft patency at discharge,[79] whereas Khan showed a decreased graft patency in the off-pump group at 3 months.[66] Two studies showed no difference in graft patency at 1 year.[76,79] A meta-analysis at 1 year confirmed that there is no significant difference between off-pump and on-pump revascularization.[100]

Despite the extensive peer-reviewed literature, the potential benefits of off-pump versus on-pump surgery are still not clear. For the most important clinical endpoints, even pooled analysis of randomized trials is severely underpowered to demonstrate a difference. Nonrandomized trials are subject to selection bias and therefore do not reach the level of evidence of randomized trials. Most retrospective nonrandomized trials do appear to show some benefit in specific outcomes other than mortality, as well as a benefit in specific high-risk subgroups. There is consistently a lower number of grafts performed off-pump, but it is still not clear whether this represents less complete revascularization or

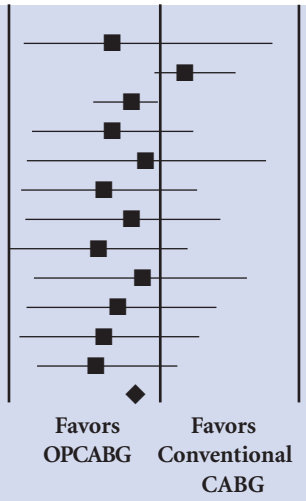
Table 23–6.

Death: OPCABG Versus Conventional CABG for High-Risk Groups

Risk Groups	Citation	Treated	Control	Effect	Lower	Upper	*p* Value
Diabetic	Abraham 01 (Diab)	10/254	34/973	1.13	.55	2.32	.74
Elderly	Al Ruzzeh 01 (age)	0/56	10/87	.07	.00	1.14	.01
LVD	al Ruzzeh 03 (LVD)	7/106	28/199	.43	.18	1.02	.05
Euroscore Parsonnet high	Al Ruzzh EJCS 03 (Euro5)	10/286	78/1112	.48	.25	.94	.03
Multirisks	Arom 00 (multirisk)	3/39	35/123	.21	.06	.72	.01
Renal dysfunction	Ascione 01 (RF)	3/51	16/202	.73	.20	2.60	.62
Multirisks	Ascione 02 (obese)	2/674	19/2170	.34	.08	1.45	.13
LVD	Ascione 03 (LVD)	5/74	5/176	2.48	.70	8.83	.15
Multirisks	Balkhy 03 (Female)	1/131	5/130	.19	.02	1.67	.10
Renal dysfunction	Beauford 04 (RF)	4/188	7/103	.30	.09	1.04	.05
Euroscore Parsonnet high	Belleghem (Euro6)	3/228	10/230	.29	.08	1.08	.05
Euroscore Parsonnet high	Boyd 00 (Parsonnet 15)	0/36	12/199	.21	.01	3.55	.23
Elderly	Boyd 99 (age 70)	0/30	1/60	.65	.03	16.44	.79
Multirisks	Carrier-03 (multirisk)	1/29	1/36	1.25	.07	20.89	.88
Multirisks	Chmbr-02 (multirisk)	7/332	30/1238	.87	.38	1.99	.74
COPD	Covino 01 (COPD)	0/21	1/16	.24	.01	6.30	.36
Redo emergent CABG	Czemy 04 (redo, age 75)	0/15	2/29	.35	.02	7.87	.50
Elderly	Demers 01 (age 70)	3/98	20/497	.75	.22	2.59	.65
Elderly	Deuse (multirisk)	4/53	6/66	.82	.22	3.06	.76
LVD	Deuse (multirisk)	0/29	4/31	.10	.01	2.01	.07
Multirisks	Deuse (multirisk)	1/60	6/52	.13	.02	1.12	.03
Left main disease	Dewey 01 (Left main)	1/100	34/723	.20	.03	1.51	.09
LVD	Dewey 03 (LVD)	6/204	45/713	.45	.19	1.07	.06
Atheromatous aorta	Gaudino 00 (calcified aorta)	2/82	4/129	.78	.14	4.36	.78
Euroscore Parsonnet high	Gaudino 04 (Euro>5)	7/197	12/109	.30	.11	.78	.01
LVD	Goldstein 03 (LVD)	3/100	12/110	.25	.07	.92	.03
COPD	Guler 01 (COPD)	0/40	0/18	.46	.01	23.92	.69
Elderly	Hoff 02 (Age 80)	0/59	8/169	.16	.01	2.81	.15
Redo emergent CABG	Karthik 02 (emergent)	15/417	16/411	.92	.45	1.89	.82
Redo emergent CABG	Kilo 01 (age 75, emergent)	2/44	7/44	.25	.05	1.29	.08
LVD	Kirali 02 (LVD)	0/26	0/25	.96	.02	50.35	.98
Redo emergent CABG	Locker 00 (emergent)	2/40	9/37	.16	.03	.82	.02
Elderly	Martinovic 03 (age 80)	3/68	9/74	.33	.09	1.29	.10
Euroscore Parsonnet high	McKay 01 (Parsonnet >9)	1/10	10/58	.53	.06	4.70	.57
Left main disease	Meharwal 01 (Left main)	2/174	21/991	.54	.12	2.31	.40
Multirisks	Meharwal 02 (multirisk)	35/1075	104/2312	.71	.48	1.06	.09
LVD	Meharwal HSF 02 (LVD)	14/355	58/959	.64	.35	1.16	.14
Redo emergent CABG	Ochi 03 (emergent)	3/25	4/47	1.47	.30	7.14	.63
Multirisks	Petro 00 (women)	7/304	63/1527	.55	.25	1.21	.13



Multirisks	Pompilo 99 (multrisk scor)	0/71	1/71	.33	.01	8.21	.48
Elderly	Ricci 00 (age 80)	10/97	9/172	2.08	.82	5.32	.12
Atheromatous aorta	Sharony 04 (calcified aorta)	16/245	28/245	.54	.29	1.03	.06
LVD	Shennib 02 (LVD)	1/31	5/46	.27	.03	2.46	.22
Renal dysfunction	Tashiro 02(ESRD)	0/15	0/11	.74	.01	40.24	.88
Elderly	Yokoy Baum 00 (age CVA COPD LVD redo RF)	0/28	3/58	.28	.01	5.57	.37
COPD	Yokoy Baum 00 (age CVA COPD LVD redo RF)	0/33	1/43	.42	.02	10.72	.59
Atheromatous aorta	Yokoy Baum 00 (age CVA COPD LVD redo RF)	0/25	3/36	.19	.01	3.80	.23
LVD	Yokoy Baum 00 (age CVA COPD LVD redo RF)	0/13	1/26	.63	.02	16.53	.78
Redo emergent CABG	Yokoy Baum 00 (age CVA COPD LVD redo RF)	0/28	3/76	.37	.02	7.36	.50
Renal dysfunction	Yokoy Baum 00 (age CVA COPD LVD redo RF)	0/27	3/46	.23	.01	4.55	.29
Diabetic	Zapolanski 03 (Diab)	1/142	41/1109	.18	.03	1.35	.06
Combined (51)		**195/6865**	**844/18124**	**.58**	**.49**	**.68**	**.00**

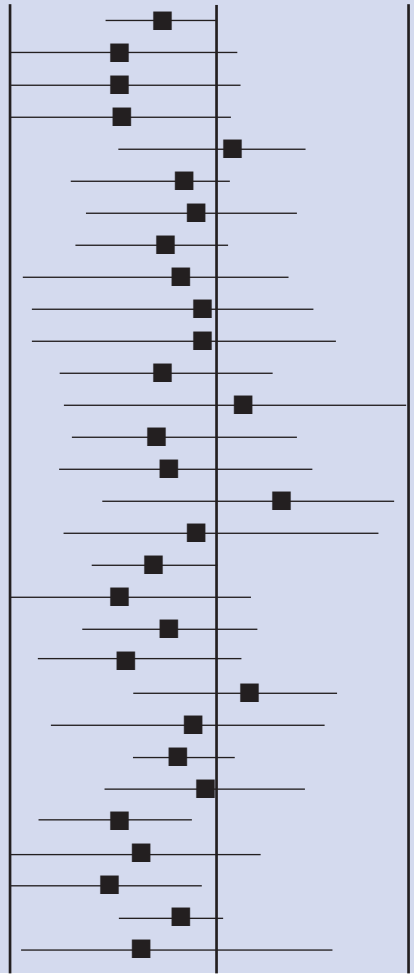


Diab = diabetic; ESRD = end-stage renal disease; LVD = left ventricular dysfunction.
Source: Used with permission from Puskas et al.[100]

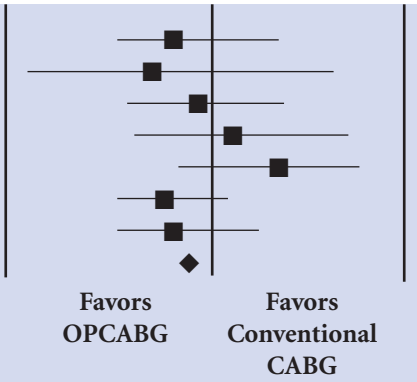
Table 23–7.

Stroke: OPCABG versus Conventional CABG in High-Risk Groups

Citation	Treated	Control	Effect	Lower	Upper	*p* Value
Abraham 01 (Diab)	3/254	35/973	.32	.10	1.05	.05
AlRuzzh EJCS 03 (Euro5)	0/286	14/1112	.13	.01	2.22	.10
Ascione 01 (RF)	0/51	14/202	.13	.01	2.15	.09
Ascione 02 (obese)	0/674	15/2170	.10	.01	1.73	.05
Ascione 03 (LVD)	1/74	2/176	1.19	.11	13.35	.89
Balkhy 03 (Female)	1/131	4/130	.24	.03	2.20	.17
Beauford 04 (RF)	1/188	1/103	.55	.03	8.81	.66
Belleghem (Euro6)	1/228	6/230	.16	.02	1.38	.06
Boyd 00 (Parsonnet 15)	0/36	10/199	.25	.01	4.31	.30
Boyd 99 (age 70)	0/30	4/90	.32	.02	6.03	.42
Carrier 03 (multirisk)	0/28	1/37	.43	.02	10.88	.60
Chmbr- 02 (multirisk)	1/332	15/1238	.25	.03	1.87	.14
Czerny 04 (redo, age 75)	0/15	0/29	1.90	.04	100.63	.75
Gaudino 00 (calcified aorta)	1/82	3/129	.52	.05	5.07	.57
Gaudino 04 (Euro>5)	1/197	1/109	.55	.03	8.90	.67
Goldstein 03 (LVD)	1/100	0/110	3.33	.13	82.72	.44
Hoff 02 (Age 80)	0/59	3/169	.40	.02	7.85	.53
Karthik 02 (emergent)	3/417	10/411	.29	.08	1.06	.05
Kilo 01 (age 75, emergent)	0/44	3/44	.13	.01	2.66	.12
Magee 01 (Diab)	3/346	31/2545	.71	.22	2.33	.57
Martinovic 03 (age 80)	1/68	6/74	.17	.02	1.44	.07
McKay 01 (Parsonet > 9)	1/10	3/58	2.04	.19	21.80	.55
Meharwal 01 (Left main)	0/174	3/991	.81	.04	15.74	.89
Meharwal 02 (multirisk)	6/1075	25/2312	.51	.21	1.26	.14
Meharwal HSF 02 (LVD)	1/355	3/959	.90	.09	8.68	.93
Petro 00 (Women)	1/304	53/1527	.09	.01	.67	.00
Pompilo 99 (multirisk scor)	0/71	3/71	.14	.01	2.70	.13
Ricci 00 (age 80)	0/97	16/172	.05	.00	.82	.00
Sharony 04 (calcified aorta)	13/245	23/245	.54	.27	1.09	.08
Shennib 02 (LVD)	0/31	2/46	.28	.01	6.09	.39



Yokoy Baum 00 (age CVA COPD LVD redo RF)	2 / 28	8/58	.48	.10	2.43	.37
Yokoy Baum 00 (age CVA COPD LVD redo RF)	0 / 33	1/43	.42	.02	10.72	.59
Yokoy Baum 00 (age CVA COPD LVD redo RF)	3 / 25	5/36	.85	.18	3.91	.83
Yokoy Baum 00 (age CVA COPD LVD redo RF)	2 / 13	3/26	1.39	.20	9.59	.73
Yokoy Baum 00 (age CVA COPD LVD redo RF)	2 / 28	2/76	2.85	.38	21.25	.29
Yokoy Baum 00 (age CVA COPD LVD redo RF)	4 / 27	14/46	.40	.12	1.36	.13
Zapolanski 03 (Diab)	2 / 142	32/1109	.48	.11	2.03	.31
Combined (37)	**55/6298**	**374/18055**	**.45**	**.34**	**.60**	**.00**

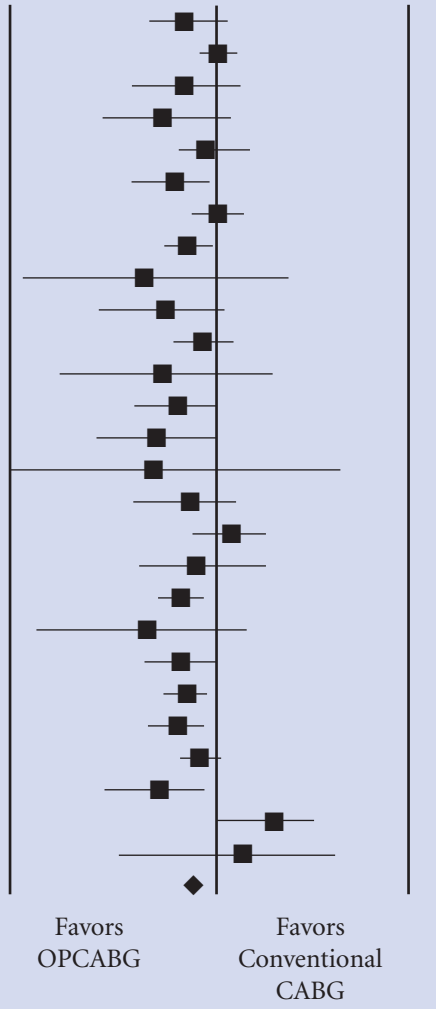


See Table 23.6 for abbreviations. CVA = cerebrovascular accident.
Source: Used with permission from Puskas et al.[100]

Table 23–8.

Atrial Fibrillation: OPCABG versus Conventional CABG in High-Risk Groups

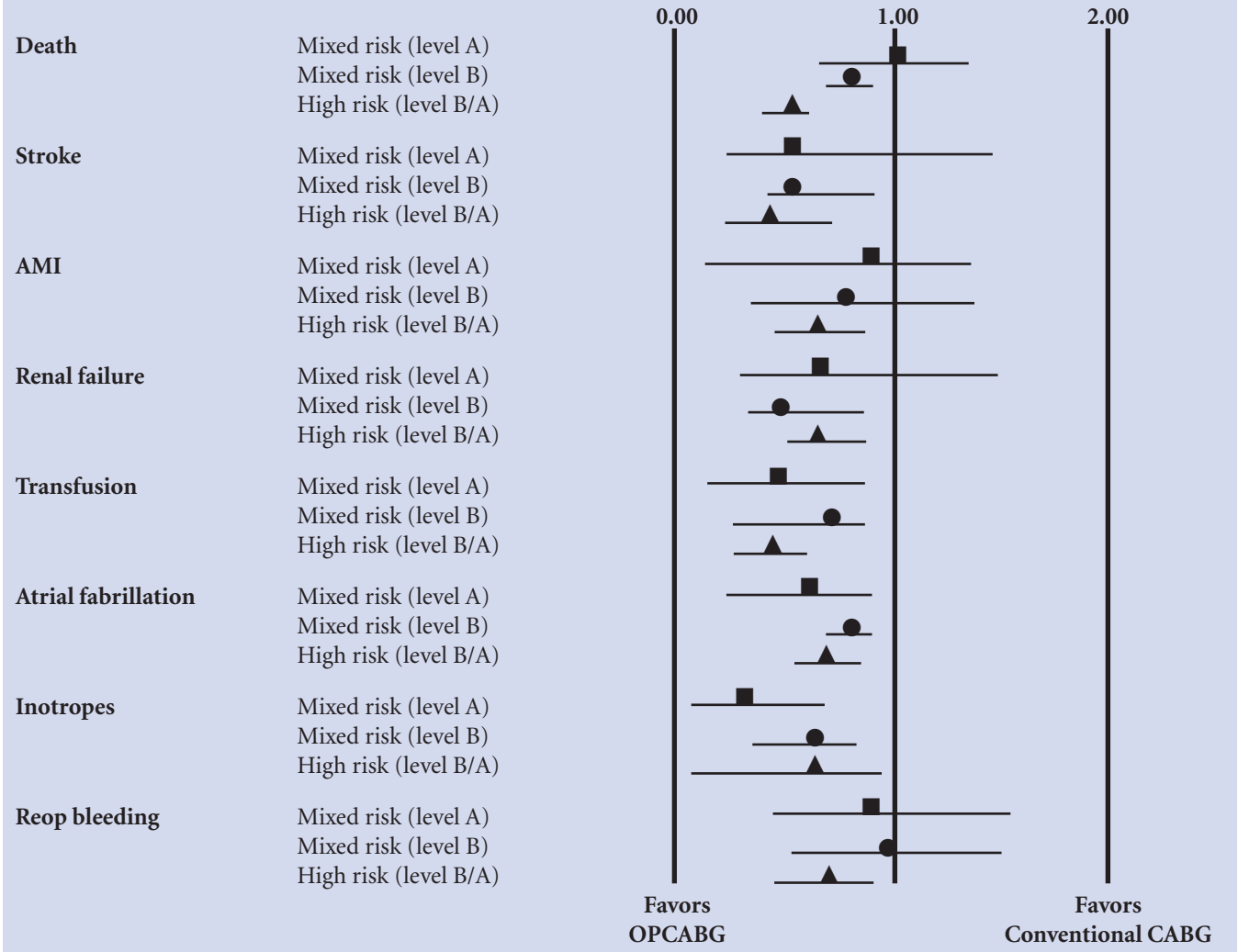
Citation	Treated	Control	Effect	Lower	Upper	*p* Value
Al Ruzzeh 01 (age)	16/56	35/84	.56	.27	1.16	.11
AIRuzzh Ejcs 03 (Euro5)	66/286	257/1112	1.00	.73	1.36	.99
Arom 00 (multirisk)	7/39	34/123	.57	.23	1.42	.23
Ascione 01 (RF)	7/51	52/202	.46	.19	1.08	.07
Ascione 03 (LVD)	15/74	37/176	.96	.49	1.87	.89
Balkhy 03 (Female)	25/131	40/130	.53	.30	.94	.03
Beauford 04 (RF)	58/188	32/103	.99	.59	1.66	.97
Belleghem (Euro6)	46/228	71/230	.57	.37	.87	.01
Boyd 00 (Parsonnet 15)	0/39	11/199	.21	.01	3.59	.23
Boyd 99 (age 70)	3/30	17/60	.28	.08	1.05	.05
Chmbr- 02 (multirisk)	36/332	158/1238	.83	.57	1.22	.35
Czerny 04 (redo, age 75)	2/15	10/29	.29	.05	1.56	.14
Demers 01 (age 70)	41/98	268/497	.61	.40	.95	.03
Goldstein 03 (LVD)	20/100	35/110	.54	.28	1.01	.05
Guler 01 (COPD)	0/40	0/18	.46	.01	23.92	.69
Hoff 02 (age 80)	14/59	52/169	.70	.35	1.39	.30
Karthik 02 (emergent)	110/417	97/411	1.16	.85	1.59	.36
Kilo 01 (age 75, emergent)	14/44	16/44	.82	.34	1.97	.65
Magee 01 (Diab)	55/346	592/2545	.62	.46	.84	.00
McKay 01 (Parsonet > 9)	1/10	5/15	.22	.02	2.28	.18
Meharwal 01 (Left main)	17/174	157/991	.58	.34	.98	.04
Maharwal 02 (multirisk)	154/1075	455/2312	.68	.56	.83	.00
Meharwal HSF 02 (LVD)	35/355	152/959	.58	.39	.86	.01
Petro 00 (women)	79/304	473/1527	.78	.59	1.03	.08
Pompilo 99 (multirisk scor)	10/71	22/71	.37	.16	.84	.02
Shennib 02 (LVD)	9/31	5/46	3.35	1.00	11.25	.04
Tashiro 02 (ESRD)	2/15	1/11	1.54	.12	19.47	.74
Combined (27)	**842/4608**	**3084/13412**	**.71**	**.62**	**.81**	**.00**



See Table 23.6 for abbreviations.
Source: Used with permission from Puskas et al.[100]

Table 23–9.

Comparison of Pooled Outcomes for Mixed-Risk and High-Risk Patients



Note: ***Mixed-risk patients (level A)*** *= Cheng 2004 (37 randomized trials; 3369 patients);* ***mixed-risk patients (level B)*** *= Beattie 2004 (13 nonrandomized trials; 198,204 patients) or Reston 2003 (53 trials; 46,621 patients);* ***high-risk patients (level B/A)*** *= ISMICS Consensus Meta-Analysis 2004 (42 nonrandomized trials and 3 randomized trials; 26,349 patients).*
Used with permission from Puskas et al.[100]

patient selection. For the goal of OPCABG in seeking to improve patient outcomes by avoiding side effects attributable to cardiopulmonary bypass, there does appear to be some reduction in morbidity. The following conclusions were reached in the ISMICS consensus statement:

- OPCABG should be considered a safe alternative to conventional CABG with respect to mortality in patients undergoing surgical myocardial revascularization. With the appropriate use of modern stabilizers and heart positioning devices and adequate surgeon experience, similar completeness of revascularization and graft patency can be achieved with OPCABG.
- OPCABG can be recommended to reduce perioperative morbidity. It also can be recommended to minimize midterm neurocognitive dysfunction, although no long-term benefit has been demonstrated.
- OPCABG should be considered equivalent to conventional CABG for quality of life. There does appear to be a decrease in resource utilization with decreased duration of ventilation, ICU, and hospital stay with off-pump surgery.
- OPCABG should be considered specifically in high-risk patients undergoing surgical revascularization and in patients with specifically identified risk factors to reduce perioperative mortality, morbidity, and resource utilization.

The percentage of patients undergoing OPCABG continues to remain static at 20 to 25%. Advocates continue to feel

strongly that significant benefit is afforded patients. Other practitioners feel just as strongly about conventional CABG. The strongest evidence of benefit appears to be in patients at highest risk for complications. The data forthcoming in the foreseeable future are unlikely to shed further light on the extensive body of literature that has accumulated over the past decade.

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CHAPTER 24

Myocardial Revascularization with Carotid Artery Disease

Cary W. Akins • Richard P. Cambria

Next to operative mortality, permanent stroke is the most dreaded complication of myocardial revascularization not only because of the devastating consequences to the patient but also because of the increased cost of hospitalization and posthospital care. Perioperative stroke following coronary bypass grafting (CBG) is of increasing concern because the average age of coronary bypass patients continues to rise and with it the risk of stroke. This chapter will investigate the relationship of carotid artery disease to perioperative neurologic complications following myocardial revascularization and evaluate treatment options for dealing with severe concomitant carotid and coronary artery disease (CAD).

PERIOPERATIVE STROKE

Incidence of Perioperative Stroke

The risk of stroke coincident with CBG is well defined. In 1986, Gardner and colleagues[1] found the risk of stroke to be a direct function of patient age. Patients younger than 45 years of age had a stroke rate of 0.2%, which rose to 3.0% for patients in their 60s and to 8.0% for patients older than age 75. Other risk factors associated with stroke were preexisting cerebrovascular disease, ascending aortic atherosclerosis, long cardiopulmonary bypass time, and perioperative hypotension.

Tuman and colleagues[2] in 1992 investigated the effect of age on cardiac performance and neurologic injury in coronary bypass patients. Whereas the rates of low cardiac output and myocardial infarction (MI) were constant as patient age increased, the incidence of neurologic damage rose exponentially after age 65. The stroke rate rose from 0.9% for patients younger than 65 years to 8.9% for patients older than age 75.

To place the problem of the increasing age of coronary bypass patients into a more contemporary context, at our institution the mean age of coronary artery bypass (CAB) patients rose from 56 years in 1980 to over 68 years in 2001. In addition, in 1980 only 6% of patients were age 70 or older, whereas by 2001 over 45% were age 70 or older, and 13% were age 80 or older.

In 1995, John and colleagues[3] reported a stroke rate of 1.4% for 19,224 coronary bypass patients from the New York State Cardiac Surgical Database. Multivariable predictors of stroke included aortic calcification, renal failure, prior stroke, smoking, carotid artery disease, age, peripheral vascular disease, and diabetes. In their review of 10,860 patients having primary myocardial revascularization, Puskas and colleagues[4] noted that stroke occurred in 2.2%. Multivariable predictors of stroke were age, previous transient ischemic attack, and carotid bruits.

Cost of Perioperative Stroke

Puskas and colleagues[4] also found that perioperative stroke was associated with significantly more in-hospital morbidity, longer length of stay, and almost twice the hospital cost. Patients who suffered a perioperative stroke had a 23% hospital mortality rate. Roach and colleagues[5] noted a 21% mortality rate for patients suffering a perioperative stroke following coronary artery bypass grafting (CABG) with a mean hospital stay of 25 days among survivors.

Causes of Perioperative Stroke

Possible causes of perioperative neurologic injury are listed in Table 24-1. The most common cause of perioperative stroke is atherosclerotic or thrombotic emboli from the heart or major vessels. Intracardiac emboli can arise from mural thrombus secondary to MI, left atrial thrombus associated with valvular disease or atrial fibrillation, or suture lines in the aorta or left side of the heart. Catheters in the left side of the heart also can be a source of perioperative emboli. Less

Table 24–1.

Potential Causes of Perioperative Neurologic Injury During Coronary Artery Bypass Grafting

Vascular occlusion, usually embolic
Heart
Aorta
Innominate, carotid, or vertebral arteries
Low-flow phenomenon
Insufficient perfusion pressure on cardiopulmonary bypass
Poor collateral circulation
Vascular spasm
Intracranial hemorrhage

commonly, entrapped air may cause neurologic events, although rarely focal deficits.

The aorta is also a possible source of emboli. Cannulation of the ascending aorta for bypass, aortic occlusion clamps, and intra-aortic cardioplegia delivery devices may dislodge existing atherosclerotic material from the aorta. Wareing and colleagues[6] found aortic atherosclerosis to be a risk factor for perioperative stroke. Intraoperative echocardiography of the ascending aorta to identify atherosclerosis and the subsequent alteration of operative techniques to address identified problems improved the stroke risk in their patients.

Embolism from atherosclerotic carotid bifurcation disease is a well-defined cause of perioperative neurologic injury. Carotid plaque morphology has an important impact on the stroke risk of patients with carotid stenosis. A companion study to the North American Symptomatic Carotid Endarterectomy Trial found that plaque ulceration was a significant incremental risk factor for stroke across all degrees of carotid stenosis.[7]

Many studies list flow-limiting carotid stenosis as a risk factor for perioperative stroke, but whether the carotid lesion is an etiologic factor or only a nonspecific marker of overall risk is unclear.[1,8–10] The Buffalo Cardiac Cerebral Study Group found that while carotid stenosis predicted increased risk of perioperative stroke and death, most strokes occurred over 24 hours after the myocardial revascularization, and the anatomic distribution of the strokes did not correlate well with the site of the carotid lesion.[10,11]

Neurologic injury can result from inadequate blood flow on cardiopulmonary bypass. Adequate perfusion pressure on bypass has been verified by Schwartz and colleagues,[12] who found that cerebral blood flow depends on arterial perfusion pressures, not on cardiopulmonary bypass flow rates. Low cerebral blood flow occurred with perfusion pressures of less than 60 mm Hg and was not influenced by the pump flow rate. Adequate perfusion pressure is very important in the presence of carotid stenosis, particularly with internal carotid occlusion.[8] When there is occlusion of carotid or intracerebral arteries, brain blood flow depends on collateral circulation, which, in turn, depends on perfusion pressure. Whether carotid or intracerebral vascular spasm can contribute to neurologic injury is unknown.

Finally, intracranial hemorrhage can lead to neurologic injury following cardiopulmonary bypass, but the fact that this is truly rare is surprising, given that patients are fully anticoagulated for cardiopulmonary bypass. In our institution, where computed tomographic (CT) scanning is routine to evaluate suspected perioperative stroke to guide the use of heparin, the finding of primary intracerebral bleeding is extraordinarily uncommon.

Of all the potential causes of perioperative neurologic injury listed in Table 24-1, carotid stenosis is the one situation about which the surgeon routinely can take action to remove the pathology. Because carotid stenosis is a significant risk factor for perioperative stroke, the need to define carotid disease prior to coronary artery grafting becomes obvious. The logical extension that surgical correction of carotid stenosis can decrease the risk of stroke has been the basis of our approach, and that of others, for many years. While level I evidence to support this approach does not exist, the safety of the combined operative approach has been verified, as will be discussed.

Relationship of Carotid Stenosis to Perioperative Stroke

Early studies relating the presence of carotid stenosis to perioperative stroke used auscultatory evidence of carotid disease as a surrogate for carotid stenosis. In 1988, Reed and colleagues[13] from our institution documented a 3.9-fold increase in the odds ratio for stroke in the presence of a carotid bruit.

Yet carotid bruits are reliable indicators of neither the presence nor degree of carotid stenosis. Sauve and colleagues[14] found poor correlation between carotid bruits and the degree of carotid stenosis. Indeed, as carotid lesions progress to high degrees of stenosis, carotid bruits may become inaudible. Despite these limitations, auscultation for carotid bruits remains a common mode of detecting carotid stenosis, particularly in asymptomatic patients.

Currently, Doppler ultrasound–based noninvasive studies are the initially applied and often definitive (and sufficient) diagnostic testing modality for carotid stenosis. While quality control is essential with noninvasive testing, verification of its accuracy has been demonstrated many times.[15,16]

Brener and colleagues[8] studied 4047 cardiac surgical patients and found a 9.2% rate of stroke or transient ischemic attack in patients with asymptomatic carotid stenosis, significantly greater than the 1.3% rate in patients with no carotid stenosis.

Faggioli and colleagues[17] in 1990 reported that routine carotid noninvasive testing in CAB patients with no ischemic

neurologic symptoms yielded an odds ratio for stroke of 9.9 with greater than 75% carotid stenosis. In patients over age 60 with greater than 75% carotid stenosis, the stroke rate was 15 versus 0.6% for patients of the same age with no carotid disease. Perioperative strokes occurred in 4 (14.3%) of 28 patients who had greater than 75% carotid stenosis who did not have concomitant carotid endarterectomy compared with no strokes in the 19 patients with greater than 75% carotid stenosis who had a prophylactic carotid endarterectomy with their CABG.

In 1992, Berens and colleagues,[18] using routine carotid duplex scanning for cardiac surgical patients 65 years of age or older, found that the risk of stroke was 2.5% for carotid stenoses greater than 50%, 7.6% for carotid stenoses greater than 50%, 10.9% for carotid stenoses greater than 80%, and 10.9% for unilateral carotid artery occlusion.

Thus, adequate evidence exists that significant carotid artery stenosis is an important incremental risk factor for the development of perioperative neurologic injury following CABG. In addition, the study by Faggioli and colleagues[17] suggests that carotid endarterectomy performed with CABG yields a lower stroke rate.

Mechanism of Perioperative Stroke with Carotid Stenosis

How carotid stenoses cause perioperative strokes is not well understood, especially since patients are fully anticoagulated on cardiopulmonary bypass. Perioperative strokes may result from emboli from the carotid plaque possibly due to dynamic plaque events. Loss of pulsatile perfusion or an inadequate perfusion pressure on bypass may lead to diminished flow distal to a significant stenosis, resulting in a watershed stroke. However, Reed and colleagues[13] and Ricotta and colleagues[10] found that over one-half of strokes occur after the immediate postoperative period. Such delayed strokes in patients with uncorrected carotid stenoses may be related to the prothrombotic milieu that occurs in the early days after cardiopulmonary bypass, potentially causing destabilization of a previously asymptomatic carotid lesion.

Relationship of Uncorrected Carotid Stenosis to Late Stroke

In 1985, Barnes and colleagues[19] assessed the late risk of untreated asymptomatic carotid stenosis in 65 patients who had cardiovascular operations, of whom 40 had CABG. At mean follow-up of only 22 months, 10% of coronary bypass patients had died, and 17.5% had suffered a stroke. Noninvasive testing revealed progression of the carotid artery disease in one-half the patients within 4 years. Contemporary randomized trials of surgery versus medical therapy for significant carotid stenosis have defined the late risk of carotid-related stroke in medically treated patients. In the landmark Asymptomatic Carotid Surgery Trial, actuarial risk of stroke at 5 years was 12% in medically treated patients.[20]

CAROTID STENOSIS IN CORONARY ARTERY BYPASS PATIENTS

Incidence of Carotid Stenosis in Coronary Artery Bypass Patients

In 1977, Mehigan and colleagues,[21] using noninvasive testing in 874 patients prior to coronary artery grafting, found a 6% incidence of significant extracranial cerebrovascular disease. Ivey and colleagues[22] reported that routine ultrasonic duplex scanning for a history of neurologic events or cervical bruits in 1035 patients having isolated CABG revealed significant carotid artery stenosis in 86 patients (8.3%). Faggioli and colleagues[17] evaluated 539 neurologically asymptomatic CAB patients using noninvasive methods and found that 8.7% had a carotid stenosis greater than 75%. The rate rose from 3.8% for patients younger than age 60 to 11.3% for patients over age 60. Berens and colleagues,[18] using routine carotid artery scanning in 1087 candidates for cardiac surgery who were 65 years of age or older (91% with coronary disease), found that 186 (17.0%) had a greater than 50% carotid stenosis and that 65 (5.9%) had a greater than 80% carotid stenosis. Predictors of carotid artery disease were female gender, peripheral vascular disease, history of transient ischemic attacks (TIAs) or stroke, smoking history, and left main CAD. D'Agostino and colleagues,[23] using noninvasive carotid artery testing in 1279 CABG candidates, found that 262 (20.5%) had greater than 50% stenosis in at least one carotid artery and that 23 (1.8%) had bilateral stenoses greater than 80%. Significant multivariable predictors of carotid artery disease were age, diabetes, female sex, left main CAD, prior stroke, peripheral vascular disease, and smoking.

Diagnosis of Carotid Artery Disease

Physical examination

Palpation of a carotid artery provides little information about carotid stenosis, except for the correlation of a weak common carotid pulse with a very proximal flow-limiting stenosis, and theoretically can dislodge thrombus or embolic debris. As noted earlier, auscultation of carotid bruits cannot reveal the degree of carotid stenosis.

Essentials of noninvasive testing

Ultrasound-based Doppler interrogation for carotid stenosis exploits the Doppler effect; namely, the reflected or altered frequency of an ultrasound wave is shifted in proportion to the velocities of the sampled, flowing blood, which are increased in regions of significant arterial stenosis.

Current carotid noninvasive studies use several modalities combined into what is called *triplex imaging*. These include B-mode imaging to localize the bifurcation and characterize plaque morphology. Sophisticated high-resolution scanning is available for detailed plaque characterization, but this is largely an investigational tool and not a component of routine testing. Pulsed, ranged-gated Doppler is used to interrogate the common, internal, and external carotid arteries and establish the direction of vertebral artery flow in its cervical portion. Vertebral artery origins generally are obscured by bony structures. Doppler interrogation produces two data sets—first is Doppler-shifted flow velocities in regions of interest, and second is spectral analysis of turbulent flow, which lends a qualitative determination of stenosis severity. Doppler samples must be obtained in the tightest portion of the stenosis for accuracy.

Derived Doppler velocities include peak systolic velocity (PSV), end-diastolic velocity (EDV), and the ratio between the PSV in the internal carotid artery and in the proximal common carotid artery (ICA/CCA ratio). The derived ratio corrects for baseline variations in hemodynamics, such as cardiac output and increased overall flows, that might be noted in contralateral internal carotid occlusion. PSV is the single most important criterion, followed by the ICA/CCA ratio. EDV is helpful in discriminating severe versus "very severe" lesions. An ICA/CCA ratio of more than 4.0 equates to a greater than 70% diameter stenosis, the general threshold for a flow-reducing lesion at basal conditions according to the physics of critical arterial stenosis.

Supplementing direct Doppler interrogation are a number of indirect testing methods that can add additional information concerning the hemodynamic significance of the lesion and/or the status of intracranial collateral blood flow. Periorbital directional Doppler insonation of ophthalmic arteries and transcranial Doppler (TCD) are the principal indirect testing modalities; neither is applied routinely. Selective use, in particular of TCD, can provide helpful information on such variables as tandem lesions in the carotid siphon or middle cerebral stem, direction and adequacy of collateral flow through the circle of Willis, and intraprocedural monitoring.

Some general comments about the efficacy of ultrasound-based carotid noninvasive tests are in order because many vascular surgeons proceed to carotid endarterectomy based solely on these preoperative studies.[16] Surgeons must be familiar with the specifics of noninvasive diagnostic criteria, and laboratories must have quality-control documentation of accuracy. Thorough knowledge of the translation of ultrasound-derived data to corresponding degrees of internal carotid artery stenosis is necessary. This is not a trivial consideration because the original Doppler velocity diagnostic criteria considered stenosis measurements at the carotid bulb (E method), whereas randomized trial data consider stenosis percentage referenced to the diameter of the normal distal internal carotid artery (N method).[24] While complete coverage of these important diagnostic caveats is beyond the scope of this chapter, comprehensive reviews are available.[25]

Indications for noninvasive testing

Current indications for screening patients for carotid artery disease prior to surgical myocardial revascularization include

1. An audible bruit in the neck
2. History of a prior stroke
3. History of transient ischemic attacks
4. Patients with severe peripheral vascular disease
5. Patients with a prior carotid endarterectomy
6. Elderly patients

All of these indications are self-explanatory except the last. Because the incidence of carotid stenosis rises dramatically in patients over age 65, there must be an age at which it becomes cost-effective to screen all patients for carotid disease. However, that age limit has not yet been determined. One would have to demonstrate the cost advantage of routine carotid endarterectomy versus that of strokes related to uncorrected carotid stenoses.

Role of carotid angiographic modalities

CATHETER-BASED CAROTID ANGIOGRAPHY: At our institution until the mid-1990s, symptomatic patients with an audible bruit or asymptomatic patients with a noninvasive test suggesting severe carotid stenosis had catheter-based carotid angiography. While catheter-based carotid angiography yields excellent detailed images of the carotid and intracranial vessels, angiography is expensive, requires potentially nephrotoxic contrast material, and is not without risks, including arterial dissection and stroke. Cholesterol embolization owing to catheter manipulation in a diseased aorta can cause emboli to other vascular distributions, especially renal and/or other visceral arteries. (Indeed, in the Asymptomatic Carotid Atherosclerosis Study, one-half of the 2.3% stroke risk with carotid endarterectomy was referable to mandated angiography.[26]) For these reasons, conventional carotid angiography had all but vanished from the practice of many vascular surgeons by the year 2000.[27] Ironically, current enthusiasm for carotid stenting has resurrected carotid angiography as a diagnostic and therapeutic tool.

MAGNETIC RESONANCE ANGIOGRAPHY: Great enthusiasm accompanied the introduction of magnetic resonance angiography (MRA) in the early 1990s to define carotid lesions because, compared with catheter-based angiography, it was noninvasive, lacked nephrotoxicity, and when used with diffusion-weighted brain imaging, yielded an extremely accurate map of the intracranial circulation. However, its limitations soon became obvious. These relate to the nature of the magnetic resonance vascular imaging, which relies on reflected magnetic pulses of flowing blood cells that vary as a function of flow turbulence. Since turbulent flow is characteristic of high-grade carotid stenoses, signal "dropout" in magnetic resonance imaging (MRI) is common. The literature verifies poor correlation of MRA with the precise degrees of stenosis. Indeed, MRA alone can overestimate carotid stenosis

severity. Thus, in a reversal of prior algorithms, we insist that stenosis severity information from MRA be verified by a duplex study.

COMPUTED TOMOGRAPHIC ANGIOGRAPHY: Computed tomographic angiography (CTA) is the noninvasive test of choice when supplemental information is required after duplex scanning. While CTA requires iodinated contrast material, it can provide excellent arterial mapping from the aortic arch to the intracranial vasculature, which can be important to both vascular and cardiac surgeons. Accurate assessment of residual lumen diameter within a carotid artery lesion is obtained from both axial and three-dimensional (3-D) reconstructed images, with the important limitation that such accuracy diminishes in highly calcified lesions.

Definition of Severe Carotid Artery Stenosis

The definition of severe carotid stenosis has changed as techniques used to investigate carotid artery disease have changed. Severe carotid stenosis by direct carotid angiography reduces the residual lumen diameter to less than 1.5 mm or by more than 70%. With MRA, severe stenosis causes signal dropout. The definition of severe stenosis with ultrasound-based scanning was presented earlier.

EFFICACY OF CAROTID ENDARTERECTOMY AS A TREATMENT FOR CAROTID STENOSIS

C. Miller Fisher's original description of the relationship of ipsilateral hemispheric stroke to internal carotid artery occlusion in 1951[28] was followed by Eastcott's description of surgical therapy for symptomatic carotid artery atherosclerosis in 1953.[29] Thereafter, carotid endarterectomy became popular for stroke prevention until publication of the negative results in the multinational EC/IC bypass trial[30] in the mid-1980s. A vocal segment of the neurology community decried the apparent lack of evidence verifying the efficacy of carotid endarterectomy in stroke prevention, which led to a series of large-scale, prospective, randomized trials comparing carotid endarterectomy with medical therapy. In summary, there is now Level I evidence verifying the efficacy of carotid endarterectomy for stroke prevention in both symptomatic and asymptomatic patients.

Carotid Endarterectomy for Symptomatic Carotid Stenosis

In 1986, Hertzer and colleagues[31] studied 211 patients with TIAs or strokes and a carotid stenosis greater than 50%, of whom 126 had medical treatment and 85 had carotid endarterectomy. Although there was no difference in survival between the two groups at a mean follow-up of 36 months, carotid endarterectomy yielded significantly better freedom from late stroke for patients with (1) a greater than 70% unilateral stenosis, (2) greater than 50% bilateral stenoses, and (3) a greater than 50% carotid stenosis in association with contralateral internal carotid artery occlusions. This study set the stage for several large-scale, randomized trials.

In 1991, the results of the randomized North American Symptomatic Carotid Endarterectomy Trial (NASCET) of medical treatment or carotid endarterectomy were reported.[24] All patients had either hemispheric retinal TIAs or nondisabling strokes within 120 days of entry into the trial and 70 to 99% stenosis in the symptomatic carotid artery. The actuarial risk of any ipsilateral stroke at 2 years was significantly lower at 9% in the 328 surgical patients versus 26% in the 331 medical patients. The data-safety monitoring committee halted further randomization given the widely disparate 18-month follow-up data. For major or fatal ipsilateral strokes, the risk was 2.5% for surgical patients versus 13.1% for medical patients ($p < .001$). When all strokes and deaths were included, carotid endarterectomy still was better than medical treatment. Subsequent follow-up studies from the NASCET investigators indicated that the benefit of carotid endarterectomy in symptomatic patients also extended to those with even moderate (50 to 69%) carotid artery lesions.[32]

Also in 1991, the Veterans Affairs Cooperative Study of symptomatic carotid stenosis reported its results of randomization of 189 men with stenoses greater than 50% to medical or surgical treatment.[33] After 1 year, there was a significant reduction in stroke or TIAs in the patients having carotid endarterectomy (7.7%) compared with medically treated patients (19.4%). The results were even more divergent for patients with a carotid stenosis greater than 70%.

The European Carotid Surgery Trial randomized 2518 patients with nondisabling stroke, TIA, or retinal infarction in conjunction with stenosis in the ipsilateral carotid artery to medical or surgical treatment.[34] For the 778 patients with severe stenoses of 70 to 99%, the cumulative risk of stroke at carotid endarterectomy of 7.5%, plus an additional late stroke rate at 3 years of 2.8%, was less than the 16.8% rate for medically treated patients. At 3 years, the cumulative risk of operative death, operative stroke, ipsilateral ischemic stroke, and any other stroke was 12.3% for the surgical cohort versus 21.9% for the medical group ($p < .01$). Finally, the risk of fatal or disabling ipsilateral stroke at 3 years was 6.0% for the carotid endarterectomy patients versus 11.0% for the medical control patients ($p < .05$).

Although the benefit of carotid endarterectomy in these studies was due in part to the high risk of stroke in medically treated patients, the results were significant even in an era when the 30-day combined stroke and death risk of carotid endarterectomy was about 7.5%. While the combined stroke and death risk with carotid endarterectomy is higher in symptomatic versus asymptomatic patients, the current combined risk is closer to 3 to 5%.[20,27,35,36]

Carotid Endarterectomy for Asymptomatic Carotid Stenosis

Hertzer's group studied operative and nonoperative treatment in 290 previously unoperated patients who had greater than 50% asymptomatic carotid stenoses.[37] During follow-up to 3 years, prophylactic carotid endarterectomy in 95 patients had a significantly reduced incidence of neurologic events compared with medical treatment in 195 patients ($p = .05$).

Data from Moneta and colleagues[38] indicate that carotid endarterectomy patients had a significantly lower stroke risk compared with the natural history of patients without intervention. This study also suggested that late coronary events were so frequent as to question the wisdom of intervention for the carotid artery lesion. Accordingly, a series of trials in asymptomatic patients were performed.

The Veterans Affairs Cooperative Study of asymptomatic carotid stenosis, defined as greater than 50% diameter reduction by angiography, randomized 444 men to medical or surgical treatment.[39] At a mean follow-up of 4 years, the combined incidence of ipsilateral neurologic events was 8.0% for the surgical patients versus 20.6% for the medical patients ($p < .001$). The difference in stroke alone between the two groups (8 versus 20%) did not achieve statistical significance because of the study's sample size, nor was there a significant difference when all strokes and deaths were analyzed. Excessive late mortality (about 40% at 4 years in both groups) was due largely to associated CAD. These mitigating factors limited definitive conclusions about the efficacy of carotid endarterectomy in asymptomatic patients in this trial.

In 1995, the results of the Asymptomatic Carotid Atherosclerosis Study of 1662 patients randomized to surgical or medical treatment were published.[26] At mean follow-up of 2.7 years, aggregate risk for ipsilateral stroke and any perioperative stroke or death for the surgical group was 5.1%, significantly lower than the rate of ipsilateral stroke of 11.0% for the medical group, a benefit limited to male patients. Critics suggested that the low combined stroke and death rate (2.3%) in the surgical patients was not representative of results across a broader spectrum of hospitals.

In 2004, the Asymptomatic Carotid Surgery Trial (ACST) contributed important data on the value of carotid endarterectomy for asymptomatic carotid stenosis.[20] Touted as the world's largest surgical trial from 126 hospitals in over 30 countries, the study randomized over 3000 patients to carotid endarterectomy or medical therapy, which included at least aspirin. Over 40% of randomized patients had over 3 years of follow-up. Risk of any stroke, any ipsilateral stroke, or any disabling stroke was halved in surgical patients, who had a perioperative combined stroke and death rate of about 3%. The time threshold to achieve statistical benefit, i.e., cancel perioperative morbidity, by actuarial analysis was 2 years, suggesting that patients selected for endarterectomy should have a life expectancy of greater than 2 years. Indeed, the only subgroup in which endarterectomy did not achieve statistical significance was in patients over 75 years of age.

In summary, Level I evidence supports the advantage of carotid endarterectomy over medical management for patients with severe asymptomatic carotid artery stenoses.

CAROTID STENTING

Following the success of percutaneous transluminal coronary angioplasty, particularly with adjunctive stenting, percutaneous interventionalists increasingly sought to treat carotid stenosis with angioplasty and stenting.[40–42] Technical aspects of the procedure to guard against procedure-related stroke dominated the first years of its evolution. Today, use of distal embolic protection devices potentially makes carotid stenting comparable with carotid endarterectomy in safety and efficacy.[43] Emerging reports (mostly from industry-sponsored trials) indicate that carotid stenting can produce equivalent outcomes to carotid endarterectomy.[44–47] In one large series, the 30-day combined stroke and death rate was 7.4%, and most strokes were minor.[48] Results improved with experience, and late stroke-free survival was comparable with that for carotid endarterectomy.

In 2004, the initial randomized trial of carotid endarterectomy versus stenting with routine embolic protection, designed as a "noninferiority" trial, i.e., insufficiently powered to detect superiority of one treatment, concluded that carotid stenting was not inferior to carotid endarterectomy in high-risk patients.[47] Study endpoints (composite death/stroke/MI at 30 days and 1 year) and the high 30-day combined stroke and death rate (5.7%) in asymptomatic patients limit the value of the data. While a number of trials of carotid stenting versus carotid endarterectomy in various patient subsets are underway, the recently published French carotid endarterectomy versus stenting study in patients with symptomatic, severe carotid stenosis indicated that stenting is associated with a 2.2-fold increased risk of stroke or death at 30 days compared with endarterectomy. The trial was halted by the data-safety monitoring committee after the randomization of 527 patients.[49] Furthermore, published evidence documents an increased periprocedural risk of stroke after carotid stenting in elderly patients.[50]

Scant data are available about carotid artery stenting versus endarterectomy in patients requiring CABG. Investigators from the Cleveland Clinic compared patients treated with either carotid artery stenting before or carotid endarterectomy with open-heart surgery. After propensity scoring, the authors found no significant differences in combined stroke/death/MI in the two approaches.[51]

MYOCARDIAL ISCHEMIC EVENTS IN PATIENTS AFTER CAROTID ENDARTERECTOMY

Although this chapter is focused primarily on managing CAB patients who have concomitant carotid artery disease,

some comment on the impact of CAD on short- and long-term risks of carotid endarterectomy patients is appropriate.

Incidence of Coronary Artery Disease in Carotid Endarterectomy Patients

Mackey and colleagues[52] found that 53% of carotid endarterectomy patients had evidence of CAD by clinical history or electrocardiographic studies. Using thallium exercise testing in 106 carotid endarterectomy patients, Urbinati and colleagues[53] found that 27 (25%) had significant defects on myocardial scanning. In 1985, the Cleveland Clinic reported the results of routine preoperative coronary angiography in 506 carotid endarterectomy patients.[54] Only 7% of patients had normal coronary arteries, and 28% had mild to moderate CAD. However, 30% had advanced but compensated disease, 28% had severe, correctable disease, and 7% had severe, inoperable CAD.

Risk of Myocardial Ischemic Events

Short-term risks

The impact of CAD on the short-term risks of carotid endarterectomy is well documented. In 1981, Hertzer and colleagues[55] reported that hospital mortality in 335 carotid endarterectomy patients was 1.8%, of which 60% of deaths were due to CAD. In the Mackey and colleagues study cited earlier, carotid endarterectomy patients with clinical CAD had an operative mortality of 1.5% and an MI rate of 4.3% compared with no mortality and an infarction rate of 0.5% for patients without CAD.[52] While the frequent coexistence of CAD with carotid artery disease is often invoked as the principal cause of short- and long-term morbidity in carotid endarterectomy patients, the risk of perioperative MI will vary with the risk profile of the cohort studied. For example, in the protected carotid artery stenting versus endarterectomy trial, 30-day non-Q-wave MI occurred in 6.6%.[47] In our cohort of over 2000 carotid endarterectomy patients, the perioperative MI rate was 1.2%.[27] A National Surgical Quality Improvement Program (NSQIP) database report of over 13,000 endarterectomy procedures had a perioperative MI rate of 1.4%,[56] similar to results from the ACST trial.[20] Clearly, improved care has lowered coronary ischemic risks during carotid endarterectomy.

Long-term risks

Mackey's study of carotid endarterectomy patients reported the 5- and 10-year survival rates of patients with CAD to be 68.6 and 44.9%, respectively, versus 86.4 and 72.3% for patients with no CAD.[52] When Urbinati and colleagues[53] followed their carotid endarterectomy patients, the 7-year freedom from all cardiac events was 51% for patients with silent myocardial ischemia compared with 98% for patients with normal thallium exercise testing.

In the Hertzer and colleagues study[55] of 209 patients with clinically suspected CAD, 5-year mortality rate for hospital survivors was 27%, and 37% of late deaths were due to MI. Actuarial survival at 11 years was significantly better for the patients with CAD who had bypass grafting. A later study from the same group of 329 carotid endarterectomy patients followed to 10 years confirmed that MI caused more late deaths (37%) than did stroke (15%).[57] Again, 10-year survival was significantly better for patients having CABG.

In our Massachusetts General Hospital cohort of over 2000 carotid endarterectomy patients treated between 1990 and 1999, 10-year actuarial survival was 45%. Among variables associated with increased late mortality, concomitant CAD [odds ratio (OR) 1.4; $p = .0002$] figured prominently.[27]

TIMING OF CAROTID AND CORONARY ARTERY SURGERY

If one accepts that (1) uncorrected carotid stenosis increases the risk of stroke for patients with severe carotid and CAD who have only isolated CABG, (2) carotid endarterectomy is the indicated treatment for severe symptomatic and asymptomatic carotid stenosis, (3) CAD increases the early and late risk of death for carotid endarterectomy patients, and (4) CABG is an indicated treatment for CAD, then the important question becomes not the indication for but the timing of the two operative procedures.

Staged Carotid and Coronary Artery Operations

One approach is to perform the carotid endarterectomy and CAB operations as staged procedures. By convention, doing the carotid endarterectomy before coronary bypass grafting is referred to as a *staged procedure,* whereas doing the CABG before the carotid artery operation is called a *reverse staged procedure.*

Most surgeons who advocate a sequential operative approach to patients with severe combined disease usually do the carotid endarterectomy first if the patient is not ischemic and is hemodynamically stable. Improvements in patient management, especially use of regional anesthesia, often can allow safe initial isolated carotid endarterectomy. Recent data from studies powered to detect an impact of regional anesthesia have verified that composite outcomes of stroke/death/ MI after carotid endarterectomy are reduced significantly with use of regional anesthesia.[56,58] However, other practical considerations, such as imminent need for the large doses of heparin required for cardiopulmonary bypass, airway and/or neck swelling, and the risk of perioperative coronary ischemic events, remain real issues.

For unstable cardiac patients, particularly those with asymptomatic carotid stenosis, some cardiac surgeons opt to

perform initial myocardial revascularization followed by an interval carotid endarterectomy. The principal risk with this approach is the potential for neurologic complications either during or shortly after the myocardial revascularization.

Currently, we advocate concomitant carotid and coronary artery operations for virtually all patients with severe combined disease. However, in patients with severe bilateral carotid stenosis, a staged approach may be appropriate, especially if the patient is stable cardiovascularly. We occasionally treat the more severe of the two carotid artery lesions with initial isolated endarterectomy, followed by combined CABG and endarterectomy of the other carotid artery within a few days. Use of a reversed staged approach, namely, doing one carotid endarterectomy with myocardial revascularization followed several days later by the other carotid endarterectomy, is rare because of an increased stroke risk with reversed staged procedures (to be discussed below).

Concomitant Carotid and Coronary Artery Operations

In 1972, Bernhard and colleagues[59] published the first report of successful combined carotid endarterectomy and CABG in 15 patients. Since then, numerous groups have published their results. The strategy of performing both operative procedures during one anesthetic is based on the premise that such an approach in patients with severe combined disease ought to minimize cardiac events that frequently complicate isolated carotid endarterectomy and neurologic events that complicate isolated CABG.

Daily and colleagues[60] reported that doing both operative procedures together is more cost-effective than a staged or reversed staged approach, which require two anesthetics and can incur the additional costs of two hospitalizations.

OPERATIVE TECHNIQUES FOR CONCOMITANT CAROTID AND CORONARY ARTERY OPERATIONS

Standard Approach

The usual operative technique for concomitant carotid endarterectomy and CABG has been to perform the carotid endarterectomy during harvesting of CAD conduits prior to cardiopulmonary bypass, the approach we use at our institution, where the carotid operation is performed by vascular surgeons as the cardiac surgical team harvests whatever saphenous vein or other conduits may be needed.

Technical components of carotid endarterectomy have evolved over time. Preoperative aspirin has been validated in large database studies.[61] We use routine electroencephalographic monitoring, selective shunting, and either eversion endarterectomy (presuming no need for a shunt) or patch closure. Simple primary closure is associated with a higher rate of restenosis.[62] After the carotid endarterectomy is completed, the neck incision is loosely approximated over a sponge. Final closure, usually over a plastic drain, is done after cardiopulmonary bypass is completed and heparinization is reversed.

Alternative Approaches

Minami and colleagues[63] reported using some perceived advantages of cardiopulmonary bypass, namely, heparinization, hypothermia, and hemodynamic control, to perform carotid endarterectomy in 116 patients while on bypass for CABG. Operative mortality was 1.7%, and total stroke risk was 4.3%. Weiss and colleagues[64] perform the carotid endarterectomy on bypass with systemic hypothermia to 20°C with the heart protected with cardioplegia. They had no neurologic events and one postoperative death in 23 patients. Theoretically, hypothermia on cardiopulmonary bypass provides an extra margin of ischemic protection for the brain during the carotid endarterectomy and avoids the need for intravascular shunting. The level of systemic hypothermia used has varied among surgical groups employing this approach.

Whether performing the carotid and coronary artery operations on cardiopulmonary bypass saves total operative time is not proven, but it prolongs aortic occlusion and cardiopulmonary bypass times, something most cardiac surgeons would prefer to avoid. A deeper level of hypothermia is not favored by most cardiac surgeons, particularly as the trend toward using lesser degrees of hypothermia has become more popular.

HIGHLIGHTS OF POSTOPERATIVE MANAGEMENT

In our institution, postoperative management of patients following concomitant carotid endarterectomy and CABG does not differ importantly from the management of patients having isolated myocardial revascularization. We believe that maintenance of a good coronary perfusion pressure and, by extension, good cerebral perfusion pressure in the early postoperative hours is beneficial. Early clearing of perioperative edema with diuresis seems to be efficacious.

The routine anticoagulation protocol for our myocardial revascularization patients, aspirin begun within 6 hours of completion of the operation, is adequate for patients who have either primary or saphenous vein patch closure of the carotid arterotomy. When a prosthetic patch is used, the patient has considerable residual disease higher in the carotid system, or contralateral carotid disease is uncorrected, especially if the plaque is ulcerated, some surgeons

prefer early anticoagulation with heparin, followed by long-term warfarin anticoagulation.

If a surgeon decides not to treat a severe carotid stenosis either with a staged approach or concomitant operation, the increased incidence of stroke in the early days after isolated myocardial revascularization seen with the reversed staged approach would seem to suggest that heparinization of the patient is appropriate once the acute bleeding risk of the CAB operation is past.

RESULTS OF STAGED AND CONCOMITANT CAROTID AND CORONARY ARTERY OPERATIONS

Early Results

Staged carotid and coronary artery operations

Several studies report the results of staged operations for concomitant carotid and CAD, but only one study randomized patients to concomitant or reversed staged operation. Hertzer and colleagues[65] published a study containing a randomized subgroup of patients with unstable coronary artery syndromes and incidental asymptomatic carotid stenosis. Over 5 years, these authors treated 275 patients with severe combined disease. Their criteria for carotid endarterectomy was symptomatic and/or severe (>70%) carotid artery disease. Only 24 (9%) of the patients had CAD that was stable enough to allow carotid endarterectomy prior to CABG. Of those 24 patients, 1 (4.2%) suffered a perioperative stroke after the carotid endarterectomy and died of an MI awaiting CABG. Symptomatic or severe bilateral carotid artery disease in 122 patients was treated with combined carotid and coronary artery operation with an operative mortality rate of 6.1% and a perioperative stroke rate of 7.1%.

The remaining 129 patients with unstable coronary artery symptoms and unilateral, asymptomatic, severe carotid stenoses were randomized to either a combined operation or a reversed staged operation. Patients having concomitant carotid and coronary artery operations had a mortality rate of 4.2% versus a combined rate of 5.3% for the two operations in the staged patients. The incidence of stroke in the concomitant operations was 2.8%, which was significantly lower than the 14% risk of the reversed staged operations (6.9% during the isolated CABG and 7.5% during the delayed isolated carotid endarterectomy). This randomized study emphasizes the advantage of concomitant operations over reversed staged procedures.

In 1999, Borger and colleagues[66] performed a meta-analysis of nonrandomized observational studies published from centers that documented results with both staged and concomitant operations. They identified a trend toward increased risk of stroke and death with combined operations. The results of this study need to be viewed with caution for several reasons. First, using meta-analysis to compare observational and nonrandomized studies limits its statistical power. Second, in most series, unstable patients had combined operations and stable patients had staged procedures. Third, the criteria for entry into these studies was operations completed, not intention to treat. One cannot be sure if some patients for whom a staged approach was planned were not studied because the second operation was never performed due to a poor result from the first procedure.

Concomitant carotid and coronary artery operations

Since the late 1970s, some surgeons in our group have had an aggressive approach to patients with combined carotid and CAD, using concomitant operative repair as the standard approach. Staged operations were reserved for the few patients with very stable CAD. Our first report in 1989 in a small group of patients suggested that combined operation was safe (2% stroke or death risk). That study was among the first to document the disparate cardiac risk among patients having combined operations versus patients having isolated CABG.[67]

In 1995 we published our results of combined operations between 1979 and 1993 in the first 200 consecutive patients.[68] Hospital mortality was 3.5%, MI 2.5%, and perioperative stroke 4.0%.

More recently, we published results of concomitant operation between 1979 and 2001 in 500 patients, with that approach being used in virtually all patients with combined disease since our second report.[69] Mean patient age was 69 years, about 6 years older than that for all CAB patients during that time period. Three-quarters of the patients had unstable angina pectoris, and 53% had prior MI. Although the distribution of single-, double-, and triple-vessel disease was as expected at 4%, 21%, and 75%, respectively, 42% of patients had significant left main CAD. Of the 500 patients, 329 (66%) were neurologically asymptomatic, 21% had transient ischemic attacks, and 13% had a prior stroke. Unilateral severe carotid stenosis was found in 336 patients (67%); 32% had disease in the contralateral carotid artery.

Urgent or emergency operations were required in 54% of patients; 3% were on the intra-aortic balloon preoperatively. The average number of grafts per patient was 3.7. While only 50% of the first 200 patients received at least one mammary artery graft, 90% of the last 300 patients received a mammary artery graft.

Hospital mortality was 3.6%, MI was 2.0%, and stroke occurred in 4.6%. Of the 23 strokes, 12 were ipsilateral to the carotid endarterectomy and 11 contralateral or bilateral, suggesting that, in our experience, concomitant carotid endarterectomy and CABG have neutralized the impact of carotid stenosis as a risk factor for stroke during surgical myocardial revascularization.

Significant multivariate predictors of hospital death were preoperative TIAs, preoperative MI, and nonelective

operation. Peripheral vascular disease predicted postoperative stroke. Significant predictors of prolonged postoperative hospital stay were failure to use a mammary artery graft, perioperative stroke, and advanced age.

Vermeulen and colleagues[70] found that the only significant multivariate predictor of hospital death in 230 combined operations was left main CAD. Postoperative neurologic events were predicted by severe left ventricular dysfunction and preoperative neurologic events, either stroke or TIAs.

Several series of concomitant carotid endarterectomy and CABG published since 1985 are noted in Table 24-2. Our results stand in contrast to some others, particularly reports using administrative data. Brown reported a 17.7% stroke risk for combined operations in Medicare patients in Midwestern states.[71] A Canadian study found that the combined risk of stroke and death for CABG alone was 4.9% versus 13% for combined carotid and coronary artery operations.[72] However, data available from the New York State Registry indicate that such results can be explained largely by the disparate cardiac risk profiles of the two patient groups. Ricotta and colleagues[9] used propensity scoring to match risk-factor profiling and found no difference in combined stroke and death risk for the two operations after case-control matching.

Late Results

Follow-up in our series of combined operations revealed the following 10-year actuarial freedoms from late events: death, 43%; MI, 87%; percutaneous transluminal coronary angioplasty, 92%; reoperative myocardial revascularization, 96%; total stroke, 85%; and ipsilateral stroke, 90%.[69]

Vermeulen and colleagues[70] found their 10-year actuarial freedom from cardiac events to be 50%, from neurologic events to be 81%, and from all events to be 41%. The only significant multivariate predictors of late cardiac mortality were advanced age and severe left ventricular dysfunction.

In a study of 127 combined carotid and coronary artery operations, Rizzo and colleagues[73] reported a 5-year survival rate of 70%, freedom from MI of 84%, and freedom from stroke of 88%. Survival was worse for patients with low ejection fractions. Late strokes were fewer in patients who were

Table 24–2.

Series of Combined Carotid and Coronary Operations with More than 100 Patients

Reference	Year	Patients (no.)	Mean age (y)	Deaths (%)	MI (%)	Stroke (%)
Dunn[74]	1986	130	60	6 (4.6)	—	13 (10.0)
Hertzer[65]	1989	170	65	9 (5.3)	—	12 (7.1)
Vermeulen[70]	1992	230	63	8 (3.5)	4 (1.8)	13 (5.6)
Rizzo[73]	1992	127	65	7 (5.5)	6 (4.7)	8 (6.3)
Takach[75]	1997	255	66	10 (3.9)	12 (4.7)	10 (3.9)
Darling[76]	1998	420	69	10 (2.4)	1 (0.2)	13 (3.1)
Khaitan[77]	2000	121	69	7 (5.8)	—	9 (7.4)
Minami[78]	2000	340	65	9 (2.6)	2 (0.6)	16 (4.7)
Evagelopoulos[79]	2000	313	66	28 (8.9)	10 (3.2)	7 (2.2)
Estes[80]	2001	174	69	9 (5.2)	—	10 (5.7)
Zacharias[81]	2002	189	69	5 (2.7)	2 (1.1)	5 (2.7)
Char[82]	2002	154	68	6 (3.9)	—	6 (3.9)
Chiappini[83]	2005	140	65	9 (6.4)	—	9 (6.4)
TOTAL		2763	65	123 (4.4)	37 (2.0)	131 (4.7)
Akins[69]	2005	500	69	18 (3.6)	10 (2.0)	23 (4.6)

neurologically asymptomatic preoperatively, more common in patients who were transiently symptomatic, and most frequent in patients with prior stroke.

CONCLUSION

The risk of perioperative stroke following myocardial revascularization rises with the increasing age of CABG patients, and increasing age is accompanied by an increased incidence of carotid artery disease. Several studies have defined severe, uncorrected carotid stenosis as a major risk factor for perioperative stroke. Therefore, in addition to patients with audible carotid bruits or a history of ischemic neurologic events, patients who are 65 years of age or older ought to have noninvasive carotid artery evaluation prior to CABG. Also, randomized trials have established the safety and efficacy of carotid endarterectomy as the most appropriate treatment for both symptomatic and asymptomatic severe carotid stenosis. Another randomized study has demonstrated the advantage of concomitant carotid endarterectomy and CABG over reversed staged operations. Thus, we advocate combined carotid and coronary artery operations for virtually all patients with severe concomitant coronary and carotid artery disease, which on its own merits would require treatment.

ACKNOWLEDGMENT

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CHAPTER 25

Myocardial Revascularization after Acute Myocardial Infarction

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The ability of surgical interventions to minimize myocardial loss following myocardial infarction has advanced dramatically over the past two decades. Acute myocardial infarction still afflicts approximately 1.5 million individuals each year in the United States,[1] and 30% of these patients die before reaching the hospital, while 5% die during hospital admission.[1] Prompt medical attention, including transport to the hospital, diagnosis, and treatment of the myocardial infarction, is critical to patient survival. Since 1989, the death rate due to acute myocardial infarctions has declined 24%, while the actual number of deaths declined only 7%.[2] Over the last 40 years, especially during the 1980s, new pharmacologic agents, interventional cardiology procedures, and coronary artery bypass surgical techniques have advanced and have led to a decrease in the overall morbidity and mortality associated with acute myocardial infarction.[3,4] Despite this overall improvement, mechanical and electrical complications such as cardiogenic shock, rupture of the ventricular septum or free wall, acute mitral regurgitation, pericarditis, tamponade, and arrhythmias challenge the medical community caring for patients presenting with acute myocardial infarction on a daily basis.[3,4] Of these complications, cardiogenic shock complicating acute myocardial infarctions has the most significant impact on in-hospital mortality and long-term survival. The loss of more than 40% of functioning left ventricular mass and its accompanying systemic inflammatory response are major causes of cardiogenic shock and are determined by the degree of preinfarction ventricular dysfunction, the size of the infarcted vessel, and pathologic level of inflammatory mediators.[5–7] Restoration of blood flow to the threatened myocardium offers the best chance of survival following acute coronary occlusion, but the means and timing of revascularization continue to be a highly debated and studied topic. Thrombolytics, percutaneous transluminal coronary angioplasty (PTCA), intracoronary stenting, and coronary artery bypass graft (CABG) surgery have decreased the mortality associated with acute myocardial infarctions. Advances in myocardial preservation and mechanical support lead the surgical armamentarium in the treatment of acute myocardial infarctions.

PATHOGENESIS OF ACUTE OCCLUSION

Myocardial ischemia due to coronary occlusion for as little as 60 seconds causes ischemic zone changes from a state of active systolic shortening to one of passive systolic lengthening.[8] Occlusions for less than 20 minutes usually cause reversible cellular damage and depressed function with subsequent myocardial stunning. Furthermore, reperfusion of the infarct leads to variable amounts of salvageable myocardium. After 40 minutes of ischemia followed by reperfusion, 60 to 70% of the ultimate infarct is salvageable, but this decreases dramatically to 10% after 3 hours of ischemia.[9,10] Animal model evidence has also demonstrated that 6 hours of regional ischemia produces extensive transmural necrosis.[11] The exact timing in humans is even more difficult to analyze because of collateral flow, which is a major determinant of myocardial necrosis in the area at risk in humans.[10] The collateral blood supply is extremely variable, especially in patients with long-standing coronary disease. However, collateral flow is jeopardized with arrhythmias, hypotension, or the rise of left ventricular end-diastolic pressure above tissue capillary pressure.[9] Thus loss of collateral flow to the infarct area may lead to the cellular death of salvageable myocardium. Control of blood pressure and prevention of arrhythmias are vital during this immediate time after infarction.

Many clinical trials have shown the beneficial effects of early reperfusion within 24 hours after acute myocardial infarction.[12] Although benefits of late reperfusion beyond 36 hours, particularly in asymptomatic patients, have yet to be shown in large clinical studies, advocates for aggressive management believe that reperfusion is warranted to

preserve the border areas that may be underperfused during the early days after an infarction. While some of these patients may develop objective evidence of ischemia, the clinical assumption that a hypotensive patient with a suddenly dilated and pressure-overloaded ventricle is prone to losing more muscle mass in border zones of the infarct is reasonable. This is true even in patients who have had complete revascularization. Conservative measures, such as nitroglycerin and intra-aortic balloon pumps, have demonstrated their efficacy in this population of patients without clearly salvageable myocardium by improving coronary blood supply and reducing the work demand of the left ventricle. More radical approaches such as insertion of a left ventricular assist device (LVAD) have been advocated as well. At our center, placement of an LVAD into this group of patients, allowing complete pressure-volume unloading, has occasionally resulted in sufficient improved ventricular function to allow device explantation months later.[13,14]

Table 25-1 outlines the effects of anatomic, physiologic, and therapeutic variables on the evolution of final infarct size. Anatomically, the location of the coronary obstructive lesion, additional diseased vessels, and the presence of collateral flow will determine the extent of early injury, especially for borderline areas. However, ventricular remodeling of the infarct has important consequences influencing ventricular function after myocardial infarction.[15,16] Thus appropriate and aggressive invasive therapies such as PTCA, intra-aortic balloon pump use, CABG, controlled reperfusion, and LVAD insertion can mitigate myocardial injury and salvage borderline areas, even if the interventions occur many hours or days after the initial infarction, particularly in patients with ongoing ischemia.

Reperfusion injury also contributes to myocardial damage as free oxygen radicals are released and destroy endothelial cells and produce interstitial edema. The timing and management of reperfusion effects on myocardial damage may have an impact on both survival and functional recovery of individuals following acute myocardial infarction.[17] Some centers have argued convincingly that controlled reperfusion with specially designed perfusate and a decompressed, energy-conserving ventricle resting on cardiopulmonary bypass is the best means to preserve muscle mass.[18]

Table 25–1.

Factors that Influence the Evolution and Severity of Acute Myocardial Infarction

Anatomic
Site of lesion
Size of myocardium at risk
Collateral circulation
Physiologic
Arrhythmias
Coronary perfusion pressure
Myocardial oxygen consumption
Reperfusion injury
Stunned myocardium
Therapeutic options
Medical management
Revascularization
Thrombolysis
Percutaneous transluminal coronary angioplasty
Coronary artery surgery
Controlled reperfusion
Buckberg solution and technique
Mechanical circulatory support

CARDIOGENIC SHOCK

Definition

Cardiogenic shock is defined clinically as a systolic blood pressure below 80 mm Hg in the absence of hypovolemia, peripheral vasoconstriction with cold extremities, changes in mental status, and urine output of less than 20 mL/h. Hemodynamic parameters for cardiogenic shock include cardiac index less than 1.8 L/min/m^2, stroke volume index less than 20 mL/m^2, mean pulmonary capillary wedge pressure greater than 18 mm Hg, tachycardia, and a systemic vascular resistance of over 2400 dyn(sec/cm^5). These patients are defined as type IV by the Killip classification, a widely used system to classify myocardial infarctions.[19]

Prevalence

Shock is the most common cause of in-hospital mortality following myocardial infarction.[20] The in-hospital mortality associated with cardiogenic shock has remained unchanged at approximately 80% despite the development of new treatment modalities.[20] Cardiogenic shock occurs in 2.4 to 12.0% of patients with acute myocardial infarction.[21] Since 1975, the incidence of cardiogenic shock complicating acute myocardial infarctions has remained constant at 7.5%, ranging between 5 and 15% (Fig. 25-1).[20] The progressive reduction in time delay from symptom onset to treatment may account for these constant figures. Previously, patients with excessive time delays would have died before reaching the hospital or soon thereafter, as it is known that treatment delays increase 1-year mortality incrementally (Fig. 25-2).[22] There was also a decrease in the incidence of out-of-hospital deaths due to coronary disease between 1975 and 1988.[20] The key to success in patients in shock is early intervention and revascularization. In a prospective randomized study, Hochman and

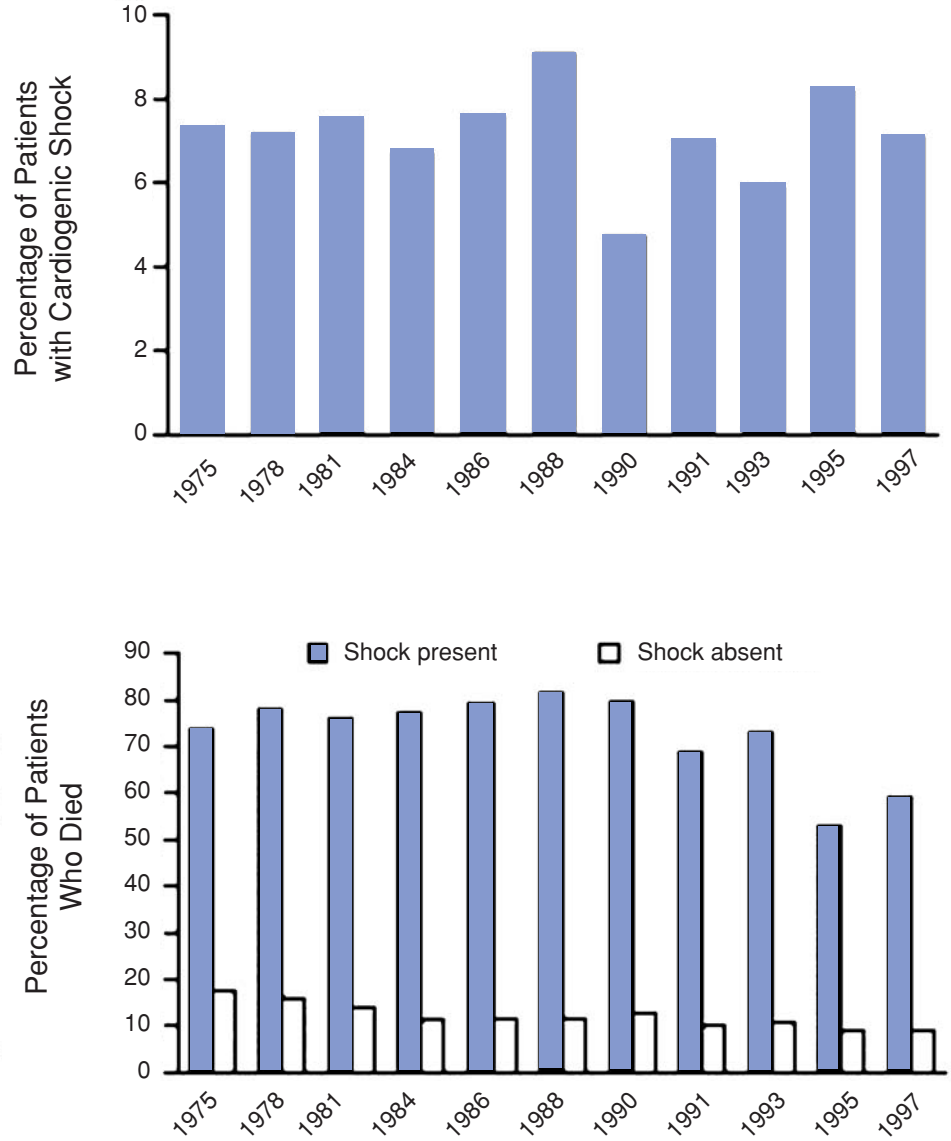

Figure 25-1. Trends in cardiogenic shock and survival based on presence or absence of shock. (*Reproduced with permission from Goldberg R, Samad N, Yarzebski J, et al: Temporal trends in cardiogenic shock complicating acute myocardial infarction. N Engl J Med 1999; 340:1162.*)

associates showed that revascularization within 6 hours of diagnosis of cardiogenic shock confers survival benefits, particularly in those patients under 75 years of age.[23,24] Use of mechanical circulatory support also may play a role by resting stunned myocardium to allow its recovery and to prevent the irreversible end-organ injury that may result from prolonged shock.[13,14]

Pathophysiology and Infarct Size

Shock is directly related to the extent of the myocardium involved, and infarctions resulting in loss of at least 40% of the left ventricle have been found on autopsy in patients with cardiogenic shock.[5,6,25] Autopsy findings also revealed marginal extension of the recent infarct and focal areas of necrosis in patients with cardiogenic shock.[5] Extensive three-vessel disease is usually found in individuals with cardiogenic shock, and extension of the infarct is an important determinant in those individuals.[5,6,25] Limiting the size of the infarct and its extension is one of the key therapeutic interventions in patients with myocardial infarction. By following creatine phosphokinase levels, Gutovitz and colleagues[26] showed that the progression/extension of myocardial damage results in cardiogenic shock. Patients who develop shock have higher peak values. New insights into the mechanisms underlying cardiogenic shock have been gained from recent clinical studies/registries (e.g., SHould we emergently revascularize Occluded Coronaries for cardiogenic Shock [SHOCK]) that also highlight the contribution of the pathologic systemic inflammatory response after myocardial

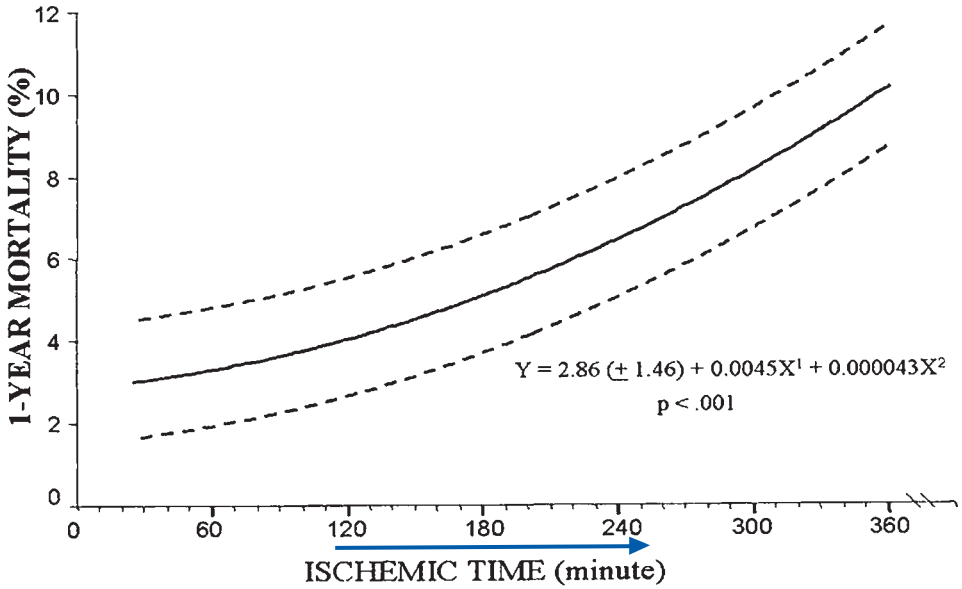

Figure 25-2. Relationship between time to treatment and 1-year mortality, as a continuous function, was assessed with a quadratic regression model. Dotted lines represent 95% confidence intervals of predicted mortality. (*Reproduced with permission from De Luca G, Suryapranata H, Ottervanger JP, et al: Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction. Circulation 2004; 109:1223.*)

infarction.[7] Noting that many patients in cardiogenic shock possessed only moderately depressed ejection fraction (30%) and systemic vascular resistance was within the normal range (on average), investigators in the SHOCK trial found evidence of an elevated inflammatory response in some patients (fever, leukocytosis, and decreased systemic vascular resistance), which may have contributed to the clinical syndrome of shock.[23,24] In addition, data are now emerging that link cytokine release, nitric oxide–dependent mechanisms, complement cascade activation, and other inflammatory mediators to cardiac injury.[27–34] The role of systemic inflammation in cardiogenic shock is still being clarified, and adjunctive anti-inflammatory therapy, including nitric oxide inhibitors and complement inhibitors, are currently being investigated.

MEDICAL MANAGEMENT OF MYOCARDIAL INFARCTION

The management of patients with acute myocardial infarctions demands expeditious treatment and decision making. With the ultimate goal of reperfusing the ischemic myocardium, treatment strategies should be directed toward reducing myocardial oxygen demand, maintaining circulatory support, and protecting the threatened myocardium before irreversible damage and expansion of the infarct occur.

Clinical assessment and risk stratification begins at triage during presentation, where electrocardiographic changes and cardiac biomarkers are used to identify patients suitable for revascularization versus medical management. At our center, clinical algorithms have been instituted to rapidly aid decision making.[35] Patients presenting with ongoing chest pain for more than 20 minutes *and* ST-segment elevation in two contiguous leads *or* new (or not known to be old) left bundle-branch block *or* anterolateral ST depression are classified as having ST-elevation myocardial infarction (STEMI). These patients are referred for primary percutaneous intervention in the cardiac catheterization suite 24 hours a day, 7 days a week, if no contraindications exist. The other group of patients, those with non-ST segment elevation myocardial infarction (NSTEMI), present with chest pain at rest for 10 minutes or more *and* ST-segment depression greater than 0.5 mm *or* ST-segment elevation 0.6 to 1 mm *or* T-wave inversions greater than 1 mm *or* positive troponin levels *or* a history of unstable angina in a patient with coronary artery disease risk factors. These patients are treated medically with a combination of antiplatelet therapy, intravenous heparin, and other traditional medications discussed below.

Both clinical and basic science research have demonstrated that reperfusion is the main treatment option for acute myocardial infarction. Unfortunately, the majority of patients with myocardial infarction receive only conservative medical management; only 40% of patients having an acute myocardial infarction receive thrombolytic therapy, the most common means of reperfusion.[36]

A major tenet of medical management is the provision of adequate arterial oxygenation, defined as >90% saturation. Supplemental oxygen and mechanical ventilation, including positive end-expiratory pressure and endotracheal intubation, aid in the management of pulmonary edema.

Nitroglycerin dilates epicardial arteries, increases collateral flow, and decreases ventricular preload. Although clearly beneficial in the treatment of myocardial infarction, nitrates may increase ventilation-perfusion mismatch and cause hypotension due to preload reduction.

Adequate analgesia is also beneficial. Morphine sulfate, the most commonly used analgesic, reduces preload and afterload, myocardial oxygen demand, anxiety, and circulating catecholamines. Side effects include hypotension and respiratory depression, each of which is treatable with basic resuscitative efforts.

Antiarrhythmic therapy, including lidocaine, is indicated under certain guidelines, along with atropine and countershock therapy when arrhythmias occur. Since arrhythmias are one of the most common complications after myocardial infarction, electrocardiographic (ECG) monitoring is recommended for the first 48 to 72 hours.

Arterial monitoring and the balloon flotation catheter aid in the management of patients who are hemodynamically unstable, developing congestive heart failure, or developing mechanical complications of a myocardial infarction. Long-term therapy for uncomplicated myocardial infarction includes the use of beta blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors.

Medical management includes the use of vasopressors and inotropic agents as first-line treatment strategies for cardiogenic shock. Optimizing filling pressure by balancing fluid management and diuretics is essential. Pulmonary capillary wedge pressures should be kept in the 16– to 22–mm Hg range.[3]

The use of dobutamine and dopamine is part of the pharmacologic armamentarium. These agents affect adrenergic receptors in different ways. Dopamine at doses of 5 to 8 μ/kg per minute stimulates beta-adrenergic receptors; at higher doses, alpha-adrenergic receptors are activated. At rates of more than 10 μ/kg per minute, left ventricular filling pressures rise and increase myocardial oxygen consumption. Dobutamine affects beta-adrenergic receptors and thus decreases afterload while stimulating the myocardium. Although vasopressors are necessary to maintain adequate perfusion pressures, they also increase afterload of the heart and increase myocardial oxygen demand, potentially worsening ischemia and extending the area of infarction. Neither of these drugs has been shown to provide a survival benefit in this setting.

While medical management of cardiogenic shock complicating acute myocardial infarctions is associated with high mortality, early revascularization will reduce mortality. As will be discussed later, early revascularization with PTCA or CABG has been shown to be the treatment of choice in this cohort.

In contrast to using inotropic agents to improve circulation, beta blockers have been used successfully to reduce death after infarction, probably due to their ability to reduce myocardial oxygen demand and arrhythmias. In hypotensive patients or individuals suffering bradycardia after infarctions involving the right coronary artery, beta blockade is contraindicated. Other mainstay therapies mentioned earlier—heparin, nitrates, and morphine—also comprise the traditional medical management of these critically ill patients.

STATES OF IMPAIRED MYOCARDIUM

Coronary insufficiency can result in three states of impaired myocardium: infarcted, hibernating, and stunned. Each state requires separate clinical interventions and carries different prognostic implications. Infarcted myocardium is irreversible myocardial cell death due to prolonged ischemia. Hibernating myocardium is a state of impaired myocardial and left ventricular function at rest due to reduced coronary blood flow and impaired coronary vasodilatory reserve that can be restored to normal if a normal myocardial oxygen supply-demand relationship is reestablished.[37–39] Hibernating myocardium is defined as contractility-depressed myocardial function secondary to severe chronic ischemia that improves clinically immediately following myocardial revascularization. Stunned myocardium is left ventricular dysfunction without cell death that occurs following restoration of blood flow after an ischemic episode. If a patient survives the insult resulting from a temporary period of ischemia followed by reperfusion, the previously ischemic areas of cardiac muscle eventually demonstrate improved contractility (Table 25-2).

Hibernating Myocardium

Hibernation may be acute or chronic. Carlson and associates[40] showed that hibernating myocardium was present in

Table 25–2.

States of Myocardial Cells after Periods of Ischemia

Condition	Viability of cells	Cause of injury	Return of function
Infarcted	Nonviable	Prolonged ischemia	No recovery
Stunned viable	Limited ischemia	Delayed with reperfusion	Recovery
Hibernating	Viable	Ongoing ischemia	Prompt, sometimes unpredictable recovery

up to 75% of patients with unstable angina and 28% with stable angina. The entity also occurs after myocardial infarction. Angina after myocardial infarction commonly occurs at a distance from the area of infarction.[41] In fact, mortality is significantly higher in patients with ischemia at a distance (72%) compared with ischemia adjacent to the infarct zone (33%).[41] It is the hibernating myocardium that may be in jeopardy and salvageable, although its presence is usually incidental to the occurrence of the acute infarction. By distinguishing between hibernating myocardium and irreversibly injured myocardium, a more aggressive approach to restoring or improving blood flow to the area at risk is reasonable. Function often improves immediately after revascularization of appropriately selected regions.

Stunned Myocardium

In the 1970s it was observed that after brief episodes of severe ischemia, prolonged dysfunction upon reperfusion with gradual return of contractile activity occurred. In 1982 Braunwald and Kloner[42] coined the phrase "stunned myocardium." Stunning is a fully reversible process despite the severity and duration of the insult if the cells remain viable. However, myocardial dysfunction, biochemical alterations, and ultrastructural abnormalities continue to persist after return of blood flow. Within 60 seconds of coronary occlusion, the ischemic zone changes from a state of active shortening to one of passive shortening.[6] Coronary occlusion lasting less than 20 minutes is the classic model reproducing the stunning phenomenon.[42–44]

The most likely mechanisms of myocardial stunning are calcium overload, generation of oxygen-derived free radicals, excitation-contraction uncoupling due to sarcoplasmic reticulum dysfunction, or a combination thereof. Other mechanisms that may contribute to the stunning phenomenon include insufficient energy production, impaired energy use by myofibrils, impaired sympathetic neural responsiveness, impaired myocardial perfusion, damaged extracellular collagen matrix, and decreased sensitivity of myofilaments to calcium (Table 25-3).[43,45,46]

Stunned myocardium can occur adjacent to necrotic tissue after prolonged coronary occlusion and can be associated with demand-induced ischemia, coronary spasm, and cardioplegia-induced cardiac arrest during cardiopulmonary bypass. Clinically these regions are edematous, and even hemorrhagic, and can lead to both systolic and diastolic dysfunction.[47] They also have a propensity for arrhythmias, which can lead to more extensive ventricular stunning and hypotension with subsequent infarction of these regions.

In summary, infarcted myocardium is nonviable myocardium, while hibernating myocardium is viable myocardium that is chronically dysfunctional due to impaired blood supply. Stunned myocardium is viable myocardium that is acutely dysfunctional after adequate blood supply has been restored.

Table 25–3.

Mechanisms of Contractile Dysfunction after Myocardial Stunning

Generation of oxygen-derived free radicals*
Excitation-contraction uncoupling due to sarcoplasmic reticulum dysfunction
Calcium overload
Insufficient energy production by mitochondria
Impaired energy use by myofibrils
Impairment of sympathetic neural responsiveness
Impairment of myocardial perfusion
Damage to the extracellular collagen matrix
Decreased sensitivity of myofilaments to calcium

**Regarded as the primary mechanism of myocardial stunning.*
Source: Modified with permission from Bolli.[43]

Diagnosis of Viable Myocardium

Mechanisms to identify patients with myocardial stunning and hibernation include ECG findings, radionuclide imaging, positron emission tomography (PET), dobutamine echocardiography, and more recently magnetic resonance imaging (MRI). Thallium identifies perfusion-related defects of the myocardium and can distinguish between viable and scarred myocardium as well. However, early redistribution of thallium does not distinguish between hibernating and scarred myocardium since many segments with irreversible defects by thallium improve after reperfusion.[48] Redistribution imaging and reinjection imaging improve the predictive value of thallium imaging in distinguishing hibernating myocardium.

PET measures the metabolic activity of myocardial cells. It has high positive and negative predictive values.[49] It is now regarded as the best method to determine myocardial viability, particularly in patients with severe left ventricular dysfunction in whom other modalities are less accurate.[39,50,51]

Dobutamine echocardiography identifies hibernating and stunned myocardium by monitoring changes in segmental wall motion while the heart is stressed inotropically and chronotropically by dobutamine infusion. It has high specificity, sensitivity, and more importantly, positive predictive value.[52]

MRI has also been established as an effective method to assess hibernating myocardium.[53] It has been proven to accurately diagnose the degree of both acute and chronic myocardial infarction and predict functional recovery.[54–56]

Figure 25-3. Short-axis MRI images of anterior myocardial infarction. (*Reproduced with permission from Stuart Clarkson, GE Healthcare, and Luigi Natale, MD, Universita Cattolica, Rome, Italy.*)

A number of advantages exist with cardiac MRI, such as superior image resolution allowing accurate identification of transmural infarction (Fig. 25-3). By providing morphologic, functional, and metabolic information, it may ultimately supplant other modalities for the diagnosis of cardiac injury and recovery.

Finally, multislice computed tomography has been used to measure hibernating myocardium, and early data suggest it may be a reliable and sensitive method compared to MRI, although its use in clinical practice is limited.[57]

Treatment of Stunned Myocardium

Several approaches to management of this critically ill group should be taken. Blocking the production of oxygen free radicals will reduce both additional cell death and edema in stunned myocardium. By reducing inflammation, the prothrombotic effects on injured endothelial cells also can be reduced and thus enhance ventricular recovery. Several techniques attack the production or effects of these oxygen free radicals. Allopurinol blocks the xanthine oxidase-hypoxanthine pathway and decreases superoxide anion radicals; however, clinical trials have yielded conflicting results.[58–60]

Iloprost, an analogue of prostacyclin, has demonstrated some effectiveness in reducing stunning in animals. The proposed mechanism is inhibition of neutrophil and platelet function and reduction in the production of oxygen free radicals. In the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial, iloprost did not show improved ventricular function after reperfusion with tissue plasminogen activator (t-PA).[61]

Recombinant superoxide dismutase (SOD), an oxygen free radical scavenger, is a hydrophilic enzyme that does not cross the cell membrane. Additionally, SOD works most effectively if it is in tissue prior to reperfusion injury and oxygen free radical production.[62,63] Perhaps because of these

two limitations, the use of SOD has not yet shown clinical effectiveness.[64]

Adenosine, a naturally occurring nucleoside and arrhythmic agent, was given to patients after thrombolysis or mechanical reperfusion in a double-blind, randomized trial (Acute Myocardial Infarction Study of Adenosine [AMISTAD II]). A significant reduction in infarct size was seen with infusion 15 minutes before fibrinolysis or coronary intervention, although no differences were seen in clinical outcomes after 6 months.[65]

Treatment after coronary artery bypass has been investigated with mixed results. In the GUARDIAN trial, cariporide, a sodium-hydrogen exchanger, was administered to high-risk patients undergoing percutaneous or surgical revascularization. Patients in the surgical arm demonstrated a significantly lower rate of death and/or myocardial infarction after 36 days.[66] A lower rate of myocardial infarction was reconfirmed in the larger EXPEDITION trial; however, a high rate of neurologic complications has prevented widespread clinical use.[67]

Other pharmacologic agents, including calcium antagonists, nitrates, beta-blocking agents, and angiotensin-converting enzyme inhibitors, also have been studied with some beneficial results.[68–72] Recent clinical studies have shown that patients receiving calcium channel blockers had improved recovery from stunning over nitrate therapy.[73,74] Intracellular adhesion molecule blockers and P-selectin blockers also may prove beneficial in the coming years.

The use of inotropic agents can overcome stunning in both animal experiments and human observation. It is recognized that contractility of reversibly injured myocardium can be enhanced by catecholamines. Thus inotropic agents may have a role in supporting the patient with borderline function until the stunned myocardium can recover.[63]

Hemodynamic stability must be maintained while stunned myocardium is recovering or being treated by one of the above-mentioned means. Short-term mechanical circulatory devices can aid in the support of patients until the myocardium has sufficiently recovered.

Summary

Differentiation between infarcted, hibernating, and stunned myocardium guides therapeutic options in patients with poor ventricular function. If adequate regions of hibernating myocardium are present as documented by PET, thallium scanning, or dobutamine echocardiography, revascularization may allow ventricular recovery. In patients without evidence of hibernating or stunned myocardium, medical management or transplantation is a better option.

Further distinction is required between stunned and hibernating myocardium. Hibernating myocardium requires revascularization to restore blood supply to the area. Stunned myocardium requires only support, which may take the form of pharmacologic manipulations, including addition of epinephrine, dobutamine, and/or amrinone. If conservative measures fail, an intra-aortic balloon pump (IABP) or short-term LVAD support becomes necessary.

RATIONALE FOR AGGRESSIVE MANAGEMENT OF MYOCARDIAL INFARCTION

Randomized trials have shown beneficial effects of early reperfusion within 12 hours and possibly up to 24 hours after acute myocardial infarction.[12,23,24] Early reperfusion clearly reduces infarct size in the major areas at risk. Controlled reperfusion may even be superior. The arguments are more difficult to make for patients outside the 24-hour window; however, patients with ongoing ischemia often have ischemic border regions that are prone to arrhythmias and necrosis. In addition, these patients are at risk for prolonged periods of hypotension with resulting end-organ injury and further left ventricular dysfunction. Even if revascularization does not appear critical, ventricular unloading with IABP or LVAD may provide the bridge to recovery needed in patients dying after myocardial infarction. The major limiting factors to aggressive surgical management are major comorbidities, which make continuation of life undesirable or unlikely, and an unclear neurologic status, especially after a period of cardiopulmonary arrest.

REPERFUSION

Although restoration of blood flow to ischemic regions is essential, the accompanying reperfusion injury initially can worsen rather than improve myocardial dysfunction. The area at risk is affected not only by reperfusion, but also by the conditions of reperfusion and the composition of the reperfusate.[17] Thus controlling reperfusion itself may aid in reducing myocardial infarct size and ventricular injury.

At the cellular level, myocardial ischemia results in a change in energy production from aerobic to anaerobic metabolism. The consequences of ischemia vary from decreased adenosine triphosphate production and increased intracellular calcium to decreased amino acid precursors such as aspartate and glutamate. These changes can be reversed only by reperfusion.

However, as oxygen is reintroduced into a region, oxygen free radical generation ensues with resulting cellular damage. Cellular swelling and/or contracture leads to a "no-reflow phenomenon" that limits the recovery of some myocytes and possibly adds to irreversible injury of others. The production of oxygen free radicals during ischemia and at the time of reperfusion is the leading mechanism proposed to explain cellular injury. Four basic types of reperfusion injury have been described: lethal cell death,

Table 25–4.

Potential Types of Reperfusion Injury

Lethal	Cell death secondary to reperfusion
Vascular	Progressive damage causes an expanding zone of "no reflow" and deterioration of coronary flow reserve during the phase of reperfusion
Reperfusion arrhythmias	Arrhythmias, mainly ventricular, that occur shortly after reperfusion
Stunned myocardium	Postischemic ventricular dysfunction

Source: Modified with permission from Kloner RA: Does reperfusion injury exist in humans? J Am Coll Cardiol 1993; 21:537.

microvascular injury, stunned myocardium, and reperfusion arrhythmias (Table 25-4).

Buckberg and coworkers[17,18,75–91] conducted studies of controlled reperfusion after ischemia and produced a clinical application for controlled reperfusion. The conditions of reperfusion and the composition of the reperfusate allowed more muscle salvage, less post-ischemic edema, and greater immediate recovery of systolic shortening than uncontrolled reperfusion.[75] The composition of the reperfusate was designed to provide oxygen, reduce calcium influx, reverse acidosis, mobilize edema, and replenish substrates. To accomplish this, the cardioplegic solution was hyperosmolar and basic and contained blood, a chelating agent, aspartate, and glutamate.[76] The duration of reperfusion, 20 minutes, as well as the dose, was critical.[83]

The surgical strategy of controlled reperfusion, especially as espoused by Buckberg and associates, includes several elements. First, extracorporeal circulation is established as expeditiously as possible with venting of the left ventricle as required. Initially, antegrade cardioplegia is delivered using either a warm Buckberg solution to rebuild adenosine triphosphate stores, or cold high-potassium cardioplegia to achieve rapid diastolic arrest. We routinely add retrograde cardioplegia to ensure global cooling, even in areas of active ischemia. The temperatures of the anterior and inferior walls of the ventricle are measured to ensure adequate cooling. After each distal anastomosis, cold cardioplegia is infused into each graft and the aorta at 200 mL/min over 1 minute. This is followed by retrograde infusion through the coronary sinus for 1 minute. After completion of the final distal anastomosis, warm substrate-enriched blood cardioplegia is given at 150 mL/min for 2 minutes into each anastomosis and the aorta. After removal of the aortic cross-clamp, regional blood cardioplegia is given at 50 mL/min into the graft supplying the region at risk for 18 minutes. This controlled rate of reperfusion minimizes cellular edema and myocyte damage. The proximal vein grafts are then completed, followed by re-establishment of normal blood flow. To decrease oxygen demand, the heart is allowed to beat in the empty state for 30 minutes. After this time, the patient is weaned off bypass.

Application of the Buckberg solution and technique has been shown to be effective in improving mortality rates and myocardial function after acute coronary occlusion. With ischemic times averaging 6 hours, a prevalence of multivessel disease, and cardiogenic shock, the overall mortality in patients with acute coronary arterial occlusions who underwent surgical revascularization applying this method of reperfusion was 3.9%. Postoperative ejection fractions averaged 50%.[18] Surgical revascularization in this series using controlled reperfusion compared favorably with PTCA in several large series.[18] The superior results of this method for the treatment of cardiogenic shock, a 9% mortality, have brought this method to the forefront in the treatment of cardiogenic shock.[18]

Methods of Reperfusion

Role of thrombolytic therapy

Since myocardial salvage depends on reperfusion of occluded coronary arteries, rapid dissolution of an occluding thrombus with thrombolytic therapy is an appealing intervention. Intracoronary streptokinase in patients with acute myocardial infarction demonstrates that thrombolytic therapy is a safe and efficient way to achieve the desired early reperfusion.[92] Following this study, a number of multi-institutional mega-trials showed the effectiveness of thrombolytic therapy in treating acute myocardial infarctions.

The trial of the Italian Group for the Study of Streptokinase in Myocardial Infarction (Gruppo Italiano per lo Studio della Streptokinasi nell'Infarto Miocardio [GISSI])[93] and the Second International Study of Infarct Survival (ISIS-2)[94] found a reduced hospital mortality in patients treated with streptokinase. The effectiveness of tissue-type t-PA also has been evaluated in randomized studies. The Thrombolysis in Myocardial Infarction (TIMI) study[95] and the European Cooperative Study Group (ECSG)[96] demonstrated the effectiveness of t-PA for the treatment of acute myocardial infarction.

When streptokinase and t-PA were compared, two studies failed to demonstrate any difference in mortality.[97,98] A third study, however, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial, supported the use of t-PA by demonstrating a more rapid and complete restoration of coronary flow that resulted in improved ventricular performance and reduced mortality.[99,100] After 90 minutes, 54% of the group receiving t-PA and heparin had normal flow, compared with less than 40% in the other groups. While patency rates were similar

after 3 hours, 30-day mortality was lowest in patients whose flow was normal at 90 minutes (4.4%).[99,100] This supports the importance of rapid restoration of flow. Although the actual difference in patient survival between the two groups was small (6 versus 7% mortality), the number of lives saved each year may justify the added expense of t-PA.[99,100] The mode of delivery of t-PA has been credited for the differences in the outcomes in these trials. Differences in methods of delivery between t-PA and streptokinase and adjuvant therapy with aspirin and heparin, along with cost factors of each agent, have stimulated a continuing debate over these two drugs.[36]

The addition of new antithrombotic agents has failed to provide added survival benefit. The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-3 PLUS) and GUSTO V found no difference in outcomes with thrombolysis plus glycoprotein IIb/IIIa inhibitors or low-molecular-weight heparin, and actually increased the rate of overall bleeding in patients over the age of 75.[101–103]

While thrombolysis improves survival and ventricular function, the patency of infarct-related arteries is reported to be between 50 and 85%.[93–100] Normal flow should be achieved in 60% of patients by today's standards. Thrombolytic therapy works well but is not without complications, including bleeding and intracranial hemorrhage.[104] Bleeding is usually minor and occurs mostly at the sites of vascular puncture. Intracranial hemorrhage and stroke rates are around 1% and are an "acceptable" risk. The relative benefits of thrombolytic therapy appear to decrease as patient age increases, and a higher risk of intracranial hemorrhage in the elderly may partially account for these findings.[99,105,106] Careful selection of patients suitable for fibrinolytic therapy is warranted, especially in an increasingly older population.

Cardiogenic shock

Thrombolytic therapy for patients presenting in cardiogenic shock or heart failure does not appear to improve survival in this population, but may decrease the incidence of patients developing heart failure after myocardial infarction.[107] However, a recent randomized SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial found clear survival benefits for early revascularization by PTCA or CABG over initial medical stabilization by thrombolytic therapy.[21,23]

Summary

Thrombolytic agents for the treatment of myocardial infarction have demonstrated several important points. Survival is improved by decreasing time to reperfusion. The GUSTO trial showed that patients treated within the first hour had the greatest improvement in survival, with a 1% reduction in mortality for each hour of time saved.[99,100] Thrombolytic therapy is easy to administer in the community by trained personnel, although a significant risk of bleeding exists in certain patients. Since the time to reperfusion is a critical element in preserving myocardium, thrombolytic therapy is ideal for most communities without percutaneous interventional capabilities.[108] In this setting, thrombolytics may be used for treatment of patients with acute myocardial infarction.

Role of Percutaneous Transluminal Coronary Angioplasty

Since the first reported use of PTCA by Gruntzig and associates[109] in 1979, the efficacy of this procedure in the treatment of coronary artery disease has been well recognized. A number of studies have evaluated the efficacy of primary PTCA in the treatment of acute myocardial infarction. Overall, PTCA hospital mortality rates range from 6 to 9%.[110–115]

Several different strategies employing PTCA for acute myocardial infarction have been developed and examined through clinical trials. Primary, rescue, immediate, delayed, and elective PTCA are options for the treatment of acute myocardial infarction. Primary PTCA uses angioplasty as the method of reperfusion in patients presenting with acute myocardial infarction. Rescue, immediate, delayed, and elective PTCA all are done in conjunction with or following thrombolytic therapy. Rescue PTCA is done following recurrent angina or hemodynamic instability following thrombolytic therapy. Immediate PTCA is performed in conjunction with thrombolytic therapy, and delayed PTCA occurs during the intervening hospitalization. Finally, elective PTCA is done following thrombolytic therapy and medical management when a positive stress test is obtained during the same hospitalization or soon thereafter.

Primary PTCA functions in several roles for the treatment of acute myocardial infarctions. Since there are some absolute and relative contraindications to thrombolytics, PTCA is the one of best methods of reperfusion in patients with acute myocardial infarction, according to studies that evaluated PTCA as first-line therapy. Several studies evaluated the role of PTCA compared with thrombolytic therapy. The first study, the Primary Angioplasty in Myocardial Infarction Study Group trial in 1993, concluded that immediate PTCA without thrombolytics reduced occurrence of reinfarction and death and was associated with a lower rate of intracranial hemorrhage.[111] Since then, more than 20 studies have compared PTCA to thrombolysis. The results from these studies have consistently and conclusively demonstrated the superiority of PTCA to thrombolysis, regardless of the thrombolytic agent used. The findings include a lower short-term mortality rate, lower rates of reinfarction, reduced stroke and intracranial hemorrhage rates, and a decreased composite endpoint of death, reinfarction, and stroke.[116] These findings have been reconfirmed on long-term follow-up. A higher overall rate of bleeding was observed, likely due to vascular access complications. Myocardial salvage is similar for PTCA and thrombolytic therapy. However, primary PTCA may be slightly less costly than thrombolytic therapy.[112,113]

There are limits to the use of primary PTCA. Logistic and economic constraints apply to invasive modes of therapy. Catheterization laboratories and personnel must be ready at all times. This is not practical in most communities, and transportation to tertiary care centers raises costs considerably.

Immediate PTCA following thrombolytic therapy initially did not improve clinical outcome and was associated with increased complication rates. The ECSG,[96] the TAMI trial,[114] and the TIMI-IIA trial[115] demonstrated that immediate angioplasty does not improve clinical outcome or left ventricular function compared with delayed angioplasty.[96,114,115] Immediate angioplasty was also associated with a higher risk of bleeding and emergent bypass. The ECSG trial demonstrated a lower incidence of bleeding, hypotension, and ventricular fibrillation, as well as lower mortality with delayed PTCA.[96] The TAMI trial, which compared immediate versus delayed PTCA after thrombolysis, showed no difference in global ventricular function at 1 week between the two groups in patients with angiographically patent infarct arteries.[114] Finally, TIMI-IIA concluded that immediate PTCA after thrombolytic therapy for acute myocardial infarction does not improve survival or ventricular function,[115] and is associated with increased bleeding, reinfarction, and emergency CABG. However, alternative dosing strategies have helped improve outcomes of immediate PTCA after thrombolysis. The Plasminogen-Activator Angioplasty Compatibility Trial (PACT) examined the use of reduced-dose alteplase followed by PTCA in acute myocardial infarction.[117] A higher vessel patency and TIMI coronary flow grade were found in patients who underwent thrombolysis plus PTCA compared to PTCA alone, without increased bleeding complications. Further study of long-term outcomes will be necessary before definitive conclusions regarding its efficacy can be made.

Delayed PTCA does not improve clinical outcome. The Treatment of Post-Thrombolytic Stenoses (TOPS) study group concluded that there is no functional or clinical benefit from routine late PTCA after acute myocardial infarction treated with thrombolytic therapy in patients who did not have ischemia on stress testing before hospital discharge.[118] However, the TIMI-IIB trial indicated that thrombolytic therapy followed by angioplasty in individuals with symptomatic or provokable ischemia is appropriate.[115]

Intracoronary stents

The use of intracoronary stents after myocardial infarction has expanded as PTCA has become more prevalent. Benefits of stenting include lowered rates of restenosis and abrupt closure, and a reduced need for target revascularization after PTCA. Although the STENT-PAMI trial in 1999 using first-generation stents showed lower restenosis rates compared to thrombolysis, a trend toward higher mortality was seen, and its effectiveness as first-line therapy was questioned.[119] Composite endpoints of death, reinfarction, and urgent target vessel revascularization at 30 days have now been shown to be lower in subsequent studies, such as the CADILLAC, ISAR-2, and ADMIRAL trials, which employed newer-generation stents.[120–122] In these trials, abciximab, a glycoprotein IIb/IIIa inhibitor, was added to primary stenting. A striking reduction in restenosis rates with stenting plus abciximab versus PTCA alone was evident at 12-month follow-up in the CADILLAC study (41 versus 22%).[120] Current data suggest that stenting combined with antiplatelet therapy provides superior benefit to PTCA alone. Drug-eluting stents offer the potential to lower restenosis even further through the use of anti-inflammatory medication delivered via the stent. Most recently, patients in the STRATEGY trial treated with drug-eluting stents after acute ST-elevation myocardial infarction (STEMI) had a significantly lower composite endpoint of death, reinfarction, stroke, and angiographic evidence of restenosis at 8-month follow-up compared to stenting plus abciximab (50 versus 19%).[123,124] Concerns regarding increased thrombogenicity with drug-eluting stents are present, but have not been reported in a large trial to date; further research is warranted. Intracoronary stenting with adjunctive antiplatlelet medications has been embraced by the medical community for off-label use after acute myocardial infarction since its recent introduction.

Cardiogenic shock

Primary PTCA may play a greater role in patients presenting in cardiogenic shock, and percutaneous interventions have become more common over the past 10 years (Fig. 25-4). The GISSI-1 and GISSI-2 trials demonstrated no benefit from intravenous thrombolysis, with mortality rates of 70%.[93,97] In patients presenting in or developing cardiogenic shock after acute myocardial infarction, PTCA improved survival to 40 and 60%.[125,126] This improvement was even greater when angioplasty was successful; in-hospital survival rates increased to 70%. In most of these series an IABP was used in conjunction with PTCA. The SHOCK trial showed that revascularization by PTCA or CABG within 6 hours of the onset of cardiogenic shock results in improved 1-year survival (46.7 versus 33.6% for initial medical stabilization followed by revascularization) in this high-risk group, particularly for those under the age of 75 years (Fig. 25-5).[23,24] Subgroup analysis in patients undergoing successful PTCA or with TIMI grade 3 coronary flow after PTCA in the SHOCK trial revealed that 1-year survival was even higher, at 61%.[127] Independent predictors of mortality include age, hypotension, lower TIMI flow, and multivessel PTCA.

Summary

Primary PTCA or intracoronary stenting should be performed in patients with acute myocardial infarction and contraindications to thrombolytic therapy. Patients with established or developing cardiogenic shock should be revascularized early by PTCA or stenting rather than initial medical stabilization by thrombolytic therapy. Specialized centers

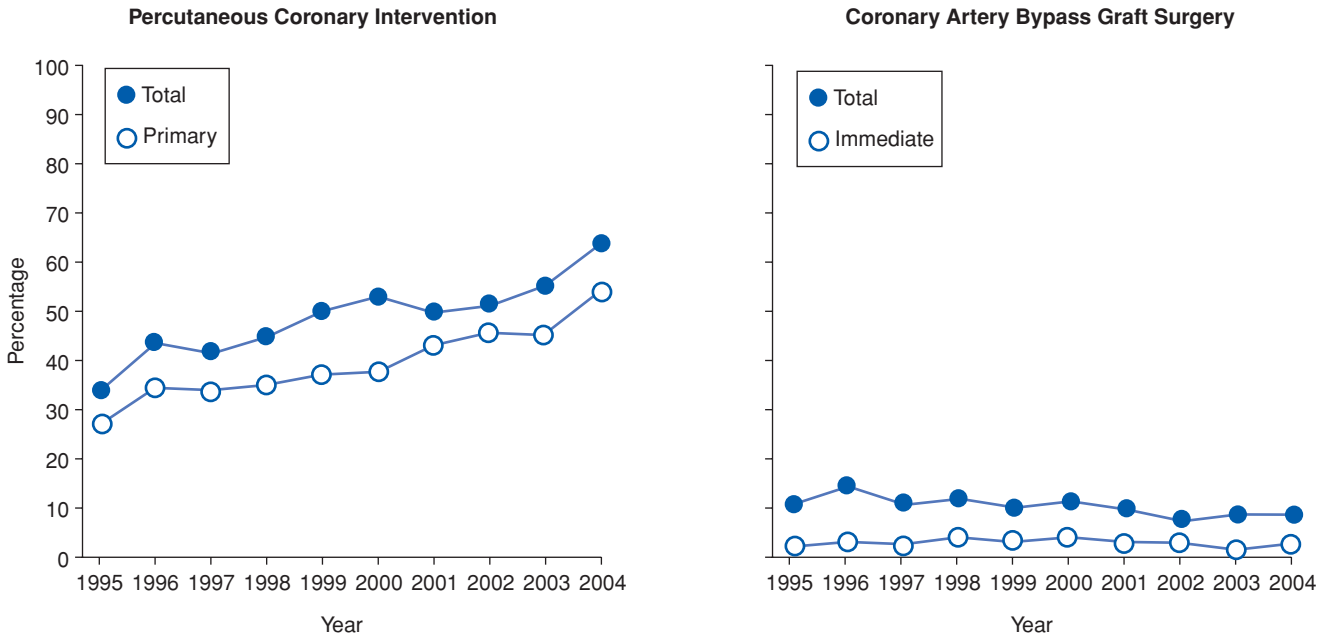

Figure 25-4. Revascularization rates in patients with cardiogenic shock at presentation (n = 7356). (*Reproduced with permission from Babaev A, Frederick PD, Pasta DJ, et al: Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA 2005; 294:448.*)

that have 24-hour catheterization facilities can provide primary PTCA or stenting as a first-line therapy. Rescue PTCA after failed thrombolytic therapy for patients with ongoing ischemia or clinical compromise is also recommended. Finally, elective PTCA should be performed on patients who have recurrent or provokable angina prior to hospital discharge.

Role of Coronary Artery Bypass Grafting

The role of surgical revascularization in the treatment of acute myocardial infarction has changed considerably over the past 30 years. Improvements in intraoperative management and myocardial preservation techniques have strengthened the surgeon's armamentarium. However, the development and use of thrombolytic therapy and PTCA offer effective alternatives to surgery.

Early studies reported increased morbidity and mortality for patients undergoing surgical revascularization within 30 days of the infarct.[128] A concern arose over a high risk of extension and hemorrhage into infarction after surgical revascularization of acute myocardial infarction.[129] Medical management was believed to be the more prudent therapy. The only absolute indications for emergent operative intervention treatment of acute myocardial infarctions during this era were papillary muscle rupture, ventricular septal defect, and left ventricular rupture. For these entities, surgery was the only hopeful option.

During the 1980s, reports appeared recommending surgical revascularization in preference to medical therapy for acute myocardial infarction.[94–100] Mortality rates under 5% were reported. Critics argued that these studies lacked randomization or consecutive entry of patients, that preoperative stratification was absent, and that enzyme levels were not included. Inherent bias that favored surgery in low-risk patients was believed to be the reason for the excellent outcomes.[137]

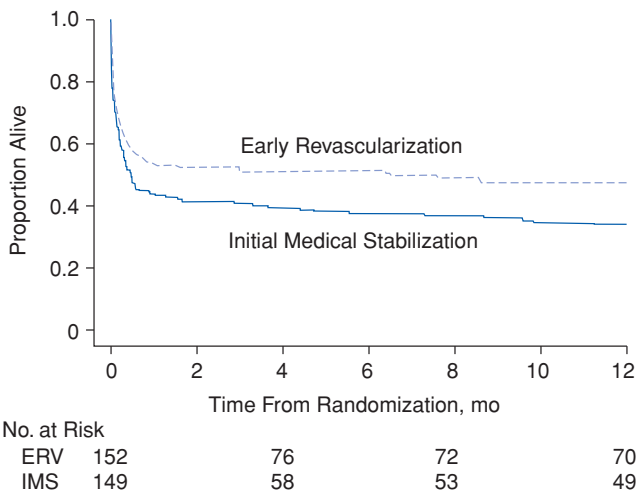

Figure 25-5. Survival estimates for early revascularization (n = 152) and initial medical stabilization (n = 149) groups in the SHOCK trial. Log-rank test $p = .04$. ERV = early revascularization group; IMS = initial medical stabilization group. (*Reproduced with permission from Hochman et al.*[24])

At the time these reports surfaced, thrombolytic therapy and interventional cardiology were emerging as alternative options for acute infarction. With the availability of thrombolytics and PTCA, large multicenter trials began looking at the efficacy and usefulness of these two techniques. Randomized trials using CABG were not done, and thus this option was never established as an option for acute myocardial infarction.

However, several centers continued to use surgical revascularization to treat acute myocardial infarction. Excellent results were achieved by coordinated community and hospital systems. However, practical, logistic, and economic constraints relegate surgical revascularization to a third option behind thrombolytics and PTCA for the primary treatment of acute myocardial infarction.

There continue to be several scenarios that require emergent or urgent surgical revascularization. Failure of thrombolytics, PTCA, or intracoronary stenting with acute occlusion may require surgical intervention. Additionally, CABG for postinfarction angina has become a critical step in the pathway of treating acute myocardial infarction. Finally, surgical revascularization may be indicated in patients with multivessel disease or left main coronary artery disease developing cardiogenic shock after myocardial infarction.

Table 25–5.

Comparison of Hospital Mortality with Respect to Time of Surgery—Transmural Versus Nontransmural Myocardial Infarction

	Mortality	
Time between CABG and MI	**Transmural MI (%)**	**Nontransmural MI (%)**
<6 hours	14	13
6–23 hours	14*	6*
1–7 days	5	4
>7 days	3	3

**p <.01 nontransmural versus transmural.*
CABG = coronary artery bypass graft; MI = myocardial infarction.
Source: Data compiled from the New York State Cardiac Surgery Registry, which included every patient undergoing a cardiac operation in the last decade in the state of New York.

Timing after infarction

If surgical revascularization within 6 hours after the onset of symptoms is feasible, the mortality rate is improved over that of medically treated, nonrevascularized patients.[130–137] While these early studies were not controlled and were criticized for selection bias, they did demonstrate that surgical revascularization may be performed with an acceptable mortality in the presence of acute myocardial infarction with improved myocardial protection, anesthesia, and surgical techniques. However, with the advent of thrombolytic therapy, PTCA, and an aging population, the surgical patient we encounter today bears little resemblance to the patient population represented in these early data.

Recent analyses of the New York State Cardiac Surgery Registry, which included every patient undergoing a cardiac operation in the last decade in the state of New York, resulted in valuable information regarding the optimal timing of CABG in acute myocardial infarction. In this large and contemporary patient population, there is a significant correlation between hospital mortality and time interval from acute myocardial infarction to time of operation, particularly if CABG was performed within 1 week of acute myocardial infarction. In addition, patients with transmural and nontransmural acute myocardial infarction have different trends in mortality when the time course is taken into consideration. Mortality for the nontransmural group peaked if the operation was performed within 6 hours of acute myocardial infarction, then decreased precipitously (Table 25-5).[138] On the other hand, mortality for the transmural group remained high during the first 3 days before returning to baseline.[139] Multivariate analyses confirmed that CABG within 6 hours for the nontransmural group and 3 days for the transmural group were independently associated with in-hospital mortality.[138,139] Optimal timing of CABG in patients with acute myocardial infarction is a controversial subject. Early surgical intervention has the advantage of limiting the infarct expansion and ventricular remodeling that may result in possible ventricular aneurysm and rupture.[140] However, there is the theoretical risk of reperfusion injury, which may lead to hemorrhagic infarction resulting in extension of infarct size, poor infarct healing, and scar development.[141] The data from these studies caution against early revascularization, particularly among patients with transmural acute myocardial infarction within 3 days of onset. Some have advocated the use of mechanical support to stabilize and allow elective rather than emergent surgery.[142] Utilizing mechanical support "prophylactically" instead of CABG to improve outcome, however, would require placement of such support in many unnecessary cases. If revascularization cannot be delayed, aggressive mechanical support such as a LVAD must be available since mortality is most likely due to pump failure. Furthermore, mechanical circulatory support has been shown to be efficacious as a bridge to ventricular recovery or transplantation for this patient cohort.[14] While emergent cases such as structural complications and ongoing ischemia clearly cannot be delayed, nonemergent cases, particularly patients with transmural acute myocardial infarction, may benefit from delay of surgery. Early surgery after transmural acute myocardial infarction has a significantly higher risk and surgeons should be prepared to provide aggressive cardiac support including LVADs in this ailing population. Waiting in some cases may be warranted.

Risk factors

In addition to timing of surgery as discussed above, risk factors include urgency of the operation, increasing patient age, renal insufficiency, number of previous myocardial infarctions, hypertension,[143] reoperation cardiogenic shock, depressed left ventricular function and the need for cardiopulmonary resuscitation,[144] left main disease, female gender, left ventricular wall motion score,[145] IABP, and transmural infarction.[146] Characteristics associated with better outcome early after myocardial infarction include preservation of left ventricular ejection fraction, male gender, younger patients, and subendocardial versus transmural myocardial infarction.

Cardiogenic shock

Surgical revascularization in acute myocardial infarction complicated by cardiogenic shock has been shown to improve survival. Cardiogenic shock, as discussed earlier, is accompanied by 80 to 90% mortality rates; various mechanisms of cardiogenic shock are shown in Fig. 25-6. DeWood and colleagues[147] were the first to demonstrate improved results with revascularization in patients with cardiogenic shock complicating acute myocardial infarction. Patients who were stabilized with an IABP and underwent emergent surgical revascularization had survival rates of 75%. Early surgical revascularization is associated with survival rates of 40 to 88% in patients in cardiogenic shock due to nonmechanical causes. Guyton and coworkers[148] reported an 88% in-hospital survival and a 3-year survival of 88%, with no late deaths reported. Furthermore, the SHOCK trial demonstrated survival benefit in early revascularization by CABG or PTCA within 6 hours of the diagnosis of cardiogenic shock for those under 75 years of age.[23,24] Patients comprising the CABG cohort in the SHOCK trial had more severe disease, with higher rates of three-vessel disease, left main coronary artery disease, diabetes, and elevated mean coronary jeopardy scores than the PTCA cohort.[149] Despite this, 87.2% of these patients achieved successful *and* complete revascularization with CABG, compared with successful revascularization in 77.2% with PTCA, and only 23.1% with complete revascularization with PTCA. Overall, mortality was no different between groups at 1 year (Fig. 25-7). On subgroup analysis, patients older than age 75, with left main coronary disease or three-vessel disease, or with diabetes had trends toward better survival at 30 days and 1 year after CABG compared to PTCA. Thus for patients in cardiogenic shock, surgical revascularization has become an established and viable option for select patient groups.

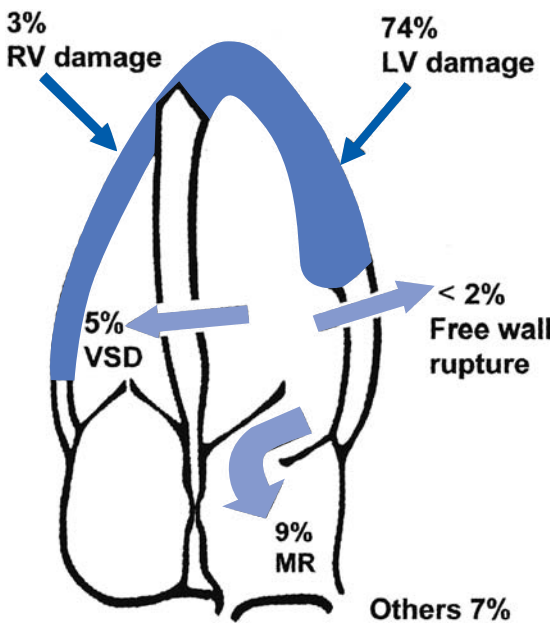

Figure 25-6. Mechanisms of cardiogenic shock. Apical four-chamber echo view with relative incidence of the mechanisms responsible for cardiogenic shock in the SHOCK and MILIS 4 registries. LV = left ventricle; MR = mitral regurgitation; RV = right ventricle; VSD = ventricular septal defect. (*Reproduced with permission from Davies CH: Revascularization for cardiogenic shock. Q J Med 2001; 94:57.*)

Advantages of coronary artery bypass grafting

Reported survival rates are similar for CABG and PTCA in the treatment of acute myocardial infarction. To date there have been no large randomized clinical trials comparing CABG with PTCA and thrombolytics after myocardial infarction. For patients with stable angina and elective revascularization for ischemic heart disease, a number of trials have been conducted comparing CABG to stenting.[150–153] In these studies, trends favoring CABG for multivessel disease were seen after 2 years in composite cardiac event endpoints, rate of reinfarction, and mortality; revascularization rates were five times higher in the stenting groups.[154] Most notably, survival after CABG for two or more diseased vessels was significantly higher than stenting with 2-year follow-up in a retrospective study of the New York State Cardiac Surgery Reporting System and Percutaneous Coronary Intervention Reporting System.[155] These results must be interpreted with caution, however, as patients with acute infarctions less than 24 hours pretreatment were excluded. Due to the lack of prospective, randomized trials, recommendations must be based on retrospective and observational studies. CABG offers several potential advantages. First, surgical revascularization is the most definitive form of treatment of the occlusion. CABG offers the longest patency of revascularized stenotic and occluded arteries in elective cases; 90% of internal mammary artery grafts are patent at 10 years. Second, CABG also offers more complete revascularization, since all the vessels are treated. This concept becomes especially important in patients with multivesssel disease or patients in cardiogenic shock, in whom remote myocardium may continue to be comprised with only "culprit vessel" revascularization and inadequate restoration of collateral flow.[156,157] A complete revascularization returns global myocardial perfusion to normal levels and offers the best chance for myocardial salvage. Third, difficult distal

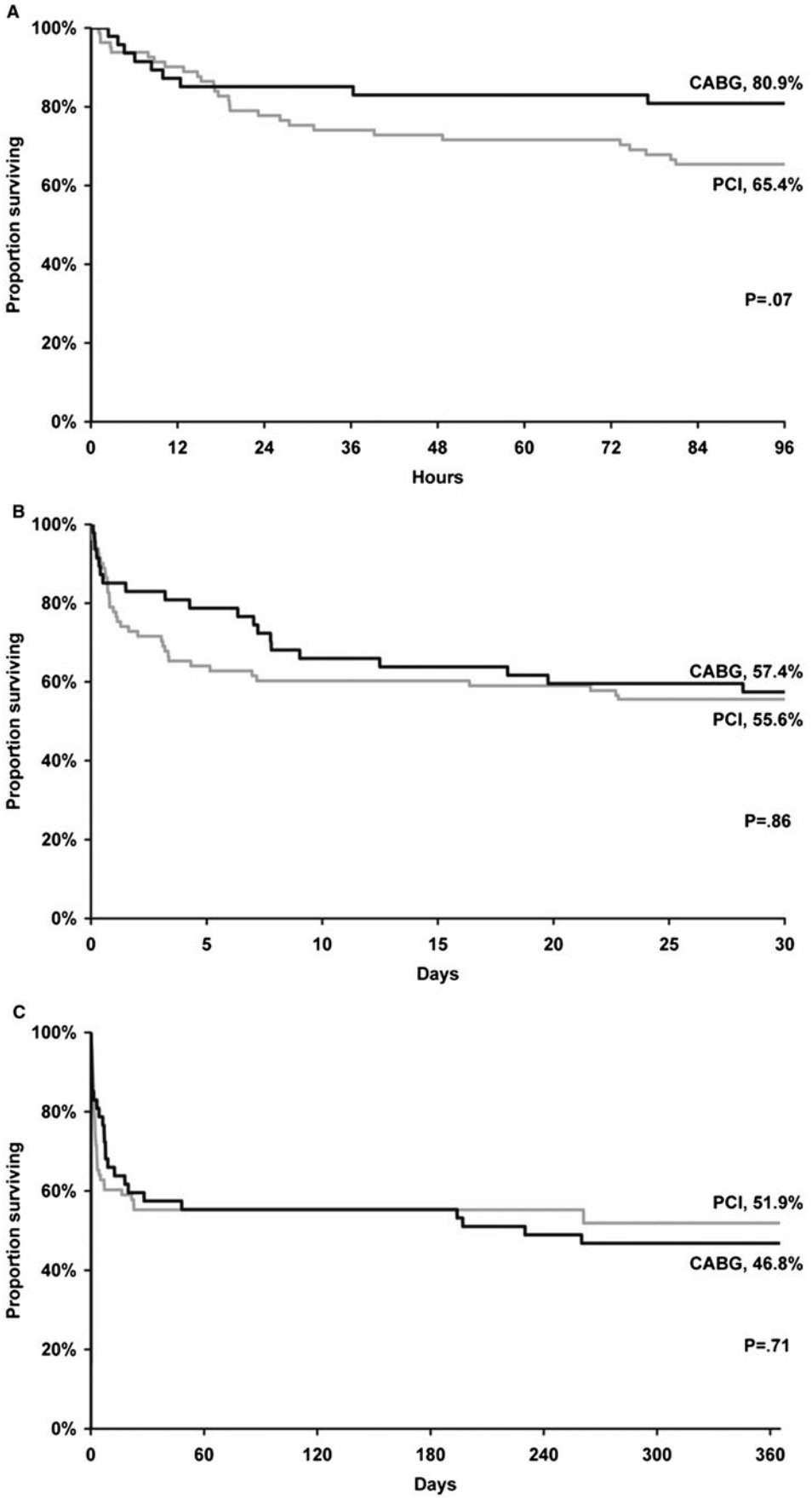

Figure 25-7. Kaplan-Meier survival estimates at 96 hours (A), 30 days (B), and 1 year (C) in patients treated with emergency percutaneous coronary intervention (PCI) versus emergency coronary artery bypass graft (CABG) in the SHOCK trial. *(Reproduced with permission from White et al.[149])*

obstructions can be reached. Fourth, there is controlled reperfusion to reverse ischemic injury and reduce reperfusion injury. Fifth, as with other forms of reperfusion, CABG interrupts the progression of ischemia and necrosis and limits infarct size.

Disadvantages of coronary artery bypass grafting

Disadvantages of immediate surgical revascularization include the high mortality associated with early CABG. Off-pump procedures may reduce perioperative complications in high-risk patients, but are not yet widely practiced and have limitations.[158] Rapid availability of catheterization and operating room personnel for emergency procedures imposes logistic and economic constraints. Thus CABG is not readily applicable to the vast majority of patients in the community, and to provide this would strain health care resources. Second, it is difficult to analyze published results of CABG for acute myocardial infarction because randomized trials have not been done. Comparisons thus far have used medically treated patients as controls. Patients in the surgical group may be at lower risk; this might explain their progression to operation rather than continuing medical treatment. Crossover of patients from medical to surgical treatment also may have skewed the data.

Summary

Surgical revascularization following acute myocardial infarction can be performed with excellent results when the timing and patient cohort are appropriate. Most patients do not need such measures and would not benefit from this aggressive form of therapy. However, patients with mechanical complications, those in cardiogenic shock, and those with postinfarction angina are likely to benefit from early CABG.

USE OF THE INTRA-AORTIC BALLOON PUMP

The early use of aortic counterpulsation with an intra-aortic balloon pump (IABP) demonstrated the safety but not efficacy of this device for patients in cardiogenic shock following acute myocardial infarction.[159] While survival was not improved, aortic counterpulsation did improve the myocardial oxygen requirements and myocardial energetics were reduced in patients in shock.[113] The use of IABP is also effective for temporary hemodynamic stabilization in complications of acute myocardial infarction, such as ventricular septal rupture, acute mitral valve insufficiency,[160,161] postinfarct angina,[162] ventricular arrythmias,[163] and acute heart failure following infarction.[164,165] As revascularization techniques for the repair of occluded coronary arteries of patients in cardiogenic shock have improved, use of aortic counterpulsation has found a role as an adjuvant to treatment protocols.

IABP counterpulsation in combination with early reperfusion is effective in the treatment of acute myocardial infarction complicated by cardiogenic shock.[147,166] While the major improvement in survival is due to early reperfusion, patients who had combined reperfusion and IABP additionally have improved long-term survival. IABP improves circulatory physiology and decreases end-organ damage in the early shock period before the myocardium is reperfused and recovers function.

Aortic counterpulsation decreases the reocclusion rate, recurrent ischemia, and need for emergency PTCA in patients who have coronary artery patency established by emergency cardiac catheterization following acute myocardial infarction.[167] Prophylactic counterpulsation for 48 hours sustains patency in coronary arteries after patency is re-established following myocardial infarction. No increase in vascular or hemorrhagic complications is observed as compared with controls.[167]

Weaning from the IABP should take place only after there is clear evidence of myocardial and end-organ recovery. In general, inotropic requirements should be reduced first in order to minimize myocardial stress. The one exception is the development of limb ischemia due to the IABP catheter.

ROLE OF CIRCULATORY ASSIST

Circulatory support devices are reserved for patients who are hemodynamically unstable; however, intervention should not be delayed until after irreversible end-organ injury occurs. This group of shock patients has a mortality rate of 80%, and survival data with the use of assist devices reflect the critical condition of patients treated. Mortality rates have changed very little in the last 20 years despite improvements in medical and surgical therapy.

Patients in cardiogenic shock who are candidates for circulatory assist devices may be divided into two groups: individuals who have stunned myocardium and need a bridge to recovery, and those who have irreversible myocardial damage and need a bridge to cardiac transplantation. For example, if a patient with a previously normal ventricle develops a large myocardial infarction, we prefer short-term support, since enough recovery may occur to allow a fruitful existence with the native heart. However, if a patient with preexisting heart failure has another infarction, the need to definitively bridge the patient to transplant with a long-term implantable device is apparent. This approach is supported by results from a multicenter study, in which overall survival at 6 and 12 months was higher in patients who underwent direct LVAD implantation rather than revascularization followed by LVAD, in patients suffering cardiogenic shock (Fig. 25-8).[168] Difficulty arises in assessing the results of mechanical assistance for patients following acute myocardial infarction and cardiogenic shock because of these different objectives.

Mechanical assist devices augment systemic perfusion and prevent end-organ damage while resting the stunned

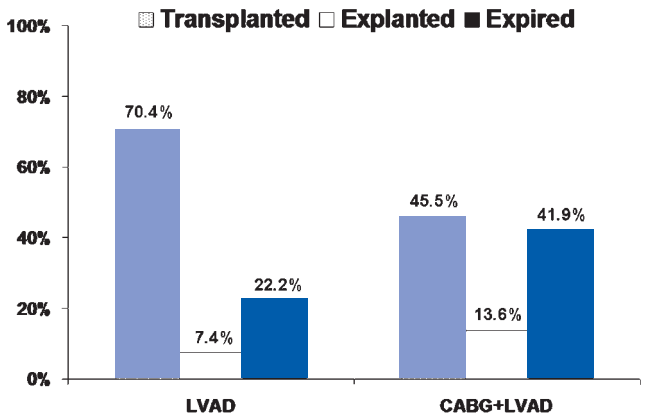

Figure 25-8. Outcomes of direct left ventricular assist device (LVAD) implantation versus coronary artery bypass graft (CABG) followed by LVAD implantation for cardiogenic shock. *(Reproduced with permission from Dang et al.[168])*

ventricle with complete or partial pressure-volume unloading.[169] Early studies of implantable LVADs have shown that end-organ function is an early predictor of mortality. Treatment of patients prior to end-organ deterioration is essential to improving the odds for long-term survival. In addition to affecting end-organ function, assist devices promote "reverse remodeling" by improving myocardial contractility and calcium handling, altering the extracellular matrix, and decreasing myocardial fibrosis.[168,170–173] Recent studies have shown that circulatory support early after myocardial infarction improved survival and offered a feasible bridge to recovery or transplantation.[13,14]

Decisions regarding specific device use depend on the degree of circulatory support needed and many other factors. Selection criteria for device placement include:

1. Potential reversibility of cardiac dysfunction
2. Cause of the cardiac dysfunction
3. Degree of right and left ventricular dysfunction
4. Amount of circulatory support needed
5. Importance of the device for myocardial functional recovery
6. Patient size
7. Anatomic location of collapse or deterioration
8. Whether the patient is a candidate for cardiac transplantation
9. Whether the patient can be anticoagulated
10. Expected duration of support
11. The patient's age and severity of comorbid conditions[174]

At New York Presbyterian Hospital (Columbia Center), several circulatory assist devices are available to aid treatment of each group. Short-term devices that can be placed percutaneously include the IABP, extracorporeal membrane oxygenation, and percutaneous assist devices. Devices that require sternotomy and are beneficial for short-term use include the ABIOMED and Thoratec pumps. Both these devices primarily treat stunned myocardium, but they are capable of bridging to transplant. These devices are easy to insert, do not require excision of ventricular muscle, and do not compromise ventricular function following device removal. These devices can be removed without the need to reinstitute cardiopulmonary bypass. These devices are effective in patients who require emergency support secondary to cardiogenic shock.

The Heartmate (Thoratec, Pleasanton, Calif) and Novacor (Ottawa Heart, Ottawa, Canada) LVADs are long-term pulsatile implantable assist devices that we use for bridging to transplantation. Initial reports of increased mortality in this high-risk patient population have been refuted by studies reporting higher-than-usual survival in acute myocardial infarction patients who received ventricular assist device support. At our facility, over 80% of this patient cohort have survived until transplantation, a result threefold better than that seen in databases of extracorporeal systems.

Second-generation assist devices employ axial flow rotors that can generate up to 6 L of flow (partial unloading of the left ventricle). These devices are driven by an electromagnetically actuated impeller drive shaft, contain fewer moving parts, and are smaller than pulsatile devices, thus making them less prone to mechanical failure and driveline infections, at least in theory.[175] The major disadvantages to axial flow pumps are the need for systemic anticoagulation, the lack of pulsatile flow, and incomplete pressure-volume unloading of the left ventricle; these concerns have limited its use in the post–myocardial infarction setting and further research is needed to clarify its therapeutic potential for these patients. A full discussion of mechanical circulatory support is reported in Chapter 67.

Weaning of Circulatory Support

Cardiac enzyme levels at the time of infarction, ECG changes, and the preinfarction condition of the ventricle help determine the likelihood of left ventricular recovery. If the ventricle is considered to be unlikely to recover, early use of a long-term device is rational. On the other hand, if recovery is possible, the heart should be rested for 3 to 5 days, loaded with the institution's choice of inotropic support including a phosphodiesterase inhibitor, and allowed to beat and eject. If a transesophageal echocardiogram or transthoracic echocardiogram on reduced support demonstrates recovery, the short-term support device should be removed in the operating room and kept available for 1 hour while the patient is observed for signs of decompensation. If the device cannot be removed within a week, the heart is not likely to recover. In this event, either a longer-term device is placed or patient support is discontinued.

We have reported a baseline left ventricular recovery in more than half of patients supported for a prolonged period with implantable devices. Upon removal of the device, most of these patients have redeveloped congestive heart failure in our experience[14] although other centers have reported high success rates.[176,177] As our understanding of the underlying

causes of left ventricular failure improve, we will be able to design targeted therapies that can be used with temporary device support to facilitate sustainable recovery.

Ethical Considerations

Programs that aggressively pursue surgical approaches to high-risk patients also must aggressively seek termination of care in futile cases. A liaison should be developed with a medical ethics individual or group to provide support for primary caregivers; however, the burden of medical decisions must rest with the attending physician. The family should not be forced to sign declarations withdrawing care unless significant controversy and/or the potential of legal action encumbers the decision. In the case of mechanical circulatory support, each pump of the device can be interpreted as a new intervention and therefore can be terminated if necessary. A precedent for this course of action has been set with mechanical ventilation. If significant neurologic or other end-organ dysfunction has developed and cardiac function has not returned, termination of support is reasonable and appropriate.

The Ethics Committee of the Columbia Presbyterian Center of The New York Presbyterian Hospital has drafted a statement that patients and physicians must review together prior to placement of a ventricular assist device (VAD), or when circumstances do not permit, immediately thereafter. The statement asserts that VAD restoration of hemodynamic stability in a patient with critical myocardial dysfunction may, for various reasons, not reach the goal of enabling the patient to receive a heart transplant or achieve adequate stability to be discharged home on the device.

The statement reads as follows:

> Every effort will be made to help our patients on ventricular assist devices (VADs) to improve to the point where they meet the criteria to receive a heart transplant, or stabilize enough to be discharged from the hospital on the VAD. However, if despite all our efforts, a patient has no reasonable chance of achieving either of these goals, we will discontinue the VAD, as it will, under these circumstances, no longer be serving the purpose for which it was originally used. When this occurs, the VAD will be discontinued only after the physicians caring for the patient are in agreement that the goals for VAD use cannot be met, and have consulted with the patient, or, when the patient is too ill, with the family or friends of the patient.

We believe that such a document is needed at the beginning of the patient's care to make clear to the family the goals of VAD use. Specifically, a VAD should not be used solely to prolong a patient's dying. Once a medical determination has been made by both the attending cardiac surgeon and the attending cardiologist that the patient cannot survive to leave the hospital, continued use of the VAD is inappropriate.

If the patient or his or her health care proxy or surrogates disagree with the decision to discontinue the VAD, the case is submitted to the ethics committee for arbitration.

SURGICAL MANAGEMENT

New York Presbyterian (Columbia Center) Approach

Patients who are potential transplant candidates and those who are dying of cardiogenic shock after myocardial infarction are all candidates for placement of a long-term implantable left ventricular assist device (LVAD) (Fig. 25-9). If at all possible, a coronary angiogram is obtained to allow revascularization with or without LVAD insertion. Surgery is delayed if the culprit vessel can be opened with angioplasty and the patient stabilized in the catheterization laboratory. If hemodynamics continue to deteriorate, the patient is taken directly to the operating suite, even if infarction occurred earlier than 6 hours before the planned procedure. Hemodynamic observations that favor early CABG are pulmonary artery pressures <60/30 mm Hg and cardiac output of more than 3 L/min. If the hemodynamics are worse, early implantation of a long-term implantable LVAD may be needed, especially if the mixed venous oxygen saturation is <50%. The decision to place a long-term LVAD is influenced by the patient score on a screening scale designed for this purpose (Table 25-6). These scores were selected to identify end-organ dysfunction (lung, liver, or kidney) and operative constraints (right-sided heart failure and bleeding). We have nearly a 90% survival if the summed scores are less than 5 points, versus 30% survival with summed scores greater than 5 points.[178] For this reason, if the total score is greater than 5 points, an attempt is made to stabilize the patient prior to beginning long-term LVAD insertion. Patients with lower scores are offered temporary LVAD.

If a patient is not a potential transplant candidate, our approach is more conservative, since we do not have a safety net if coronary revascularization fails and a temporary support device is inserted. An angiogram must be obtained; if hemodynamics are not favorable and no acute ischemia is present, we delay surgery until pulmonary arterial pressures fall. If the patient is ischemic, we proceed with CABG as described below. If the patient cannot be separated from bypass without high-dose inotropic support including alpha agonists, if the cardiac index is less than 2 L/min per meter squared, and if left-sided filling pressures remain high with mixed venous oxygen saturations of less than 50%, short-term LVAD support with the ABIOMED system is instituted. IABP alone in this patient population often does not prevent death and almost always results in significant renal, hepatic, and pulmonary dysfunction that significantly complicates patient recovery even if adequate cardiac function returns. Most important, stressing the

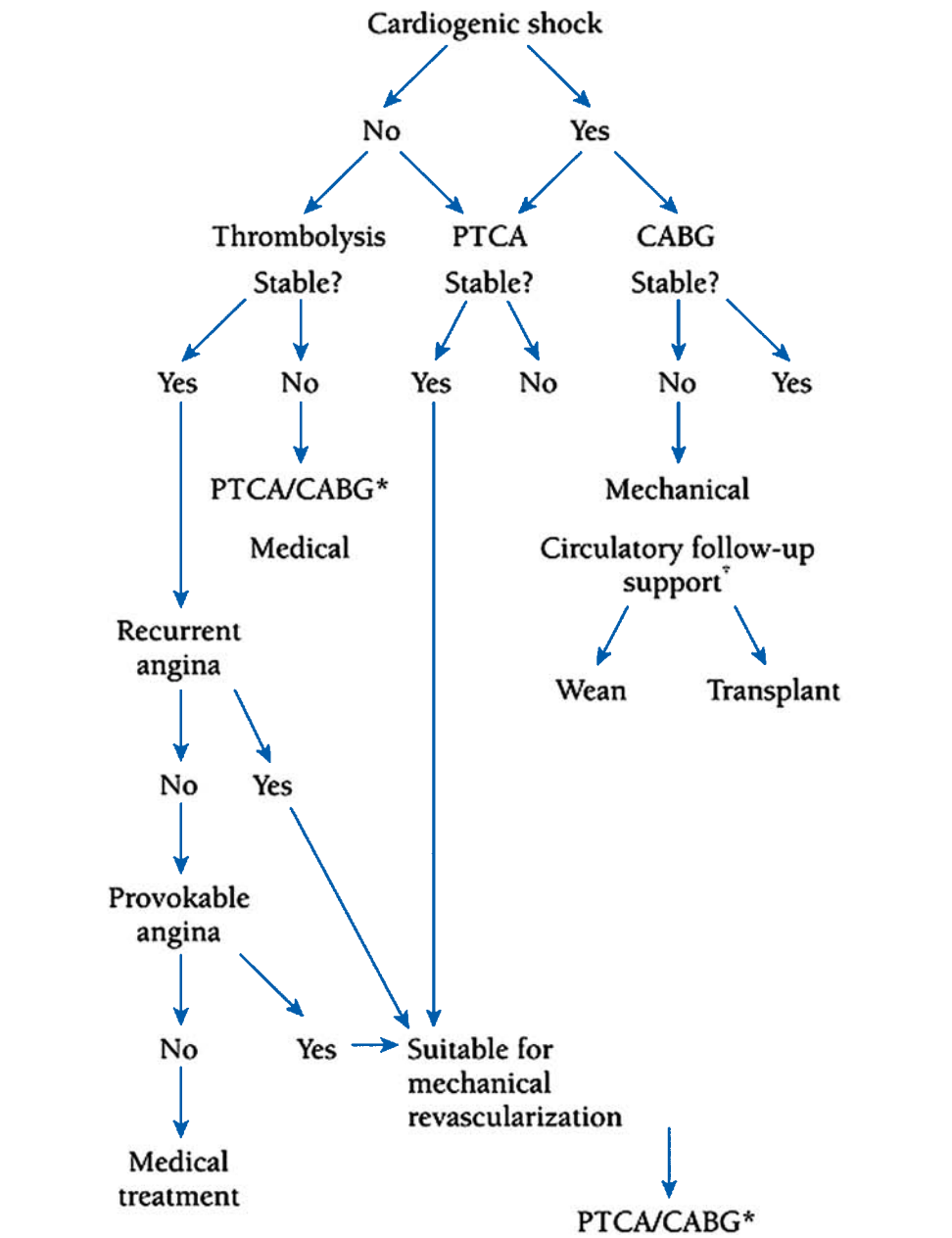

Figure 25-9. Acute myocardial infarction algorithm.

heart with high-dose inotropic agents and high filling pressures when it is weakest during the early reperfusion period after acute infarction may compromise border zone regions. This concern is especially true of patients with older infarctions (more than 6 hours). We err on the side of implanting this short-term device early, since the survival rate is only 7% if the device is inserted after a cardiac arrest in the recovery room.

Operative Techniques for Acute Myocardial Infarction

Anesthesia

Anesthesia is provided by a rapid narcotics-based regimen with perfusion and surgical teams prepared to respond to catastrophic hypotension or cardiac arrest. Transesophageal probes are always placed in these patients if possible. As the

Table 25–6.

Preoperative Risk Scale for Left Ventricular Assist Device Placement*

Criteria	Points
Urine output <30 mL/h	3
Intubated	2
Prothrombin time >16 seconds	2
Central venous pressure > 16 mm Hg	2
Reoperation	1

A combined score of >5 is associated with a 70% mortality risk.

patient is prepped, a test dose followed by a loading dose of aprotinin is given.

Bleeding

Bleeding is a significant complication of emergency CABG and often results in further myocardial depression and pulmonary hypertension. Cytokine release induced by infusion of blood products and thromboxane A_2 released by cardiopulmonary bypass stimulate pulmonary hypertension, which can be catastrophic in the setting of right ventricular ischemia. Use of aprotinin decreases bleeding during CABG[179,180] and reduces right-sided heart failure and death after LVAD insertion.[181] There are reported cases of aprotinin use following thrombolytic therapy for acute myocardial infarction.[182] Successful use of aprotinin for reoperative, emergency, or high-risk CABG is common in many institutions.

The use of clopidogrel deserves special mention, and its expanding administration can pose unique problems for the cardiac surgeon. Clopidogrel, an oral irreversible antagonist of the 5′-adenosine diphosphate that inhibits platelet activation and aggregation, is used extensively in patients with acute coronary syndromes and has been shown to lower cardiovascular risk by up to 20%, and reduce reinfarction and stroke rates;[183,184] in addition, it is commonly given prior to percutaneous interventions and after intracoronary stenting to prevent thrombosis. However, patients frequently require surgical revascularization after medical therapy or cardiac catheterization while taking clopidogrel. The risk of bleeding after clopidogrel and cardiac surgery can be substantial. In multiple reports, the risk of reoperation for hemorrhage in patients receiving clopidogrel within 7 days of cardiac surgery was six times higher, and patients required more blood, platelet, and fresh frozen plasma transfusions.[185–187] Due to these complication rates and the inability to reverse clopidogrel's effect on platelets, surgery is often delayed until platelet function is restored, which may take 7 to 10 days, or the life of the platelets. Emergent surgery while taking clopidogrel necessitates frequent blood product transfusions and confers significant morbidity, and possibly mortality. Further study is underway to determine if current dosing regimens after acute myocardial infarction can be reduced to lessen bleeding complications.

Choice of conduits

For emergency cases, the choice of conduit should not differ from elective cases in most circumstances. The internal mammary artery is not associated with a higher number of complications compared with saphenous vein grafting in emergent situations and can be used in most circumstances.[188,189] There is one reported case of successful use of polytetrafluoroethylene for coronary revascularization in a patient in shock.[190]

Intraoperative considerations

Decompression of the ventricle during revascularization after acute coronary occlusion decreases muscle damage and improves functional outcome by decreasing wall tension and reducing oxygen consumption (Figs. 25-10 and 25-11).[85] Indeed, ventricular decompression reduces metabolic energy consumption by 60%. Diastolic basal arrest, by avoiding the energy of contraction, is the second most important means of minimizing oxygen consumption and further reduces metabolic energy consumption by 30%. Cooling of the patient and heart has an impact only on the final 10% of basal energy requirements.

Reduction of myocardial energy consumption is best achieved by early institution of cardiopulmonary bypass to maintain a high perfusion pressure. If a coronary salvage catheter has been placed across a tight coronary lesion, the catheter is left in place until just before cross-clamping.

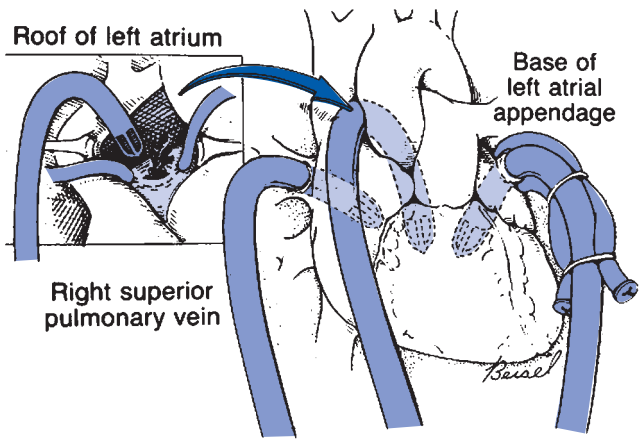

Figure 25-10. The inflow cannula for short-term left ventricular assist device support can be placed through the right superior pulmonary vein, the dome of the left atrium, or the left atrial appendage. Lighthouse tip cannulas allow improved venous return.

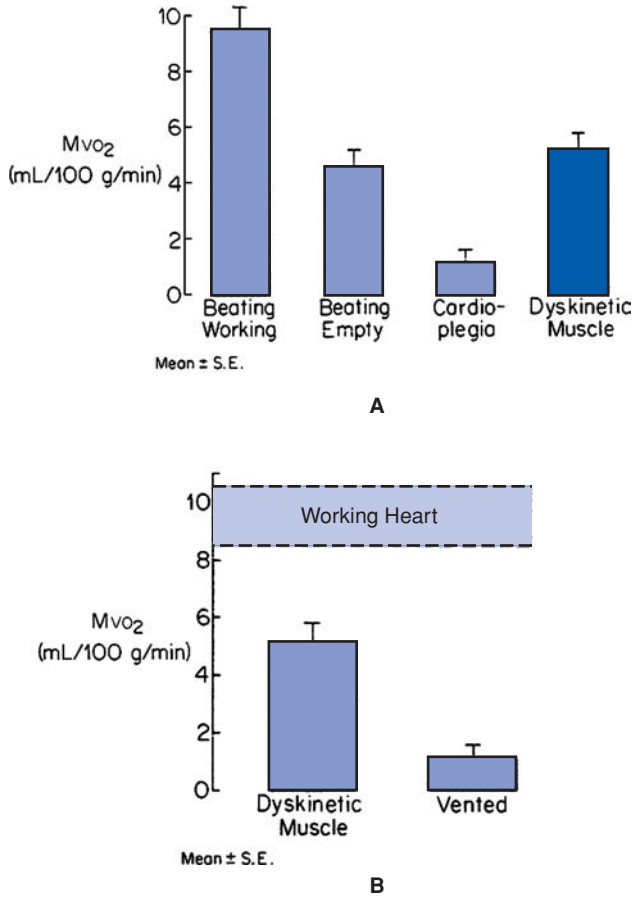

Figure 25-11. (A) Myocardial oxygen uptake (MVO_2), measured in milliliters per 100 grams per minute, in beating and working, beating and empty, and arrested hearts. Values after cardioplegia were determined both during cardiopulmonary bypass (cardioplegia) and during regional cardioplegic reperfusion in the working heart (dyskinetic muscle). Note (1) marked fall in MVO_2 with cardioplegia in the decompressed heart and (2) oxygen requirements of dyskinetic muscle increase fivefold over cardioplegia alone, and equal almost 55% of beating, working needs. (B) Regional oxygen uptake during selective cardioplegic reperfusion in dyskinetic and vented cardiac muscle. Stippled areas show requirements in working heart (8.5 to 10.5 mL/100 g/min). Note (1) high oxygen demands of dykinetic muscle and (2) marked reduction in demands when noncontracting muscle is decompressed by venting. *(Reproduced with permission from Allen et al.[85])*

Antegrade and retrograde catheters are placed prior to cross-clamping to allow quick instillation of retrograde cardioplegia and protection of the territory supplied by the occluded or compromised vessel. The standard Buckberg protocol is followed, including warm induction to allow regeneration of depleted adenosine triphosphate stores.

If the territory at risk is grafted by saphenous vein, this anastomosis is performed first to allow direct instillation of cardioplegia into the territory at risk. The proximal anastomoses should be performed prior to removal of the cross-clamp to allow complete perfusion of the entire heart upon removal of the cross-clamp. The role of off-pump CABG in this setting is appealing, but remains unproven.

While large ventricular aneurysms are treated by resection and patch, debate surrounds smaller aneurysms. Our group does not resect small aneurysms, but some groups are more aggressive. If an aneurysm is resected, the defect is repaired with a patch of bovine pericardium sewn to the fibrotic rim of the endoaneurysm surface. The native left ventricular wall is closed over the patch.

Utilization of the Dor procedure (endoventricular circular patch plasty repair) in the post–myocardial infarction setting is a controversial subject. Recent data have shown that surgical remodeling improves systolic function, ejection fraction, and intraventricular dyssynchrony.[191–193] However, a large clinical trial is needed to definitively answer this question.

Postoperative care

A higher incidence of complications in shock patients compared with nonshock emergencies has been reported. Guyton and associates[148] report a 47% complication rate associated with cardiogenic shock, compared with 13% for patients with nonshock emergencies. This increase in complications probably reflects the preoperative condition of the patients rather than the treatment itself. Long-term follow-up in patients following emergency surgical revascularization shows that survival rates are closely correlated with postoperative ejection fraction and left ventricular size.[194,195]

FUTURE THERAPIES AND TRENDS

Improving outcomes in patients suffering acute myocardial infarction can occur through pharmacologic advances, optimization of existing practices, and application of new technology. Various medications have been described that reduce ischemic-reperfusion injury and limit infarct size in animal models, such as oxygen-derived free radical scavengers, folic acid, nitric oxide inhibitors, and others;[196] clinical study of these promising drugs will determine their efficacy. Sudden death after myocardial infarction may be reduced with administration of omega-3 fatty acids.[197] Reducing transport time to the hospital after the onset of symptoms and implementation of clinical guidelines have been initiatives of many hospitals and emergency services. The increased number of local hospitals able to perform primary percutaneous interventions has meant quicker revascularization, and thus improved outcomes.[22] This trend should continue in the future. Mechanical circulatory support has advanced greatly over the past 10 years, and pumps have become smaller, safer, less invasive, easier to use, and easier to implant. The indications for LVAD use are expanding in this population, and they may allow myocardial recovery to occur in select patients requiring hemodynamic support after acute infarction. The option of living long-term with these devices has also become a reality. Finally, the rapidly emerging field of cellular therapy holds great promise for repair of damaged

myocardium. A number of cell types, such as endothelial progenitor cells, mesenchymal stem cells, skeletal myoblasts, resident cardiac stem cells, and embryonic stem cells, are being investigated;[198] the optimal cell type, mode of delivery (intracoronary artery infusion, intravenous infusion, transendocardial injection, and transepicardial injection), and timing of administration have yet to be determined. Nevertheless, early clinical trials suggest that cellular therapy may offer benefits. One-year follow-up of 59 patients suffering acute myocardial infarction in the TOPCARE-AMI trial who received either circulating progenitor cells or bone marrow–derived progenitor cells demonstrated increased cardiac function and reduced ventricular dimensions, without adverse events.[199] Numerous other clinical trials are underway to address questions regarding mechanisms of benefit, cell viability, and dosing. Future randomized clinical trials will be required to establish outcome benefit.

CONCLUSION

The treatment of acute myocardial infarction should be divided into two approaches. Uncomplicated acute myocardial infarction can be treated in most community hospitals. In most areas of the country, these patients are treated effectively with thrombolytic therapy and medical management. For communities and facilities that have catheterization laboratories, primary angioplasty may be more cost-effective and produces improved results. At this time, emergency coronary artery bypass surgery is not the most cost-effective approach; randomized controlled studies to demonstrate advantages of emergency CABG have not yet been performed.

The approach to acute myocardial infarctions complicated by cardiogenic shock presents a more difficult problem. Mortality rates are high with medical management. Reperfusion therapy is the only real hope for improved survival in this group of patients. Thrombolytic therapy is associated with poor outcomes. Early PTCA and CABG are the primary options in patients under the age of 75. Mechanical circulatory assistance has an important role for supporting patients until the myocardium recovers. Use of pharmacologic agents and means to control reperfusion are important areas of current research and development. Assist devices and artificial heart programs offer indispensable options and must be considered in this patient population, especially since all therapies offer suboptimal results.

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CHAPTER 26

Minimally Invasive Myocardial Revascularization

Volkmar Falk • Friedrich W. Mohr

The term *minimally invasive coronary artery bypass grafting* is not well defined. According to one definition, avoidance of cardiopulmonary bypass (CPB) is considered essential in decreasing the morbidity associated with conventional coronary artery bypass grafting (CABG).[1] Other authors consider the median sternotomy as a potential source for morbidity, referring to the risk of mediastinitis and the associated delayed return to daily life activities.[2] Accordingly, a number of surgical strategies have evolved to avoid the need for extracorporeal circulation and to minimize surgical access. At the same time, it was widely recognized that open harvesting techniques for bypass grafts often are associated with wound-healing problems, especially in diabetic patients. As a consequence, endoscopic harvesting techniques for both venous and radial artery grafts have been developed.

OFF-PUMP CORONARY ARTERY BYPASS GRAFTING (OPCAB)

For decades, CABG was performed with cardioplegic arrest and on CPB. A decompressed, nonbeating heart, a bloodless surgical field, and easy exposure were regarded essential for success of the procedure. Results were excellent, mortality declined constantly, and standard CABG became the "bread and butter" of our profession.

Anecdotal reports on the deleterious effects of CPB and systematic reports examining the pathophysiology of extracorporeal circulation started to question the dogma of "the pump is your friend." CPB is associated with (1) a systemic inflammatory response, (2) release of cytokines, (3) activation of the clotting cascade, (4) metabolic changes, (5) microembolization, and numerous other adverse effects. Although tolerated in most cases, these effects alone or in combination may cause substantial morbidity and thus affect the results of the procedure. With an ever-aging population and increasing comorbidity, surgeons all over the world sought to further minimize the risk of CABG, and it seemed logical to question the role of CPB in CABG.

The evolution of *off-pump coronary artery bypass grafting* (OPCAB) is closely linked to the development of stabilizers that became available in the early 1990s. Initially, pure pressure stabilizers were engineered, but it soon became obvious that exposure of the back wall of the heart would require additional means of support. With the introduction of vacuum-assisted stabilizers by the Utrecht group, local myocardial immobilization was greatly facilitated and independent of the area of revascularization and OPCAB gained popularity. Despite better stabilizers, it was recognized that OPCAB requires a team approach and awareness of the sudden hemodynamic changes that may occur during the procedure.

Anesthesia Requirements

In most centers, general anesthesia is applied, and the patient is intubated. Incidental reports indicate that the operation is also possible on the awake, spontaneously breathing patient under high epidural anesthesia.[3] Standard monitoring is applied. In addition, some centers prefer online cardiac output measurement using the PICCO or similar methods.[4] A Swan-Ganz catheter is usually not helpful and potentially can cause arrhythmia when the heart is positioned during the procedure. It is of utmost importance that the patient is kept warm at all times during the procedure. Temperature management includes placing the patient on a warming blanket, using warm infusions, and keeping the room temperature high. Volume management is essential because it is the preferred means for counterbalancing hemodynamic changes. Exposure of the back wall of the heart usually causes some degree of right ventricular outflow obstruction that can be treated adequately by increasing venous return by tilting the operating room table to the right with the head low. Since no

CPB is used and filtering is not possible, intravenous volume overload must be avoided, especially in end-stage renal failure (ESRF) patients. The use of inotropes should be reserved for those with severe hemodynamic alterations only because they invariably increase the heart rate and thus complicate the procedure. In a recent review of human factors associated with manual control and tracking, it was pointed out that the human operator can at his or her best track a three-dimensional motion (such as the beating heart) only up to a frequency of 1 Hz, which happens to equal a heart rate of 60 beats per minute.[5] Higher frequencies cannot be tracked, and thus the preferred heart rate should be kept in the range of 50 to 70 beats per minute to simplify suturing. In case of atrial fibrillation, pharmacologic slowing of the heart rate and temporary ventricular pacing using an epicardial pacing wire may facilitate the procedure. The use of a Cell Saver is recommended to minimize the risk for blood transfusion, which is rarely necessary. If less than 500 mL is collected, the blood usually is discarded.

Surgical Technique

After standard median sternotomy, single or bilateral internal thoracic artery (ITA) harvesting is performed. The patient is heparinized (150 units/kg), keeping the activated clotting time (ACT) at a level above 300 seconds. If an arterial T-graft is to be performed, the radial artery should be anastomosed to the left internal thoracic artery (LITA) with the pericardium still closed because there is less motion and immediate blood supply is warranted after the distal anastomosis. In order to facilitate exposure of the heart, it is recommended to divide the pericardial and mediastinal attachments. Opening of the right pleura may become necessary in severely dilated hearts. After the pericardium is opened, pericardial stay sutures are placed to aid in exposure of the heart. Numerous methods have been proposed for placing these sutures. Ideally, three or more sutures are placed beginning at the level of the right upper pulmonary vein all the way down distally to the lowest point of the epicardial sac (Fig. 26-1). To avoid damage to the myocardium, the sutures should be covered by plastic tubing; sponges may be used alternatively. Placement of the stay sutures should be done slowly because abrupt changes in positioning of the heart may cause undesired hemodynamic alterations. The sequence for the grafts depends largely on the individual needs of the patient. In general, the left anterior descending (LAD) artery is the most important target vessel and the easiest to bypass. Therefore, revascularization should start with a LITA graft to the LAD. By lifting the stay sutures, the LAD comes easily into view. The stabilizer is placed at the site of the anastomosis, and dissection of the surrounding tissue is begun. If the vessel is covered by excessive fat or muscle, low-energy cautery and clipping of epicardial veins may help to ensure minimal bleeding from the surrounding tissue. Once the site for the anastomosis is identified, the stabilizer is placed so as to ensure enough space for suturing and equal distance to the stabilizer feet. Vacuum stabilizers should be locked only after vacuum is applied and the stabilizer sucks to the surface. Only a small amount of pressure then will be required to immobilize the heart. This not only minimizes the hemodynamic impact of the stabilizer but also decreases the amount of residual motion. Excess pressure from the stabilizer will cause increasing motion as the heart works with more force against its compression. Temporary occlusion of the target vessel can be achieved in many ways. Surrounding 4-0 felt-pledgeted sutures or Silastic tapes are used widely. The occlusion tapes ought to be placed at a distance from the anastomosis to avoid compression of the target vessel at the level of the anastomosis and thus allow for easy suturing. The suture needs to be placed deep enough in the tissue to avoid damage of the target vessel. Distal occlusion should be avoided in general and is rarely necessary even in occluded vessels. Care must be taken to stay outside stented areas because the occlusion tapes may bend or kink an implanted stent. The incision usually is made before the occlusion suture is tightened to ensure complete filing of the vessel, which will minimize the risk of back wall injury. The suture then is tightened gently until bleeding stops. If there is only minimal coronary blood flow, occlusion may not at all be necessary. A CO_2 blower-mister is used to control residual bleeding from septal branches or the distal coronary at a rate not exceeding 5 L/min. Excessive blowing can cause dissection of both the graft and the coronary artery or cause air embolism. The use of coronary artery shunts is controversial because they also may cause endothelial damage. If shunts are used, care must be taken to ensure atraumatic placement. The anastomosis is performed in a running fashion in the usual way. The circumflex artery and its branches are grafted next in a sequence that is dictated mainly by the individual anatomy and the preference of grafts. The distal circumflex artery is regarded as the most challenging vessel to graft during OPCAB because exposure may be difficult. In large hearts, it may be necessary to open the right pleura and divide the right-sided pericardium low to the level of the phrenic nerve. This will allow displacement of the heart underneath the

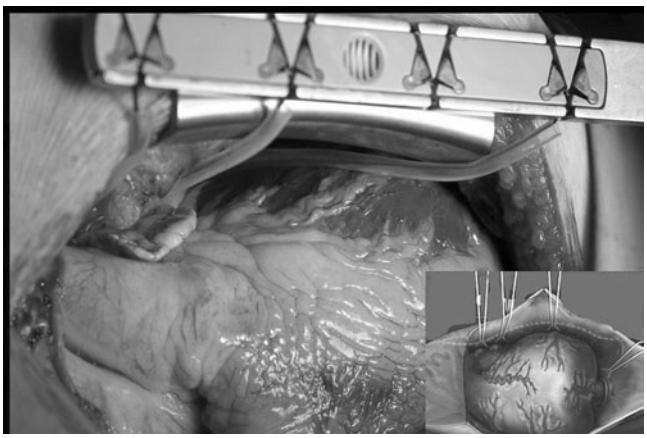

Figure 26-1. Setup for off-pump coronary artery bypass grafting. Placement of pericardial stay sutures.

sternum into the right pleural cavity. This maneuver minimizes right outflow tract obstruction and exposes all posterior vessels. After the circumflex artery, the right coronary artery (RCA) and its branches are grafted. If the RCA is the dominant vessel and the stenosis is less than 80%, it may be necessary to use a shunt because ischemia of the atrioventricular (AV) nodal artery on occlusion of the RCA can cause acute AV block. It is therefore advisable to place and connect a temporary pacing wire before occluding the vessel.

To maximize both the short- and long-term benefit of an OPCAB procedure, arterial grafting is preferred. This will obviate the need for aortic clamping, another source for emboli and independent predictor of stroke.[6] If vein grafts are used, the proximal or distal anastomosis can be performed first. It is of utmost importance to partially clamp the aorta under low pressure. This can be achieved via a brief period of inflow occlusion by manually compressing the inferior vena cava. This maneuver also should be repeated for declamping. Intraoperative graft patency control using transient-time Doppler or other means is recommended. If the operative field is dry, heparin usually is not completely antagonized. Postoperatively, aspirin is begun on the day of operation.

Special Situations

In patients with unstable angina, in low-output states, or with ejection fraction (EF) below 20%, the preoperative implantation of an intra-aortic counterpulsation pump (IACP) may be useful. Patients with atrial fibrillation (AF) show an irregular contraction pattern that may distract during suturing (regular-motion patterns allow the development of coping strategies such as the "wait and see" strategy that are less effective when motion is unpredictable[4]). It therefore may be helpful to slow the heart rate pharmacologically and temporary pace the patient in a VVI mode. If AF is paroxysmal, epicardial ablation of the pulmonary veins on the beating heart may be applied.

Results

The number of OPCABs performed has reached 30% of all coronary revascularizations worldwide, in some countries exceeding 80%. In some units, OPCAB is used almost exclusively with no patient selection.

When discussing outcomes, it is important to keep in mind that despite the fact that propensity scoring was applied for most analyses, some selection bias cannot be excluded. As pointed out by Sergeant and colleagues, clinically relevant reductions of mortality, stroke, and renal failure with the OPCAB approach mandate large cohorts of patients to reach statistical significance in the presence of above-standard on-pump performance.[7] When the first reports on OPCAB were published, concerns were raised regarding (1) incomplete revascularization[8–11] and (2) impaired graft patency due to a more challenging technique.[12] These concerns are no longer justified. In contemporary series, completeness of revascularization is achieved on a routine basis. In the SMART study, 200 unselected and randomized patients received an average of 3.4 grafts in both on- and off-pump CABG.[13] The few studies that provide angiographic data on graft patency reveal equal patency rates for on- and off-pump bypass surgery.[13,14]

Regarding operative and short-term mortality, most studies are in favor of OPCAB. In a retrospective analysis of the Society of Thoracic Surgeons database for the years 1999 and 2000, including 17,969 OPCAB patients (8.8% of total), a significant survival advantage with OPCAB compared with on-pump CABG was demonstrated by risk-adjusted multivariate logistic regression analysis [odd ratio (OR) 0.76, 95% confidence interval (CI) 0.68–0.84] and conditional logistic regression of propensity-matched groups (OR 0.83, 95% CI 0.73–0.96).[15] Similar results have been reported from another multicenter analysis consisting of some 7283 patients by Mack and colleagues. Following propensity score matching and multivariate regression analysis, the use of CPB was identified as an independent predictor of mortality (OR 2.08, 95% CI 1.52–2.83, $p < .001$).[16] Especially in high-risk populations (e.g., the elderly, those with EFs below 30%, and obese patients), OPCAB seems to offer a survival benefit.[17–20] There are only sparse data on the midterm outcome. After 2 and 4 years, similar survival has been reported.[8,21]

There is growing evidence that neurocognitive outcome is better and stroke rate is reduced after OPCAB.[23–25] According to a number of studies, CPB is an independent predictor of adverse neurologic outcome.[26] The embolic load measured by transit-time Doppler of the medial cerebral artery is reduced significantly during OPCAB.[27–29] Within the OPCAB group, partial clamping remains an independent predictor of stroke, and a no-touch technique using all arterial grafting therefore is advocated by some.[6] The risk of renal failure is decreased in off-pump surgery,[30–32] especially in high-risk groups with preoperative renal insufficiency.[33,34]

The incidence of postoperative atrial fibrillation is reduced after OPCAB,[34,35] and biochemical markers for myocardial injury (e.g., creatinine kinase and troponin) are reduced after OPCAB.[36–38] Blood loss is less, and transfusion rate is reduced.[20] Overall, OPCAB reduces hospital costs by 15 to 35%[19,39] possibly owing to decreases in length of stay and resource utilization.[19]

In a thorough meta-analysis, the International Society for Minimally Invasive Cardiac Surgery Consensus Group recently has published the current evidence for OPCAB.[20] Accordingly, OPCAB reduces mortality and length of stay and the incidence of postoperative myocardial infarction (MI), renal failure, AF, and transfusion rate in mixed-risk and high-risk patients (Fig. 26-2).

MINIMALLY INVASIVE DIRECT CORONARY ARTERY BYPASS (MIDCAB)

One goal of minimally invasive cardiac surgery has been to avoid sternotomy to reduce the amount of surgical trauma and avoid wound complications. Therefore, techniques for

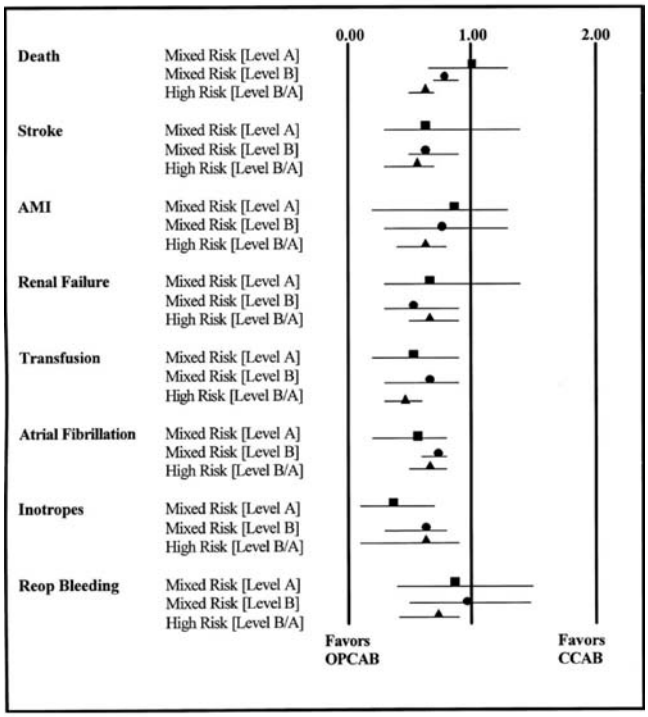

Figure 26-2. Comparison of pooled outcomes for mixed-risk and high-risk patients. *Square:* 3369 mixed-risk patients from 37 randomized trials (level A) (Cheng 2004). *Dot:* 198,204 patients from 13 nonrandomized trials (level B) (Beattie 2004). *Triangle:* 26,349 high-risk patients from 42 nonrandomized and 3 randomized trials (level A) (ISMICS Consensus Meta-Analysis 2004). (*Reprinted from Puskas et al*[20] *with kind permission from Innovations.*)

MR on the beating heart without sternotomy were developed. The operation was termed *minimally invasive direct coronary artery bypass* (MIDCAB), and since its introduction in the mid-1990s,[40–44] it has found a widespread application. In some centers, MIDCAB is the preferred method of surgical revascularization for isolated coronary artery disease (CAD) of the LAD coronary artery. In addition, MIDCAB is a valuable alternative to standard CABG or OPCAB in selected high-risk patients with multivessel disease and extensive comorbidity, who are at a high risk for sternotomy-related complications.

Anesthesia

Standard monitoring is applied, and temperature management as for OPCAB is applied. Since single-lung ventilation is used, a double-lumen tube or bronchus blocker is applied to provide selective right lung ventilation. To allow for fast extubation, short-acting anesthetics are used.

Surgical Technique

Standard MIDCAB usually is performed through a muscle-sparing minithoracotomy. After making a 5 to 6 cm anterolateral incision in the fifth iintercostal space or the inframammary fold, the pectoralis muscle is displaced bluntly with minimal division following the muscle fiber orientation (muscle-sparing approach). This will decrease the likelihood of lung herniation that has been reported infrequently with this approach. The chest then usually is entered one intercostal space higher than the actual incision. Excessive rib spreading must be avoided at all times to prevent dislocation or fracture of ribs. Removal of a rib is almost never necessary. Takedown of the LITA usually is performed under direct vision, but endoscopic ITA takedowns using a harmonic scalpel or telemanipulation systems have been reported.[44–46] For dissection of the LITA under direct vision, the left lung is deflated. The intrathoracic fascia is divided to facilitate takedown of the LITA, which usually is done in a pedicled manner. Takedown is performed from the fifth intercostal space to the origin of the subclavian artery. Additional length can be gained by dividing the mammary vein at its junction with the subclavian vein. Side branches are clipped or cauterized based on the preference of the surgeon. Heparin is administered prior to distal transsection of the graft. The ACT is kept at a level of 300 seconds. After opening the pericardium above the course of the LAD, the target vessel is identified. The pericardium should be opened 3 cm above and parallel to the phrenic nerve all the way to the aorta to allow visualization of the left atrial appendage and the groove between the aorta and the pulmonary artery. This will facilitate location of the target vessel if excess epicardial fat or an intramuscular course is present. To enhance exposure, one or two pericardial stay sutures may be used to rotate the heart. Standard reusable pressure stabilizers are used to immobilize the target region (Fig. 26-3). Vacuum stabilizers in general are too bulky and not required for a single anastomosis to the LAD. Proximal LAD occlusion is performed using

Figure 26-3. Minimally invasive direct coronary artery bypass. Through a muscle-sparing incision, the left anterior descending artery is easily exposed; standard pressure stabilizers are used.

a 4-0 felt-pledgeted suture or vessel loops. Preconditioning is not helpful, and the use of shunts is rarely necessary, but they may be applied based on the preference of the surgeon. Distal occlusion is avoided whenever possible (99% of patients). A blower-mister is used in all cases to achieve a bloodless field. The anastomosis then is performed in a standard fashion. Graft patency assessment is performed using transit-time Doppler. A single chest tube is inserted into the left pleural space, and intercostal nerve blockade is applied using local anesthetics. Patients are started on antiplatelet therapy on the day of operation. Extubation usually is performed on the table or a few hours postoperatively.

Results

A number of papers have reported excellent results with this approach. Immediate angiographic patency rates are in the range of 94 to 98% and thus similar to those reported for conventional CABG.[43,47] At 6 months, patency rates of 94% have been reported.[48] Reported in-hospital mortality for MIDCAB is less than 1% and compares favorably with the off-pump single-bypass mortality of 1.4% and with the mortality of single bypass with CPB of 3.6% that was been reported in the registry of the German Society for Thoracic and Cardiovascular Surgery in 2004.[49] The rates of perioperative major complications such as stroke, MI, and the need for target-vessel reintervention are low as compared with standard CABG.

In our own series of 1461 patients who underwent MIDCAB from 1996 to 2005, in-hospital mortality was 0.8% (predicted mortality by Euroscore 3.6%), and stroke rate was 0.4%. Conversion to sternotomy was necessary in 1.8%. A total of 709 patients received routine postoperative angiogram demonstrating a 95.6% early patency rate. At 6 month follow-up, graft patency was 94.3% ($n = 350$). Five-year survival is 91.5% (95% CI 89.51–93.5%) (Fig. 26-4*A*). The freedom from MACCE and angina after 5 and 7 years was 88.6% (95% CI 86.4–90.9%) (see Fig. 26-4*B*). These results are in accordance with the findings of other groups.[48,50,51]

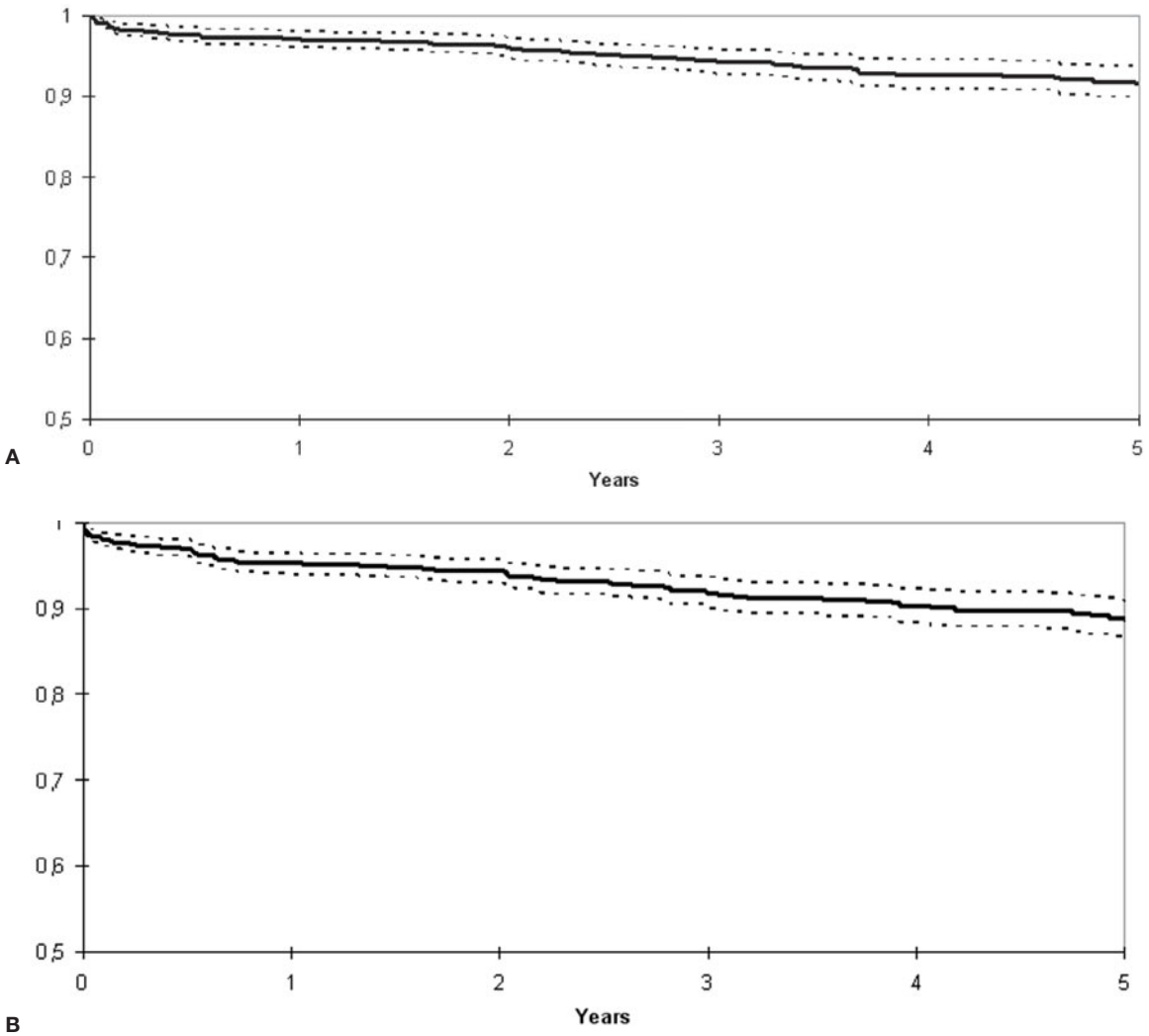

Figure 26-4. Five-year survival curve (*A*) and event-free survival curve (freedom from death, myocardial infarction, stroke, freedom from angina, freedom from reintervention) (*B*) after minimally invasive direct coronary artery bypass. Data from 1461 patients undergoing MIDCAB at the Heartcenter Leipzig.

A few randomized trials comparing MICAB versus bare metal stenting have demonstrated better early patency and superior freedom from target-vessel reintervention and angina for the surgical group up to 5 years of follow-up.[52–56]

Operating through limited access and on the beating heart remains challenging, however, and efforts to facilitate the graft-to-coronary-artery anastomosis under the constraints of a limited working field led to the development of a number of anastomotic devices,[57,58] some of which were used in MIDCAB and endoscopic bypass grafting.[59,60] Given the mixed results, most of these devices are of historic interest only.

Some studies have pointed out that the lateral approach is associated with higher pain levels than sternotomy mainly owing to the excessive rib spreading required for visualizing the LITA during takedown.[44] Rib dislocation or fracture has been reported infrequently with this approach. Direct harvesting of the LITA is regarded as technically challenging and has been one of the arguments for many surgeons to disregard MIDCAB as the primary operation for patients who require surgical revascularization of the LAD. Limited working space and incomplete vision are blamed for insufficient graft length, incomplete mobilization, and the occasional reports of LITA injury or injury of the subclavian vein.

Techniques for endoscopic LITA takedown therefore were introduced to facilitate graft takedown in MIDCAB and to avoid excessive rib spreading. A number of papers have been published on the subject, demonstrating the potential advantages of an endoscopic inferior mammary artery (IMA) harvest: less pain, better visualization, and better access to the proximal and distal portions of the graft.[45,46] Despite these advantages, endoscopic IMA harvest using standard endoscopic tools has not found widespread application. Most cardiac surgeons were not familiar with endoscopic surgical techniques and not willing to accept their limitations: monocular vision, limited dexterity, impaired hand-eye alignment, working with fulcrums, impaired tactile feedback, and increased difficulties in the handling of complications such as bleeding and injury of the graft.

With the introduction of computer-enhanced telemanipulators into the field of cardiac surgery, some of these limitations were overcome, as outlined below. The surgical skills required for a safe takedown of the ITA therefore are easily transferable into a closed-chest environment.

The technique of "robot-assisted" takedown is relatively straightforward and requires only minimal conceptual changes. The ITA is easily visualized, and takedown can be performed as a pedicle or skeletonized process based on the preference of the surgeon.[61] As compared with direct takedown through a lateral thoracotomy such as in MIDCAB, the conduit usually is longer with an endoscopic harvesting technique because distal takedown is greatly facilitated. The learning curve, which is long for a standard endoscopic technique and a source of great frustration, is relatively short for the robot-assisted endoscopic technique. Most surgeons will master the technique in 30 to 40 minutes after a step learning curve including some 20 patients.[62] While with standard endoscopic techniques any further manipulation of the graft, the pericardium, or the heart is extremely difficult, if not almost impossible, in situ preparation of the distal end for the anastomosis is accomplished easily using a telemanipulation system. In patients with a suitable anatomy and coronary morphology, the revascularization procedure can be continued and completed endoscopically on the beating heart. Bilateral endoscopic harvest, which is helpful for multivessel small-thoracotomy approaches, is greatly facilitated.

Even with improved outcomes of interventional procedures and less in-stent restenosis with the use of drug-eluting stents, MIDCAB, given its good long-term results, will remain a true alternative for patients with single-vessel disease, especially for complex ostial lesions, chronic occlusions, and repeated in-stent restenosis.

TOTAL ENDOSCOPIC CORONARY ARTERY BYPASS GRAFTING (TECAB)

The possibly least invasive approach for surgical revascularization is *total endoscopic coronary artery bypass grafting* (TECAB) on the beating heart. Although desirable, the closed-chest approach imposes a number of anatomic and technical challenges that have to be met. The closed chest can be described as a confined space that presents the human operator with the challenge of a remote work environment requiring microsurgical precision. Working through ports has long been known for limiting the available space to perform motions, for substantially decreasing the dexterity of the operator, and for altering the hand-eye coordination.[63] Active assistance, an indispensable component of open surgery, is difficult in thoracoscopic procedures. The transition from limited-access cardiac surgery to endoscopic cardiac surgery therefore complicates the procedure substantially and has rendered previous attempts at endoscopic CABG using conventional endoscopic instruments impossible. To overcome some of the instrument-related limitations, computer-enhanced instrumentation systems have been developed.

Principles of Telemanipulation Technology

The field of telemanipulation surrounds the science and technology involved in enhancing or enabling human interaction with a potentially hazardous environment or performance in confined spaces. The operator involved in the interaction is physically removed but not necessarily remote from the environment in which he or she wishes to perform work. This separation between the operator and the object is bridged by a computer-controlled electromechanical system that serves to transmit the human's actuation commands to the environment and conversely feed back sensory information from the environment to the operator. Three key components comprise a telemanipulator system. The first two components, a master and slave manipulator pair, provide kinesthetic coupling between the human operator and the remote object. This coupling implies that force commands

from the human are replicated at the environment site and that forces generated by the interaction at the environment site are reflected back to the human. This force coupling is essential to enable the human to perform physical work in the environment in a manner that is intuitive and productive. The *input manipulator* (surgical console) refers to an electromechanical system that the human operator interfaces with and serves to interpret the position of the hand and its manual actions and to transmit this information electronically to the executing manipulators. Forces that are generated in the environment are displayed haptically to some degree at the input device. The other half of the kinesthetic coupling, the *executing manipulator,* is also an electromechanical system that performs the inverse task of the input manipulator except in the remote environment. That is, it displays position commands received from the master and interprets forces generated by the environment for transmission back to the master and hence the human operator. The third key component of a telemanipulator system is the technology that provides visual feedback from the environment to the human operator. The kinesthetic coupling is of limited use if the human cannot observe the results of his or her actions in the environment. Together, both haptic and visual feedback enable a human operator to perform useful work in a remote environment while he or she is immersed in a local virtual environment.

Application of telemanipulation technology to endoscopic surgery is particularly well suited because it addresses the key performance limitations of minimally invasive surgery, namely, reduced articulation, monocular vision, and loss of hand-eye coordination.[64]

The traditional design of endoscopic instruments presents significant limitations with respect to intuitive manipulation. Motions of the tool inside the body are reversed from the intended motion outside the body because of the fulcrum effect. Since the instruments pivot around a fixed entry point in the body, scale largely depends on the ratio of internal and external shaft length.[65] Standard endoscopic instruments provide only four degrees of freedom of motion at the tip of the instrument, impairing the surgeon's ability to perform multidimensional tip motion, and do not allow for free orientation of the instrument tip relative to the tissue. Shear stress generated at the pivot point leads to a nonlinear force relationship between the handle and the tip of the instrument, increasing operator fatigue and imposing on any force feedback.[66] Another major limitation of standard endoscopic surgery is the loss of hand-eye coordination because the endoscope enters a port in the body that is not collinear with the surgeon's eyesight, thus forcing the operator to operate the tools from a perspective different from his or her own eyes.[67] By inserting a telemanipulator between the surgeon and the patient, these limitations can be resolved. Nonintuitive directional motion of the tool tip caused by the fulcrum effect can be resolved by matching the surgeon's input motions to the working tip of the tool instead of the tool handle, avoiding reversed motion and unwanted scaling artifacts. Additional degrees of freedom can be added into computer-controlled endoscopic instruments, and finally, hand-eye coordination can be restored to a surgeon using a telemanipulator because the system has full information regarding the orientation and position of the endoscope and tools on both the input and effector sides.

Surgical Technique

Standard monitoring for cardiac surgery is applied. Defibrillator pads are placed on the back and to the right side of the chest. Single-lung ventilation of the right lung is applied using a double-lumen endotracheal tube or a bronchus blocker. Temperature management follows the principles of OPCAB surgery. After draping the instrument arms and camera arm, camera and scope calibration are performed, and the endostabilizer is prepared. A holding arm for the endostabilizer is mounted to the operating table rail on the patient's right side, and the operating table is rotated 10 to 15 degrees to raise the patient's left side.

After single right-lung ventilation is initiated, the camera port is placed in the fifth intercostal space 2 cm medial to the anterior axillary line. CO_2 insufflation is begun for adequate visualization and to create working space as tolerated hemodynamically (usually 10 to 12 mm Hg of insuflation pressure). A 30-degree scope angled up is used for takedown of the LITA. The right instrument port is placed in the third intercostal space medial to the anterior axillary line, and the left instrument port is placed in the seventh intercostal space medial to the anterior axillary line. The instrument arms are centered for optimal range of motion by adjusting the respective setup joints, and the instruments are inserted. LITA takedown starts by dividing the intrathoracic fascia covering the LITA with low-power monopolar cautery. The LITA is dissected bluntly off the chest wall moving from the lateral to the medial aspect as a pedicle, keeping the lateral veins. Side branches are cauterized or clipped. Dissection is performed from the first intercostal space to the level of the bifurcation. The pedicle is not detached from the chest wall until the anastomosis is finally performed to avoid torsion of the graft. The distal end of the graft is skeletonized to facilitate suturing the anastomosis. Epicardial fat is removed, and the mediastinal and diaphragmatic attachments to the pericardium are dissected bluntly to widen the available space. The pericardiotomy is performed with a longitudinal incision in the pericardium over the suspected course of the LAD. The ideal site for the anastomosis is determined by absence of visible atheromatous plaques and avoiding proximity to bifurcations. At this point, changing the angle of the endoscope from 30 degrees, angled up to 30 degrees, angled down may enhance visualization. After heparinization (an ACT of 300 seconds is recommended), a vascular clamp is placed approximately 2 cm proximal to the transsection site. The LITA is clipped distally, cut, and spatulated in preparation for the anastomosis in situ. Graft patency is confirmed by briefly releasing the vascular clamp. The LITA pedicle is still left attached to the chest wall in order to keep orientation of the graft until the anastomosis is performed. A 12 mm

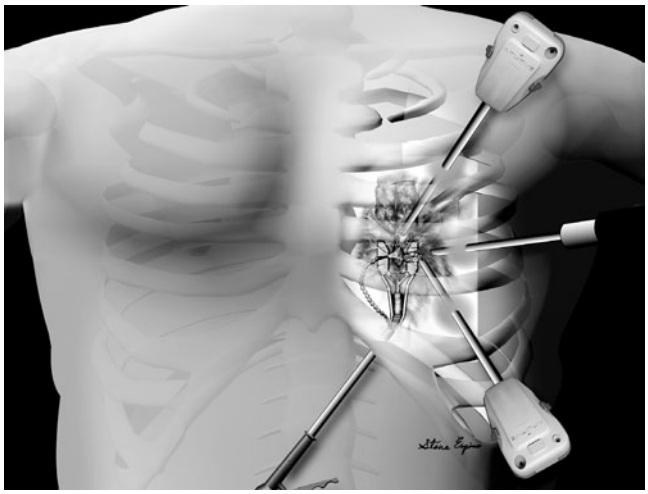

Figure 26-5. Setup for total endoscopic coronary artery bypass grafting. Two instrument ports, one central camera port, and a subxyphoidal port for the endostabilizer are required.

subxyphoid cannula is inserted under endoscopic vision. Before introduction of the endostabilizer, temporary Silastic occlusion tapes and a 7 cm 7-0 double-armed Prolene suture are introduced through this port and stored in the mediastinum. Some surgeons prefer Gore-Tex sutures to avoid the memory effect. Alternatively, nitinol clips (U-clips) may be used. The endostabilizer then is introduced under endoscopic vision by the patient-side surgeon (Fig. 26-5). Vacuum lines and irrigating saline line are connected, and the multilink irrigator is advanced into the field of view. The console surgeon then positions the stabilizer feet parallel to the LAD target site. After suction is applied, the feet are locked into position. After blunt dissection of the anastomotic target site, the Silastic tapes are placed proximal and distal to the anastomotic site, and temporary occlusion is applied. After a 5 to 6 mm arteriotomy is performed, transsection of the LITA is completed, and the graft is brought in close proximity of the target site. The anastomosis is best performed by beginning at the middle of the medial wall (12 o'clock position), suturing inside-out on the LITA and outside-in on the LAD toward and around the heel. Care has to be taken to tension the suture continuously. After the needles are broken off, an instrument knot is tied. The occlusion tapes and vascular clamp are released and evacuated through an instrument port. The pedicle may be fixed to the epicardium by stay sutures. For graft patency, control transient-time Doppler flow measurements can be performed endoscopically if a probe without a handle is available. This probe can be advanced through the stabilizer port. Alternatively, intraoperative angiography has been performed using a mobile angiography unit. The quality of these angiograms, however, may vary. After pleural effusion is drained under vision, the stabilizer and instruments are withdrawn, and the left lung is ventilated. A chest tube is inserted through one of the port holes. In case a four-arm system is used, the fourth arm is introduced after harvesting of the LITA in the third intercostal space in the anterior axillary line. It may be used to provide countertraction during epicardial fat removal and pericardiotomy and to present the pedicle during the anastomosis. The new version of the da Vinci system also will allow the use of a remotely controlled stabilizer that is placed on the fourth arm and thus can be adjusted from the console.

Results

Despite the use of advanced telemanipulator technology, the TECAB procedure remains technically demanding and is performed infrequently. Initially, TECAB was performed on the arrested heart using the Port-Access platform with femorofemoral artery bypass, endoaortic balloon clamping, and cardioplegic arrest. CPB time and cross-clamp times were in the range of 80 to 120 and 40 to 60 minutes, respectively. The reported patency rate for the TECAB procedure on the arrested heart ranged from 95 to 100% prior to discharge and 96% at 3 month follow-up angiography.[62,68–70] It was demonstrated in these initial series that equal patency rates as compared with standard bypass procedures could be achieved endoscopically in selected patients. However, operating times were in the range from 4 to 6 hours for a single bypass graft. In a more recent multicenter analysis, angiographic patency rate was 98.2%. However, the conversion rate was 23%, mostly related to problems with the Port-Access system or peripheral cannulation.[71]

Endoscopic CABG on the beating heart is even more challenging.[72–74] Based on intention to treat, the conversion rate (elective conversion to a MIDCAB procedure) in a five-center registry was 33% (37 of 117). Conversions were mostly due to calcified target vessels or the inability to locate or dissect the LAD and rarely other conditions such as arrhythmia or hemodynamic instability. In most centers, takedown of the LITA is now a routine procedure that can be performed in 30 to 40 minutes and is comparable with the times required in MIDCAB procedures. A time-consuming step is the setup of the stabilizer and preparation for the anastomosis. Time for LAD occlusion is in the range of 25 to 40 minutes and thus markedly longer than for MIDCAB or OPCAB. Operating times for a beating-heart TECAB procedure thus range from 2.5 to 3.5 hours in most centers. The patency rates for completed beating-heart TECAB procedures are in the range of 92 to 94%.[71]

TECAB can be performed safely but is currently restricted to few indications (e.g., single-vessel bypass grafting of the LAD and occasionally double-vessel grafting) but clearly has the potential for endoscopic multivessel procedures.[75,76] Exposure of the posterior and inferior wall vessels, however, will require rotation and displacement of the heart to various degrees. Endoscopic suction devices such as the Endostarfish may help exposure in a closed-chest environment and are being investigated currently for a small-thoracotomy multivessel approach (MVST). For this operation, one or both IMAs are harvested endoscopically. A small anterolateral thoracotomy is performed. Through this thoracotomy, a T-graft is performed. With the help of the Enodstarfish,

sequential grafting of obtuse marginal branches or the posterior descending artery is possible.[76]

Operating times for TECAB are still long, and conversions to MIDCAB or open surgery frequently are necessary. A number of steps that occur between ITA takedown and performing the anastomosis are challenging owing to the lack of assistance, limited space, the lack of fine tactile feedback, and a limited number of instruments. Among the difficulties are the handling of excessive epicardial fat, determination of the optimal site for an anastomosis, target-vessel calcification, and backbleeding from septal branches. In addition, difficulties with positioning of the stabilizer or incomplete immobilization render beating-heart closed-chest bypass grafting difficult.

As with all new technologies, a learning curve has to be overcome, and a structured training is considered essential for procedural success. This includes a principal understanding of the system architecture of telemanipulation systems and the underlying human-machine interface technology. Port placement is paramount to reducing the degree of difficulty and ensuring success of the procedure. Knowledge about the range of motion and kinetics of the slave arms is essential. The assessment of potential collisions among the slave arms or the slave arms and the patient's body is important to determine the optimal placement of ports. Since inside the chest a large range of motion with a number of different trajectories is required to perform the proximal-to-distal ITA dissection, the pericardiotomy, and the anastomosis, the ideal port triangle will vary according to the target.

A team approach is crucial for success, and it is important that the table-side surgeon understands the basic mechanisms of joint motion of the manipulators in order to provide a setup that allows an unrestricted range of motion. Takedown of the ITA should be accomplished routinely, before aiming at a complete TECAB procedure.

With recent refinements in telemanipulator technology, providing more range of motion and direct control of the stabilizer, endoscopic bypass grafting will evolve further and may prove beneficial for selected patients. New methods for preoperative planning and simulation, intraoperative navigation, and image guidance, as well as augmented reality techniques, are currently under investigation.[78,79] A new endoscopic stabilizer that can be operated by the surgeon from the surgeon's console (Fig. 26-6), as well as endoscopic anastomotic connectors, may help to facilitate the procedure further.[60]

ENDOSCOPIC CONDUIT HARVEST

To minimize the overall trauma of a bypass procedure, conduit harvest should be performed through limited incisions or endoscopically. There is a body of evidence indicating that while the quality of the conduit is not impaired by an endoscopic harvest, wound infections and other complications of the harvesting procedure are decreased substantially. The cosmetic advantage is obvious.

Figure 26-6. Endoscopic coronary artery bypass grafting. New endoscopic vacuum stabilizer including irrigating channel. The stabilizer is mounted to the fourth arm of the new da Vinci system and can be operated remotely by the surgeon at the console.

Endoscopic Saphenous Vein Harvesting

Despite the fact that arterial grafting yields better long-term results than venous grafting, and despite increased use of the IMA and other arterial grafts, the greater saphenous vein is still used frequently for CABG. The standard longitudinal open harvesting technique of the greater saphenous vein is associated with a 2 to 25% rate of wound complications (e.g., dehiscence, delayed healing, infection, cellulitis, sepsis, and occasionally, limb amputation), complicating ambulation of the patient, prolonging hospitalization, and causing an economic burden.[80–83] In addition, open saphenous vein harvest is associated with postoperative pain, neuropathy, and long-term pain and scarring impairing patient satisfaction.

Various techniques for endoscopic vein harvest exist that require one or two 2 cm incisions. For a single-incision technique, the greater saphenous vein is identified through a 2 cm longitudinal incision at the crease of the knee posterior to the medial femoral condyle. A space anterior and posterior at the surface of the vein is dissected, and a subcutaneous retractor or dissection cannula is introduced. An endoscope is inserted into the subcutaneous tissue. Exposure can be enhanced by insufflating CO_2. The vein is mobilized circumferentially, and side branches are either clipped, coagulated using bipolar endoscopic bipolar cautery scissors, or vaporized using a harmonic scalpel. Whenever bipolar cautery is applied, a distance of at least 2 mm between the scissors and the vein should be kept in order to avoid thermal damage. Proximal and distal control of the greater saphenous vein is accomplished with endoscopic application of a Prolene suture, clips, or ligation loops. With this technique, the entire length of the vein can be harvested from the saphenous-femoral junction to the medial malleolus through a single incision. The wound is closed in a standard fashion, and the leg is wrapped circumferentially with bandages. In

experienced hands, the procedure takes between 30 and 50 minutes.[84] As with all endoscopic techniques, a learning curve is associated with endoscopic vein harvesting, with training involving approximately 30 patients and a conversion rate ranging from 0 to 22%. This is also illustrated by the finding that endoscopically harvested veins require a significantly greater number of repairs as compared with the open technique.[84,85]

Results

The ISMICS Consensus Group recently reviewed the results of 1319 randomized and 8023 nonrandomized patients. In this meta-analysis, the risk of wound complications was reduced significantly by 69% with endoscopic vein harvesting compared with the open technique (OR 0.31, 95% CI 0.23–0.43; $p < .0001$).[85] The need for surgical intervention for wound infection also was reduced significantly (OR 0.29, 95% CI 0.12–0.70; $p = .007$). With regard to the incidence of moderate to severe postoperative pain, a reduction of 74% was found with endoscopic vein harvesting compared with the open technique (OR 0.26, 95% CI 0.12–0.55; $p < .0001$), and this reduction was 90% at 4 to 6 weeks follow-up (OR 0.10, 95% CI 0.03–0.37; $p < .0001$). The incidence of mobility disturbance at discharge was reduced by 69% (OR 0.31, 95% CI 0.15–0.65; $p = .002$). No difference was found for MI, rethoracotomy, angina recurrence or reintervention, and death over the short term.[85] However, the number of trials looking at cardiac outcomes and providing angiographic data on patency rates are too limited to allow any meaningful conclusion. The few trials that looked at vascular integrity and vessel wall trauma did not find a difference for the endoscopic versus open technique.[86,87]

Harvesting times were increased for the endoscopic technique in most trials. Although closure time was reduced significantly, this resulted in a net increase in total harvesting time. Total blood loss was reduced with endoscopic vein harvest ($p = .04$). ICU length of stay and time to ambulation were not reduced, but total hospital length of stay was reduced.[85]

Endoscopic Radial Artery Harvest

Use of the radial artery for CABG has regained popularity over the last decade. In conventional radial artery harvest, the incision runs from below the antecubital fossa to the wrist, along the medial border of the brachioradialis muscle. While wound complications are reported infrequently, delayed healing of the forearm can cause severe discomfort.[88] Objective sensory loss in 10% of patients and forearm scar discomfort in 33% undergoing open radial artery harvest have been reported.[89,90] Endoscopic techniques for graft harvest have been developed subsequently.[91]

Surgical technique

Collateral circulation from the ulnar artery to the palmar arch has to be verified pre- or intraoperatively using either the standard Allen test or modification of the test by applying Doppler or measuring oxygen saturation in patients in whom the signs of visual reperfusion are in doubt. In order to prevent brachial plexus injury, the arm should not be overextended above 90 degrees. One centimeter superior to the radial styloid prominence, a 2 to 3 cm incision is made, and the radial artery is identified and dissected. A subcutaneous retractor and a 5 mm, 30 degree endoscope are placed into the incision. By bluntly advancing the retractor through the subcutaneous tissue, the radial artery is visualized (Fig. 26-7). Side branches and surrounding tissue are divided using an ultrasonic harmonic scalpel that is placed underneath the retractor. The fascia between the brachioradialis and flexor carpi radialis muscles is divided anterior to the radial artery with the harmonic scalpel to increase the space for insertion of the subcutaneous retractor.[92] After division of all side branches, a vessel retractor is advanced from the distal incision to verify complete isolation of the conduit. The proximal radial artery is clipped distal to the origin of the ulnar artery branch and transsected with endoscopic scissors. The graft is recovered through the distal incision, and the distal end is ligated. The incision is closed in a standard fashion.

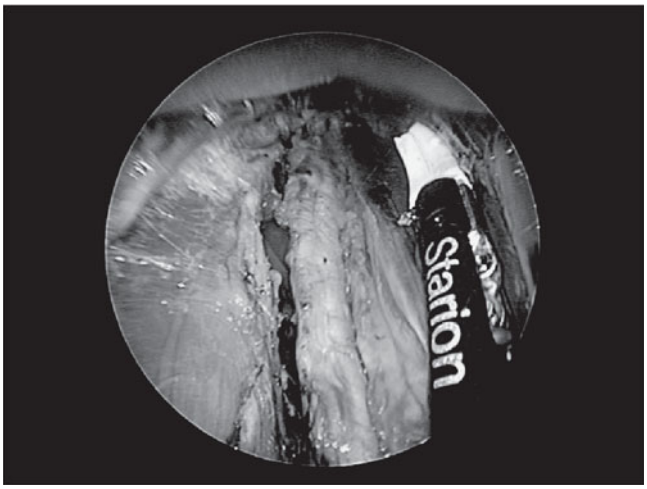

Figure 26-7. Endoscopic radial artery harvest. Endoscopic view.

Results

The reported incidences of neurologic complications after standard open harvesting technique of the radial artery vary in the literature from 2.4 to 30% and can be related to injury of the superficial radial nerve or the lateral antebrachial cutaneous nerve. With endoscopic technique, the latter usually is not encountered because the dissection is performed underneath the brachioradialis muscle. Superficial radial nerve injury, however, still may occur during distal dissection.[92] With regard to wound infections, endoscopic radial artery harvest is associated with a lower rate of infection (0 to 2.7%) compared with the open technique.[84,93] Regarding the quality of the graft, patency rates, and impact on long-term

survival, there is currently no evidence in favor of either technique. The indication for endoscopic radial harvest therefore can be based on improved wound healing, better patient comfort, and improved cosmesis.

CONCLUSION

In summary, minimally invasive bypass surgery continues to play an increasing role in surgical revascularization. There is growing evidence in favor of OPCAB, which is already the preferred method of bypass grafting in many centers. MIDCAB is still limited to patients with single-vessel disease, but excellent long-term data confirm the efficacy of the approach. Endoscopic bypass grafting using robotic assistance is still an evolving procedure that is applied only to selected patients, and its continued application will depend heavily on technological improvements. As for endoscopic vein graft harvesting, there is a body of evidence suggesting superior results compared with an open harvesting technique, which also may be true for the technique of endoscopic radial artery harvest in the future.

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CHAPTER 27

Coronary Artery Reoperations

G. V. Gonzalez-Stawinski • Bruce W. Lytle

Coronary artery reoperations are more complicated than primary operations. Patients undergoing reoperations have distinct, more dangerous pathologies; reoperations are technically more difficult to perform; and the risks are greater.[1–12] Vein graft atherosclerosis, present in most reoperative candidates, is a unique and dangerous lesion. Reoperative candidates commonly have severe and diffuse native-vessel distal coronary artery disease (CAD), a problem that has had the time to develop only because these patients did not die from their original proximal coronary artery lesions. Aortic and noncardiac atherosclerosis are also often far advanced in many reoperative candidates. Some technical hazards, including the presence of patent arterial grafts and sternal reentry, are unique to reoperations, and others, such as lack of bypass conduits and difficult coronary artery exposure, are common.

INCIDENCE OF REOPERATION

After a primary bypass operation, the likelihood of a patient undergoing a reoperation depends on patient-related variables, primary operation-related variables, adherence to strict medical control of risk factors for disease progression following bypass surgery, the possibility of alternative treatments, physician opinion about the feasibility of reoperation, and time. Studies from our institution noted a cumulative incidence of reoperation of 3% by 5 years, 10% by 10 years, and 25% by 20 postoperative years[13] (Fig. 27-1). Factors associated statistically with an increased likelihood of reoperation have been variables predicting a favorable long-term survival [e.g., young age, normal left ventricular function (LVF), and single- or double-vessel disease], variables designating an imperfect primary operation [e.g., no internal thoracic artery (ITA) graft and incomplete revascularization], and symptom status (e.g., class III or IV symptoms at primary operation). Young age at primary operation and incomplete revascularization are also markers of a severe atherogenic diathesis.

More recently, however, the proportion of isolated coronary artery operations that are reoperations has decreased. This decrease is related in part to the more aggressive use of coronary artery interventions for patients with previous bypass surgery and possibly to more effective risk factor control. In 1990 about 37% of coronary artery revascularization operations were reoperative interventions, whereas in 2002 this figure decreased to 30%[14] (Fig. 27-2). Also, surgery has changed in directions that will decrease the rate of reoperation. Use of the left internal thoracic artery (LITA) to graft the left anterior descending (LAD) coronary artery decreases the risk of reoperation compared with the strategy of using only vein grafts, and the LITA-LAD graft has become a standard part of operations for coronary artery revascularization.[15] Furthermore, it now appears that use of bilateral ITA grafts decreases the likelihood of death and reoperation when compared with the single LITA-LAD strategy[16] (Fig. 27-3). The use of other arterial conduits such as the radial artery and the gastroepiploic artery in the context of total arterial revascularization may decrease the risk of reoperation further, but as yet the long-term data are insufficient to answer this question.

The patient population of reoperative candidates has evolved. Cleveland Clinic Foundation studies have shown that in the early years of bypass surgery (1967–1978), only 28% of patients underwent reoperation solely because of graft failure, and that graft failure often occurred early after the primary operation (mean postoperative interval of 28 months after primary operation). Reoperation because of the progression of atherosclerosis in nongrafted coronary arteries was common in the 1967–1978 time period (55% of patients).[1,2] Between 1988 and 1991, almost all patients had graft failure as at least part of the indication for reoperation (92%), but that graft failure occurred late after the primary operation at a mean interval of 116 months.[3] Today, patients

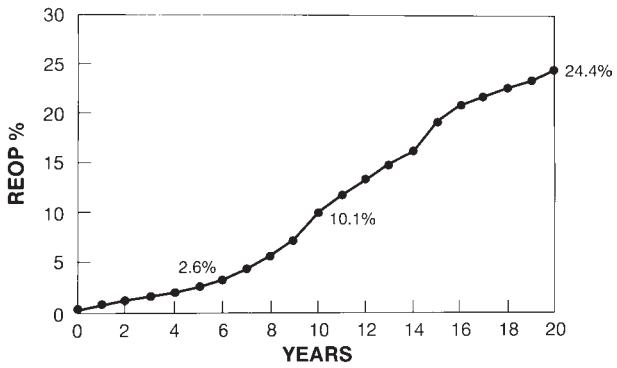

Figure 27-1. Study of 4000 patients who underwent bypass surgery from 1971 to 1974 showed that 25% of patients had undergone a reoperation within a period of 20 years after primary operation. (*Data from Cosgrove DM, Loop FD, Lytle BW, et al: Predictors of reoperation after myocardial revascularization. J Thorac Cardiovasc Surg 1986; 92:811.*)

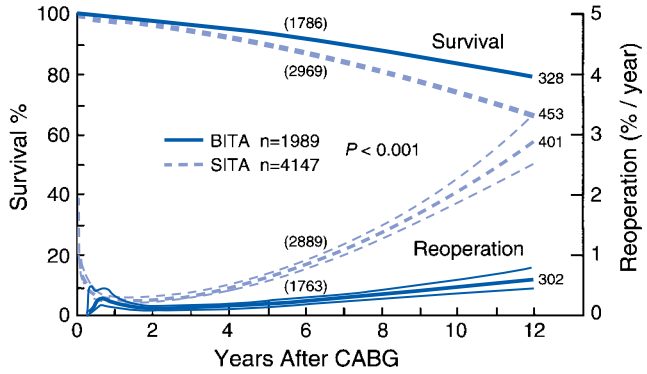

Figure 27-3. Comparison of survival and reoperation hazard function curves in the propensity-matched patients undergoing bilateral (BITA, *n* = 1989) or single ITA (SITA, *n* = 4147) CABG. (*Reproduced with permission from Lytle BW, Blackstone EH, Loop FD, et al: Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999; 117:855.*)

undergoing reoperation usually had a successful primary operation at least 10 years previously for the treatment of multivessel CAD, and the angiographic indications for reoperation are progression of native-vessel distal CAD in combination with late graft failure caused by vein graft atherosclerosis.

GRAFT FAILURE

An understanding of the pathology and causes of saphenous vein graft failure is important not only for an understanding of the causes of the need for reoperation but also for understanding the dangers inherent in either the interventional or the conservative treatment of patients with previous bypass surgery. Saphenous vein to coronary artery grafts exhibit different pathologies at different intervals after operation.[17–20] Within a few months, they often have diffuse endothelial disruptions with associated mural thrombus. The mural thrombus usually is not obstructing, and when grafts do become occluded early after operation owing to thrombosis, it may not be a result of these intimal changes but rather may be related to hemodynamic factors. Most saphenous vein grafts examined more than 2 to 3 months after operation have developed a proliferative intimal fibroplasia. This is a concentric cellular process, and it is diffuse, extending the entire length of the graft (Fig. 27-4). It evolves with time to a more fibrous lesion. It is not friable, and although intimal fibroplasia involves most vein grafts, it causes stenoses or occlusions of only a few.

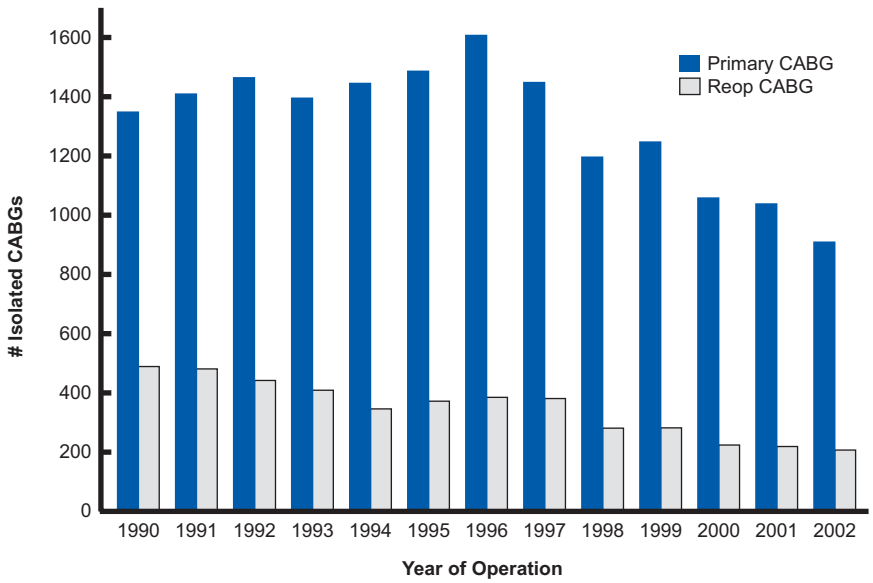

Figure 27-2. Study of 21,568 patients who underwent bypass surgery from 1990 to 2003 showed a steady decrease in the number of patients undergoing redo coronary artery operations. (*Data from Sabik JF, Blacksotne EH, Houghtaling PL, et al: Is reopration still a risk factor in coronary artery bypass surgery? Ann Thorac Surg 2005; 80:1719.*)

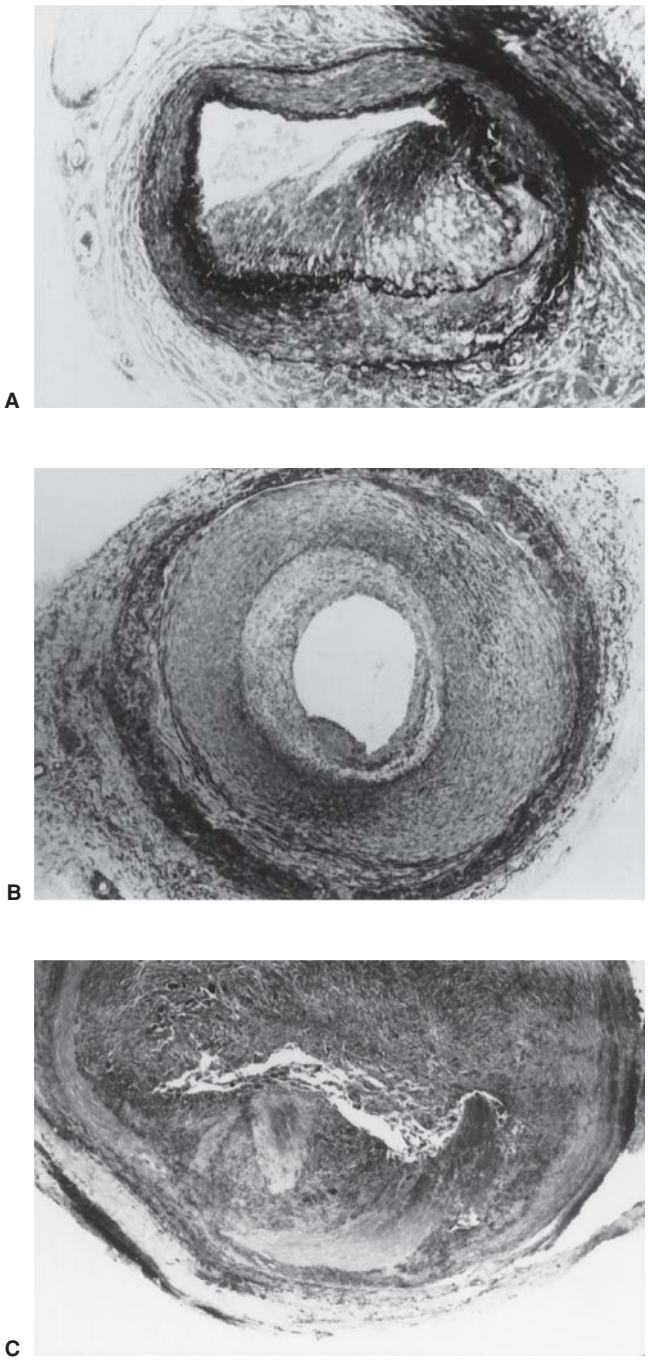

Figure 27-4. Pathology of (A) native coronary artery atherosclerosis, (B) vein graft intimal fibrosis, and (C) severe vein graft atherosclerosis. (*Reproduced with permission from Lytle BW, Cosgrove DM: Coronary artery bypass surgery, in Wells SA (ed): Current Problems in Surgery. Philadelphia, Saunders, 1992; p 733.*)

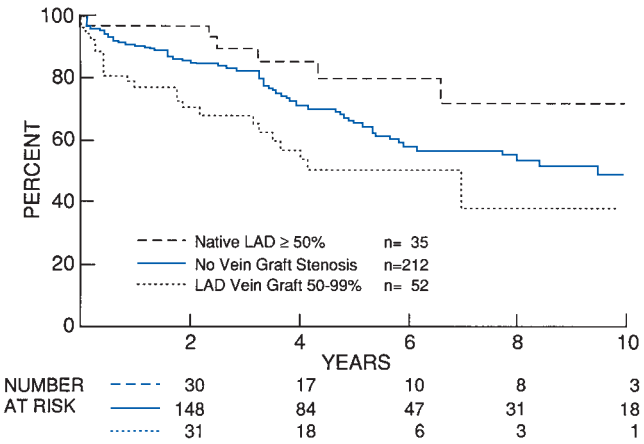

Figure 27-5. Patients with late stenoses in vein grafts to the LAD coronary artery had worse survival when compared with either patients with native coronary LAD stenoses or patients with no stenotic vein grafts. (*Reproduced with permission from Lytle BW, Loop FD, Taylor PC, et al: Vein graft disease: The clinical impact of stenoses in saphenous vein bypass grafts to coronary arteries. J Thorac Cardiovasc Surg 1992; 103:831.*)

Vein graft atherosclerosis is a distinct pathologic process that often is recognized as early as 3 to 4 years after operation and is characterized by lipid infiltration of areas of intimal fibroplasia (Fig. 27-5). The distribution of vein graft atherosclerosis mimics that of intimal fibroplasia in that it is concentric and diffuse, although as vein graft atherosclerosis progresses, stenotic lesions may become eccentric. In addition, vein graft atherosclerosis is a superficial lesion, it is very friable, and it is often associated with overlying mural thrombus. These characteristics make it different from native-vessel coronary atherosclerosis, a process that is segmental and proximal, eccentric, encapsulated, usually not friable, and usually not associated with overlying mural thrombus. Vein graft atherosclerosis is seen in a majority of grafts explanted more than 10 years after surgery whether or not those grafts are stenotic, and atherosclerotic lesions appear to account for almost all late saphenous vein graft (SVG) stenoses. The extreme friability of vein graft atherosclerosis creates a substantial risk of distal coronary artery embolization during percutaneous interventions to treat stenotic lesions and during reoperations for patients with atherosclerotic vein grafts. It is also probable that spontaneous coronary artery embolization may occur from atherosclerotic grafts. In addition, atherosclerotic stenoses in vein grafts appear to predispose to graft thrombosis. Vein graft atherosclerosis appears to be an "active" event-producing lesion.

The exact incidence of late SVG stenoses and occlusions is difficult to determine even with prospective studies because death and reoperation are nonrandom events that remove patients from prospective populations available for late coronary artery angiography. However, it appears that by 10 years after operation, approximately 30% of vein grafts are totally occluded, and 30% of patent grafts exhibit some degree of stenosis or intimal irregularities characteristic of vein graft atherosclerosis.[21,22] Although vein graft atherosclerosis is not the only factor related to late SVG occlusion, it is an important one. Native-vessel stenoses distal to the insertion site of vein grafts may decrease SVG graft outflow and contribute to graft failure, but late graft occlusion usually occurs in the presence of vein graft atherosclerosis. Furthermore, when stenotic vein grafts are replaced at reoperation, the late patency rate of the new vein grafts is good.[2]

Progress has been made toward decreasing the rate of vein graft failure. The early patency rates of SVGs have been improved by the use of perioperative and long-term platelet inhibitors,[23–25] but the best data involving patients receiving platelet inhibitors indicate that the 10-year vein graft failure rate is approximately 35%. Some studies have shown that lipid-lowering regimens decrease late vein graft disease and the risk of late cardiac events. However, the overall level of improvement has been small.[26,27] So far, the only way known to avoid vein graft atherosclerosis is to avoid using vein grafts.

ITA grafts rarely develop late atherosclerosis, and the late attrition rate of patent ITA grafts is extremely low. Left ITA to LAD grafts have a very high late (20 years) patency rate, and for most patients, the LAD is a profoundly important coronary artery.[21,28] These factors account for the impact of the LITA-LAD graft not only in decreasing the rate of late death after primary bypass surgery but also in decreasing the rate of reoperation.[15] Multiple ITA grafts provide incremental benefit in decreasing the risk of reoperation.[16] It is also important that ITA grafts do not develop graft atherosclerosis and, therefore, do not create the risk of coronary artery embolization during reoperation. The presence of patent arterial grafts may create other technical problems during repeat surgery, but embolization is not among them.

INDICATIONS FOR REOPERATION

The randomized trials of bypass surgery versus medical management that were initiated in the 1970s provided a framework of information concerning the indications for bypass surgery, and subsequent observational studies have added substance to that framework. However, no randomized trials of medical versus surgical management pertain to patients with prior surgery. The coronary pathology of patients with previous bypass surgery is different from that of patients with only native-vessel stenoses, and we cannot assume that the natural history of, for example, triple-vessel disease based on atherosclerotic vein grafts is equivalent to that of triple-native-vessel disease.

There are two nonrandomized, retrospective studies of patients who had angiograms after bypass surgery that addressed the issue of late survival.[29,30] One study showed that patients with early (fewer than 5 years after operation) stenoses in vein grafts and patients with no stenotic vein grafts had approximately the same outcomes and that these outcomes were relatively good.[29] *However, the presence of late (5 years or more after operation) stenoses in vein grafts predicted poor long-term outcomes, particularly if a stenotic vein graft supplied the LAD coronary artery. When late stenoses in LAD vein grafts were combined with other high-risk characteristics, the late survival rate was particularly dismal.* For example, patients with a 50 to 99% stenosis in a LAD vein graft combined with abnormal LVF and triple-vessel or left main stenoses had only a 46% 2-year survival without reoperation. Patients with late stenoses in an LAD vein graft had significantly worse long-term outcomes than did patients with the LAD jeopardized by a native lesion (see Fig. 27-5). This study showed that the difference in the pathology of early (intimal fibroplasia) and late (vein graft atherosclerosis) vein graft stenoses is associated with a difference in clinical outcome and that late stenoses in vein grafts are dangerous lesions.

A second study compared the outcomes of patients with stenotic vein grafts treated with reoperation (REOP group) versus those treated with medical treatment (MED group).[30] Again, this was a nonrandomized, retrospective study, and the patients in the REOP group were older and more symptomatic, had worse LVF, and had fewer patent grafts than the patients in the MED group.

The survival of patients with early (fewer than 5 years) SVG stenoses was not different in the two groups. The operative risk for the REOP group was low (no deaths among the 59 patients) and the long-term survival was good, but late survival was just as good for the patients treated medically (Fig. 27-6). It is important to note that the patients in the REOP group were more symptomatic to start with, and at late follow-up, they were less symptomatic than the patients in the MED group. Thus, reoperation for patients with early vein graft stenosis was an effective way of relieving symptoms of angina, but it appears that patients without symptoms can be treated medically with safety, at least over the short term.

However, the overall outcomes were worse for patients with late stenoses in vein grafts, and many subgroups had improved survival rates with reoperation. By multivariate testing (Table 27-1), a stenotic (20 to 99%) LAD vein graft predicted late death, and performing a reoperation increased late survival for these patients. Multivariate testing of smaller subgroups showed that the survival advantage for the REOP

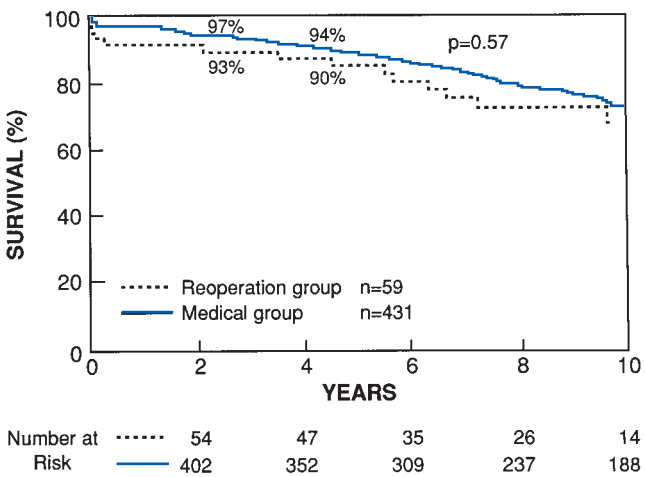

Figure 27-6. The survival of patients with early (<5 years after operation) stenoses in vein grafts was favorable with and without reoperation (p = NS). *(Reproduced with permission from Lytle BW, Loop FD, Taylor AC, et al: The effect of coronary reoperation on the survival of patients with stenoses in saphenous vein to coronary bypass grafts. J Thorac Cardiovasc Surg 1993; 105:605.)*

Table 27–1.

Patients with Late Stenoses (≥5 y) in Saphenous Vein in Coronary Artery Bypass Grafts: Multivariate Model of Variables Influencing Late Survival

	p-Value	Relative risk
Variables decreasing survival		
LVF moderate/severe	.0001	2.58
Age (at catheterization)	.0001	1.04*
3VD/LMT	.0011	2.87
LAD-SVG stenosis (20%–99%)	.0019	1.90
Variable increasing survival		
Reoperation	.0007	0.51

LVF = left ventricular function: 3VD/LMT = triple-vessel disease and/or left main stenosis.
**per year of age.*
Source: Reproduced with permission from Lytle BW, Loop FD, Taylor PC, et al: The effect of coronary reoperation on the survival of patients with stenoses in saphenous vein to coronary bypass grafts. J Thorac Cardiovasc Surg 1993; 105:605.

group was true even for patients with only class I or class II symptoms and that reoperation still improved survival for the remaining patients when patients with stenoses in LAD vein grafts were excluded from the analysis.

Univariate comparisons for the REOP and MED subgroups of patients with stenotic LAD grafts are shown in Fig. 27-7, demonstrating the improved survival for the REOP group. When patients with stenotic LAD vein grafts were subgrouped on the basis of severity of the stenotic lesions (Fig. 27-8), the patients with severely stenotic (50 to 99%) vein grafts obviously benefited from surgery, exhibiting a decreased risk of death even early in the follow-up period. For patients with moderate stenoses (20 to 49%) in LAD vein grafts, the survivals of the MED and REOP groups were equivalent for about 2 years, but after that point, survival of the patients in the MED group became rapidly worse so that by 3 to 4 years of follow-up, the survival benefit of reoperation became apparent. Although the patients in these studies did not have consistent functional testing, there is evidence that myocardial perfusion and functional studies can help to identify patients likely to benefit from reoperation. Lauer and colleagues studied 873 symptom-free postoperative patients with symptom-limited exercise thallium-201 studies and found that patients with reversible perfusion defects were more likely to die or experience major cardiac events

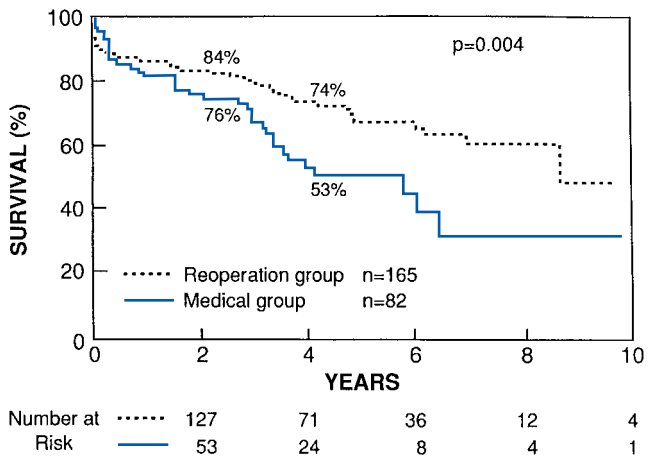

Figure 27-7. If patients had late (≥5 years after operation) stenoses in LAD vein grafts, they had a better survival rate (p = .004) with immediate reoperation than if they received initial nonoperative treatment. (*Reproduced with permission from Lytle BW, Loop FD, Taylor AC, et al: The effect of coronary reoperation on the survival of patients with stenoses in saphenous vein to coronary bypass grafts. J Thorac Cardiovasc Surg 1993; 105:605.*)

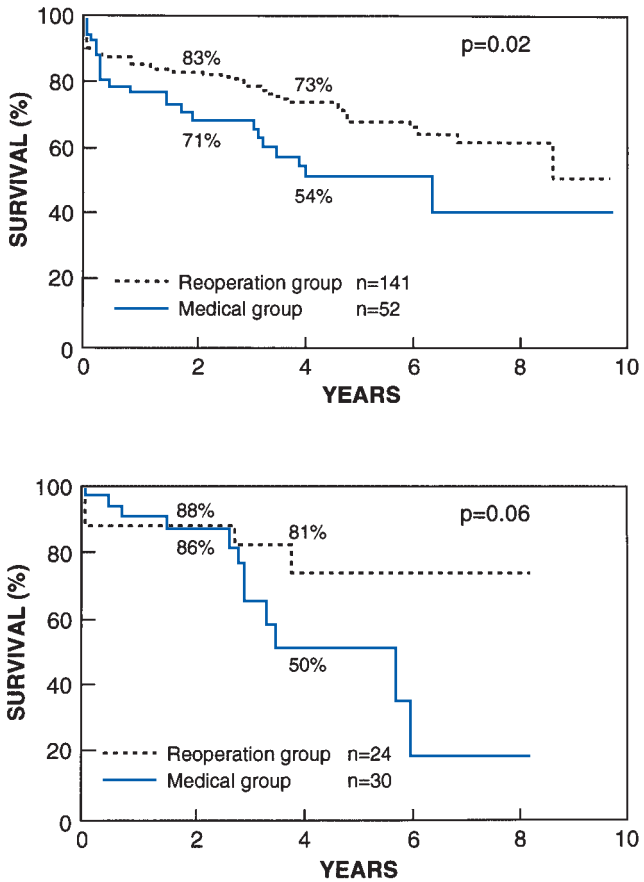

Figure 27-8. Patients with late stenoses in LAD vein grafts (*top*) had immediate improvement in their survival rate. Patients with moderate (20 to 49%) stenoses in LAD vein grafts had equivalent survival with or without reoperation for approximately 2 years, but after that point, the patients who did not have reoperation did poorly. (*Reproduced with permission from Lytle BW, Loop FD, Taylor PC, et al: The effect of coronary reoperation on the survival of patients with stenoses in saphenous vein to coronary bypass grafts. J Thorac Cardiovasc Surg 1993; 105:605.*)

during a 3-year follow-up.[31] Impaired exercise capacity also was strongly predictive of unfavorable outcomes.

Anatomic indications for reoperation to improve survival prognosis include (1) atherosclerotic (late) stenoses in vein grafts that supply the LAD artery, (2) multiple stenotic vein grafts that supply large areas of myocardium, and (3) multivessel disease with a proximal LAD lesion and/or abnormal LVF based on either native-vessel lesions or stenotic vein grafts or a combination of the two pathologies. Reoperation is also effective in other anatomic situations in which severe symptoms are the indication for invasive treatment, including patients with a patent ITA to LAD graft combined with other ischemia-producing pathology and multiple early vein graft stenoses. The combination of the anatomic characteristics just noted and reversible ischemia and/or worsening LVF during stress constitutes a particularly strong indication for reoperation.

PERCUTANEOUS TREATMENT OF POSTOPERATIVE PATIENTS

Percutaneous treatments (PCTs) represent alternative anatomic treatments for postoperative patients and often are useful. The effectiveness of PCTs is related to the vascular pathology to be treated and the clinical implications of treatment failure. Today, native coronary artery stenoses often can be treated with a low restenosis rate as long as those vessels are large enough to allow intracoronary stenting. Unfortunately, many postoperative patients have very diffuse native coronary atherosclerosis that makes PCT difficult or ineffective. Also, PCT has not been as effective in the treatment of diabetic native CAD.

The rate of technologic change in interventional cardiology has been rapid, and multiple percutaneous technologies have been used to treat stenotic vein grafts. Balloon angioplasty, first-generation PCT, was relatively dangerous to perform and produced ineffective long-term revascularization, particularly when used to treat older (atherosclerotic) vein grafts.[32] Direct coronary atherectomy (DCA) increased the risk of coronary embolization at the time of the procedure without improving the restenosis rate.[33] It has been hoped that the use of intracoronary stents, particularly covered stents and drug-eluting stents (DESs), in stenotic vein grafts might provide better outcomes, and stenting does represent an improvement over balloon angioplasty.[32] The Randomized Evaluation of Polytetrafluoroethylene Covered Stent in Saphenous Vein Grafts (RECOVERS) trial, a randomized study designed to compare rates of SVG restenosis between CABG patients treated with covered stents and with bare stents, showed identical restenosis rates at 6 months of follow-up (24.2% versus 24.8%; $p = .24$).[34] Finally, in a nonrandomized retrospective study comparing the effects of DESs with those of bare metal stents in treating SVG stenosis, Ge and colleagues reported significant differences in in-stent stenosis between groups at 6 months of follow-up (10 versus 26%; $p = .03$).[35]

However, the kinetics of treatment failure after PCT for vein grafts are different from those for native coronary vessels. Restenosis and new stenotic lesions in vein grafts continue to appear with time, and the shoulder on the adverse outcome curve that appears at 6 months to 1 year after PCT for native vessels does not appear for vein grafts. Thus, there is still some uncertainty about the clinical impact of PCTs of stenotic vein grafts. Patients with previous bypass surgery are an extremely heterogeneous group; some subgroups are at low risk without any anatomic treatment at all, and some subgroups are at high risk without effective therapy. To date, the reported studies of PCT of SVG lesions have not included clinical risk stratifications that would allow comparison of patient survival rates.

Despite persistently high restenosis rates following percutaneous interventions, there are still many indications for their use in the treatment of patients with previous bypass surgery. Realistically, the ideal uses of PCTs are in situations in which failure of the anatomic treatment is not likely to be catastrophic. These situations include symptomatic patients with (1) early vein graft stenoses, (2) native coronary stenoses, or (3) focal late SVG stenoses in vein grafts not supplying the LAD artery. There are many patients with previous surgery who will fall into a middle ground where it is not clear whether percutaneous transluminal coronary angioplasty (PTCA) or reoperation is likely to yield the best outcome, and judgments must be made on the specific advantages and disadvantages of the treatments for those particular patients. Factors making PTCA more attractive than reoperation are listed in Table 27-2.

Table 27–2.

Reoperation versus PTCA for Patients with Stenotic Vein Grafts

Factors favoring reoperation	Factors favoring PTCA
Late (≥5 years) stenoses	Early (<5 years) stenoses
Multiple stenotic vein grafts	Single stenotic vein graft
Diffusely atherosclerotic vein grafts	Other patent vein grafts
Stenotic LAD vein graft	Focal graft lesions
No patent ITA graft	Patent ITA-LAD graft
Abnormal left ventricular function	Normal left ventricular function

TECHNICAL ASPECTS OF CORONARY REOPERATIONS

Reoperations are more complicated than primary operations. The specific technical challenges that surgeons must recognize and solve that are unique to or more common during coronary reoperation are

1. Sternal reentry
2. Stenotic or patent vein or arterial bypass grafts
3. Aortic atherosclerosis
4. Diffuse native-vessel coronary artery disease
5. Coronary arteries located amid old grafts and epicardial scarring
6. Lack of bypass conduits

The overall problem of myocardial protection is more difficult during reoperations, with perioperative myocardial infarction still being the most common cause of in-hospital death.[3,6] The metabolic concepts of myocardial protection in use today are valid, but the reasons that myocardial protection sometimes fails during reoperation are related to anatomic causes of myocardial infarction. These anatomic causes of perioperative myocardial infarction include injury to bypass grafts, atherosclerotic embolization from vein grafts or the aorta to distal coronary arteries, myocardial devascularization secondary to graft removal, hypoperfusion through new grafts, failure to deliver cardioplegic solution, early vein graft thrombosis, incomplete revascularization, diffuse air embolization, and technical error.[3,36–40] To be consistently successful, coronary reoperations must be designed to avoid these causes of myocardial infarction.

Preoperative Assessment

A complete understanding of the patient's native coronary and bypass graft anatomy is essential. Achieving this goal is sometimes not as easy as it sounds, particularly if the patient has had multiple previous coronary operations. If bypass grafts, venous or arterial, are not demonstrated by a preoperative coronary angiogram, it usually means that they are occluded, but it is also possible that the angiogram simply has failed to demonstrate their location. Examination of old angiograms performed prior to previous operations and review of previous operative records often help to illustrate the patient's coronary anatomy.

It is also important to know that graftable stenotic coronary arteries supply viable myocardium. Myocardial scar and viability can be differentiated by thallium scanning, positron-emission tomography, and stress (exercise or dobutamine) echocardiography. The intricacies of establishing myocardial viability are beyond this discussion, but it is an important issue. Before embarking on a reoperation, it makes sense to be reasonably sure that there is a matchup between the patient's graftable arteries and some viable myocardium such that grafting those arteries will provide some long-term benefits.

It is also wise to have a preoperative plan for bypass conduit selection and to document that potential bypass conduits are available. ITA angiography often is helpful. Venous Doppler studies can be used to assess the presence of greater and lesser saphenous vein segments, and arterial Doppler studies can assess the radial and inferior epigastric arteries and establish the adequacy of flow to the digits during radial artery occlusion.

Median Sternotomy Incision, Conduit Preparation, and Cannulation

Most coronary reoperations are performed through a median sternotomy. Situations associated with increased risk during a repeat median sternotomy include right ventricular or aortic enlargement, a patent vein graft to the right coronary artery, an in situ right ITA graft patent to a left coronary artery branch, an in situ left ITA graft that curls under the sternum, multiple previous operations, and difficulty reopening the sternum during a previous reoperation. In such situations, vessels for arterial (via the femoral or axillary artery) and venous access for cardiopulmonary bypass are dissected out prior to sternal reentry. All bypass grafts except for the internal thoracic arteries may be prepared prior to sternal reentry. Preparation of radial artery and greater and lesser saphenous vein segments can be carried out simultaneously.

When reopening a median sternotomy, the incision is made to the level of the sternal wires; the wires are cut anteriorly and bent back but are not removed (Fig. 27-9). An oscillating saw is used to divide the anterior table of the sternum. When the anterior table has been divided, ventilation is stopped, and the assistants elevate each side of the sternum with rake retractors while the posterior table of the sternum is divided in a caudal-cranial direction. The sternal wires that have been left in place posterior to the sternum help to protect underlying structures. Once the posterior table of the sternum has been divided with the saw, the wires are removed, and sharp dissection with scissors is used to separate each side of the sternum from underlying structures. Once the sternum has been divided, it is important that the assistants retract in an upward direction, not laterally. The right ventricle is injured more often by lateral retraction while it is still adherent to the underside of the sternum than it is by a direct saw injury.

In high-risk situations, it can be helpful to perform a small anterolateral right thoracotomy (Fig. 27-10) prior to the repeat median sternotomy. Underlying structures, such as the aorta, patent bypass grafts, and the right atrium and ventricle, can be dissected away from the sternum via this approach, and thus, with the surgeon's hand placed behind the sternum, reentry is safe. This small additional incision contributes little morbidity.

Another technique for sternal reentry in high-risk patients is to heparinize, cannulate, and initiate cardiopulmonary bypass prior to median sternotomy. The advantages of this strategy are that the heart can be emptied and allowed to fall away from the sternum, and cardiopulmonary bypass already has been initiated for protection if an injury does occur. The disadvantages of this approach are that extensive mediastinal

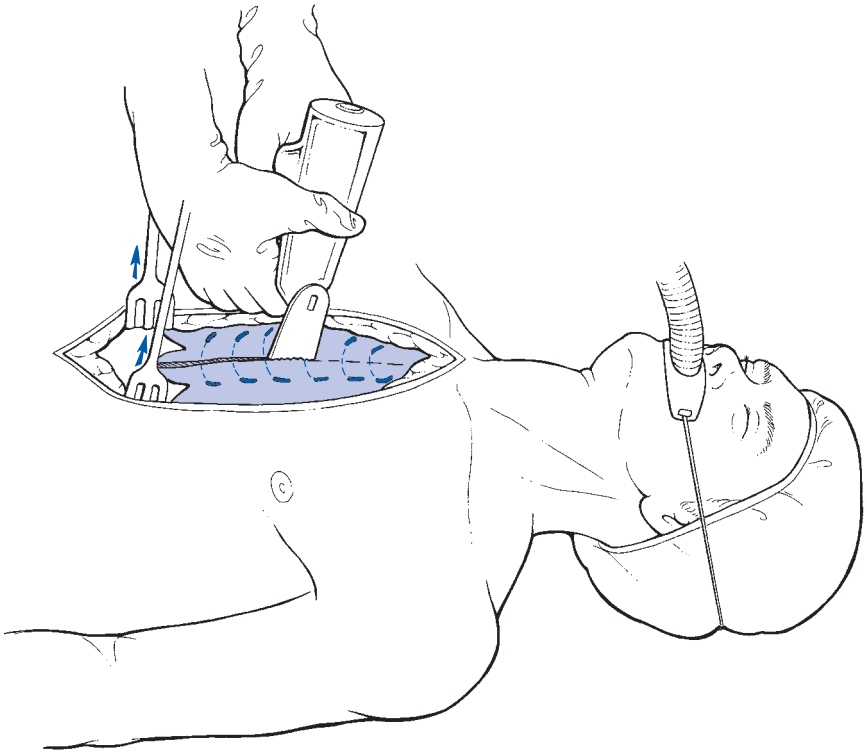

Figure 27-9. Leaving the sternal wires in place posteriorly helps to protect underlying structures while the posterior table of the sternum is divided with an oscillating saw. The direction of retraction with rake retractors should be anterior, not lateral.

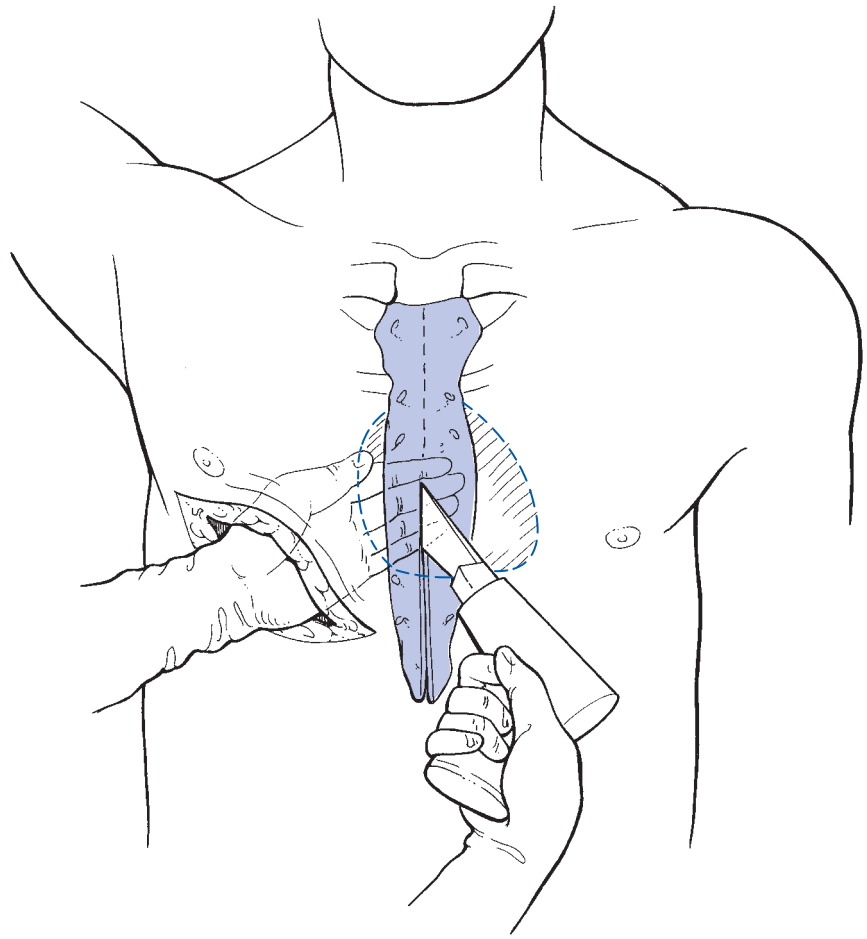

Figure 27-10. A small anterolateral right thoracotomy allows dissection of substernal structures such as patent grafts and the right ventricle or aorta away from the sternum under direct vision. While the sternum is being divided, the surgeon may place a hand behind the sternum for further safety.

dissection must be carried out in a heparinized patient, including dissection of the right internal thoracic artery if that is to be used. We rarely employ this approach except in situations in which adherence of an aortic aneurysm to the sternum or a patent right ITA-to-LAD graft creates a specific danger.

Once the sternum has been divided, the pleural cavities are entered. A general principle of dissection during reoperation is that starting at the level of the diaphragm and proceeding in a cranial direction is usually the safest approach. At the level of the diaphragm, few critical structures are injured if the wrong plane is entered. Therefore, at this point in the operation we usually dissect along the level of the diaphragm to the patient's right side until we enter the pleural cavity and then detach the pleural reflection from the chest wall in a cranial direction to the level of the innominate vein. The innominate vein is dissected away from both sides of the sternum with scissors, a maneuver that prevents a "stretch" injury to that vein.

Once the right side of the sternum is separated from the cardiac structures, it is usually possible to prepare a right ITA graft. Because of parietal pleural thickening, it is often more difficult to obtain length on ITA grafts during reoperation than it is during primary procedures, and the right ITA frequently is used as a "free" graft. Once the right ITA dissection is completed to the superior border of the first rib, an incision is made in the parietal pleura to separate the proximal ITA from the area of the phrenic nerve. Thus, if the right ITA needs to be converted to a "free" graft during aortic cross-clamping, it makes division at that point easier because the proximal ITA is clearly identifiable. Although intrapericardial dissection of the left side of the heart is left until later, freeing the left side of the anterior chest wall from the underlying structures (which may include a patent ITA graft) is undertaken now. This is difficult only if there is a patent ITA graft that is densely adherent to the chest wall. Again, it is best to enter the left pleural cavity at the level of the diaphragm and proceed in a cranial direction.

The most difficult point of dissection is usually at the level of the sternal angle, where a patent ITA graft may approach the midline and be adherent to the sternum or to the aorta. There are no tricks for dissecting out a patent ITA graft except for being careful. The danger to a patent left ITA graft during sternal reentry and mediastinal dissection is entirely related to the location of the graft at the time of the primary operation. Ideally, the pericardium should be divided at a primary operation, and the left ITA graft should be allowed to run posterior to the lung through the incision in the pericardium and to the LAD or circumflex artery (Fig. 27-11). When this is

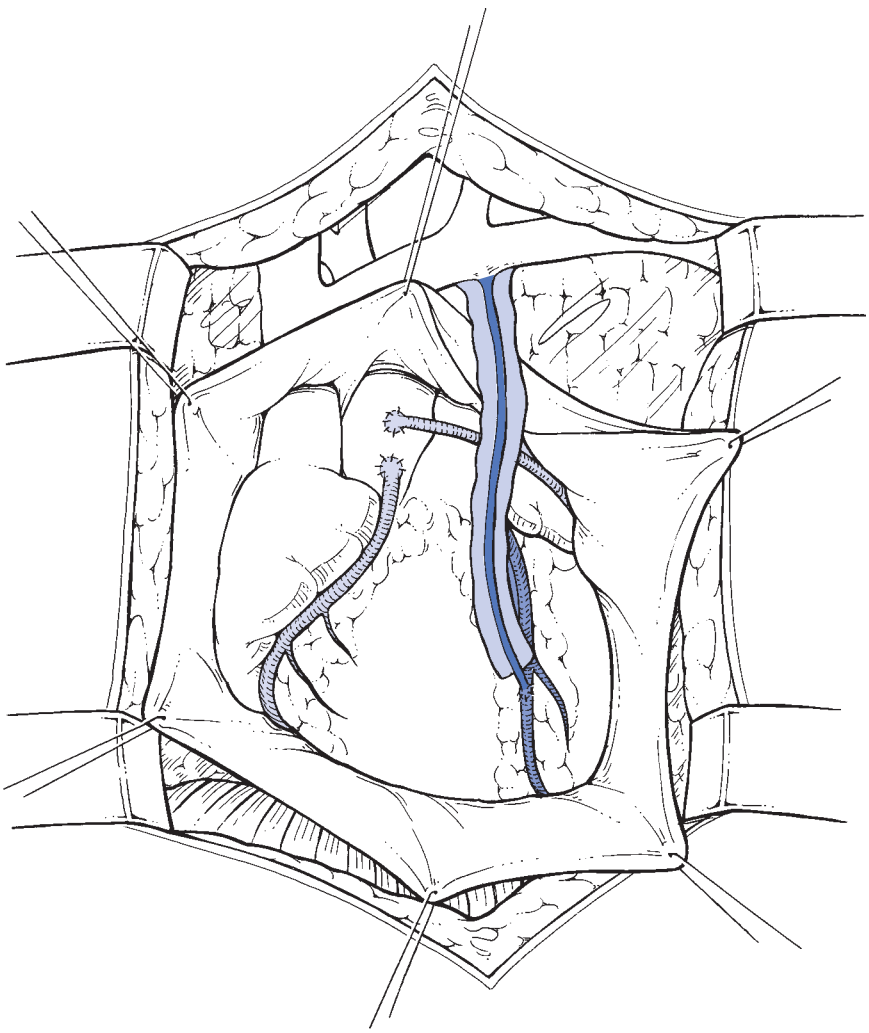

Figure 27-11. A patent left ITA-to-LAD graft should not pose a threat during reoperation. At a primary operation, the pericardium should be divided in a posterior direction, and the ITA graft should be placed in that incision. The ITA graft then will lie posterior to the lung and will not be pushed toward the midline by the lung or become adherent to the sternum.

done, the lung will lie anterior to the left ITA, and that graft will not become adherent to the aorta or to the chest wall.

Once the left side of the chest wall is free, the left IMA is prepared (if it has not been used at a previous operation), the sternal spreader is inserted, and the intrapericardial dissection of the aorta and right atrium is accomplished. Again, in most cases it is safest to find the correct dissection plane at the level of the diaphragm and then to continue around the right atrium to the aorta. The one situation in which this strategy may be dangerous is if an atherosclerotic vein graft to the right coronary artery lies over the right atrium. Manipulation of atherosclerotic vein grafts can cause embolization of atherosclerotic debris into coronary arteries, and it is best to employ a "no touch" technique with such grafts. If a vein graft to the right coronary artery lies in an awkward position over the right atrium, it is best to leave the right atrium alone and to use femoral vein and superior vena cava cannulation to establish venous drainage (Fig. 27-12). Once cardiopulmonary bypass has been established, the aorta has been cross-clamped, and cardioplegia has been given, the atherosclerotic vein graft then can be disconnected.

The goal of dissection of the ascending aorta is to obtain enough length for cannulation and cross-clamping and to avoid the most common error, aortic subadventitial dissection. The correct level of dissection on the aorta usually is found either by following the right atrium to the aorta in a caudal-to-cranial direction or by identifying the innominate vein and leaving all the tissue beneath the innominate vein on the aorta. At the level of the innominate vein, the pericardial reflection on each side of the aorta will be identifiable. Division of the pericardial reflection on the left side in a posterior direction will lead to the plane between the aorta and the pulmonary artery. Once the left side of the aorta is identified, the surgeon then may dissect posteriorly on the medial aspect of the left lung toward the hilum. The segment of tissue between these two dissection planes usually will include a patent left ITA graft, if present, and clamping that tissue will produce occlusion of the ITA graft.

When the aorta has been dissected out, heparin is given, and cannulation is undertaken. Cannulation of an atherosclerotic ascending aorta may cause atherosclerotic embolization leading to stroke, myocardial infarction, or multiorgan failure, so the ascending aorta should be studied with palpation and echocardiography to detect atherosclerosis before cannulation.[41,42] Although the most widely used alternative arterial cannulation site is the femoral artery, arteriopathic patients often have severe femoral artery atherosclerosis. The axillary artery is an alternative arterial cannulation site that we have used with increasing frequency because atherosclerotic disease is usually not present in that vessel, and its cannulation allows antegrade perfusion[43] (Fig. 27-13). If atherosclerotic disease or calcification of the aorta makes any aortic occlusion hazardous, the options are off-pump bypass surgery (see "Other Options" below) or replacement of the aorta with axillary artery cannulation,

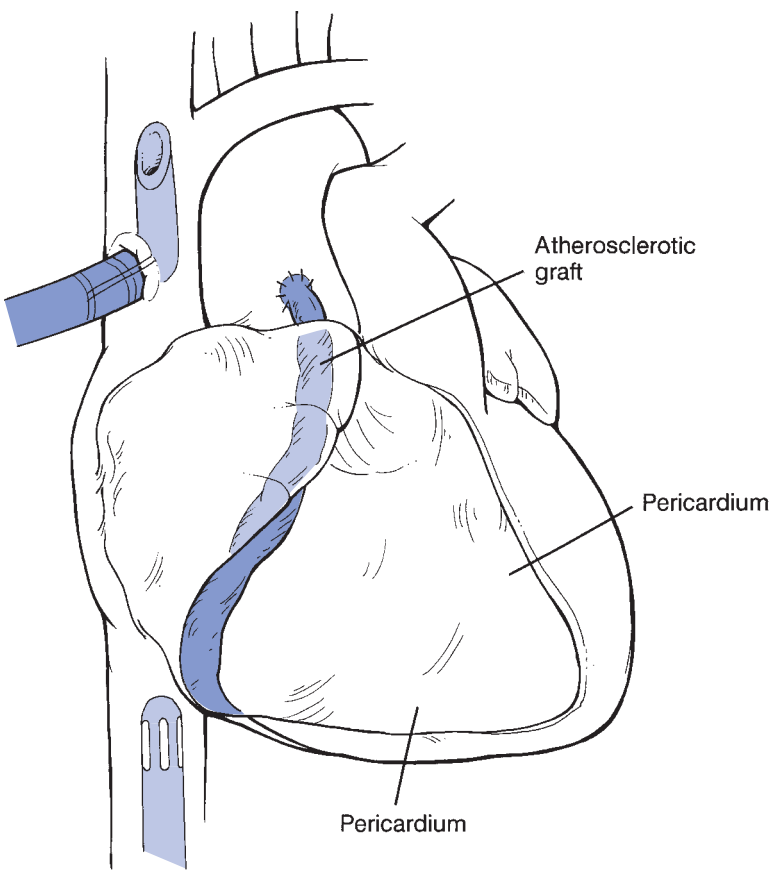

Figure 27-12. Manipulation of patent but atherosclerotic vein grafts should be avoided. If an atherosclerotic right coronary vein graft blocks access to the right atrium, femoral vein and direct superior vena cava cannulation are safer than mobilizing the vein graft in order to achieve right atrial cannulation.

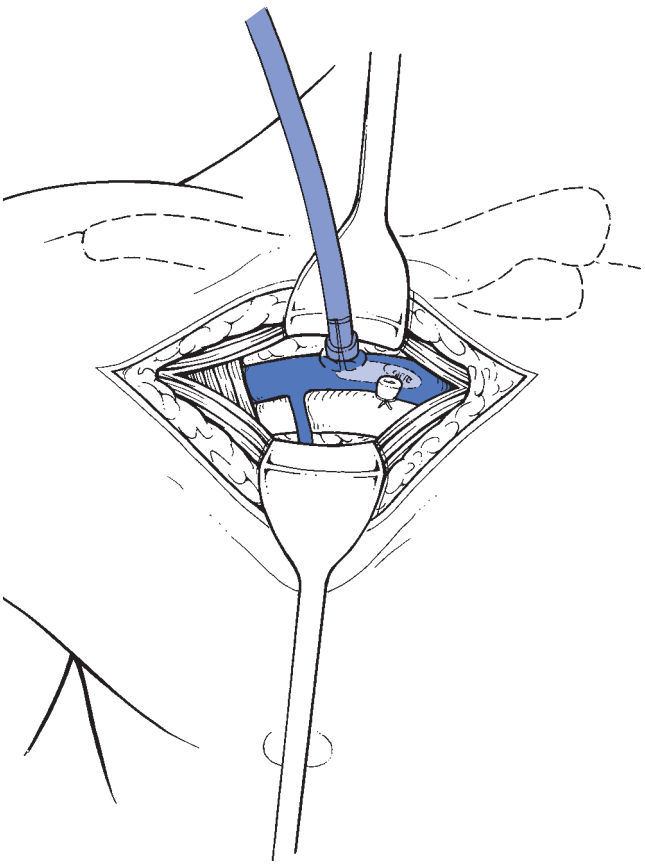

Figure 27-13. The axillary artery is an important alternative arterial cannulation site for patients with aortic and femoral artery atherosclerosis. A 21-gauge cannula will fit the axillary artery in most patients.

hypothermia, and circulatory arrest. Venous cannulation usually is accomplished with a single two-stage right atrial cannula. A transatrial coronary sinus cardioplegia cannula is inserted via a right atrial purse string with the aid of a stylet, and a needle is placed in the ascending aorta for delivery of antegrade cardioplegia and for use as a vent (Fig. 27-14).

Myocardial Protection

The myocardial protection strategy used by us during most coronary artery reoperations is a combination of antegrade and retrograde delivery of intermittent cold blood cardioplegia combined with a dose of warm reperfusion cardioplegia ("hot shot") given prior to aortic unclamping, principles developed by Buckberg and colleagues.[44,45] Multiple types of cardioplegic solutions have been described, and most appear to provide a metabolic environment that effectively protects the myocardium. Because of the potential anatomic challenges to cardioplegic myocardial protection during reoperations, the details of how the cardioplegic solution is delivered are very important. In most primary bypass operations, antegrade cardioplegia works well by itself. During reoperations, however, antegrade cardioplegia may not be effective for areas of myocardium that are supplied by patent in situ arterial grafts and may be dangerous because of the risk of embolization of atherosclerotic debris into the coronary arteries from old vein grafts. The delivery of cardioplegia through the coronary sinus and through the cardiac venous system to the myocardium (retrograde cardioplegia) has been a step forward in myocardial protection during reoperations.[46,47] Retrograde cardioplegia delivery avoids atheroembolism from vein grafts, can be helpful in removing atherosclerotic debris and air from the coronary artery system, and can deliver cardioplegia to areas supplied by in situ arterial grafts. The biggest disadvantage of retrograde cardioplegia is that it is not always possible to place a catheter in the coronary sinuses that will deliver cardioplegia consistently. It is important to monitor the adequacy of cardioplegia delivery by measuring the pressure in the coronary sinus, noting the distention of cardiac veins with arterial blood, the cooling of the myocardium, and the return of desaturated blood from open coronary arteries.

Cardiopulmonary bypass is begun, the perfusionist empties the heart and produces mild systemic hypothermia (34°C), and the aorta is cross-clamped. We usually initiate cardioplegia induction with aortic root cardioplegia. To induce and maintain cardioplegic protection, it is helpful to be able to occlude patent arterial grafts. If it has not yet been possible to dissect out a patent arterial graft so that it can be clamped, the systemic perfusion temperature is decreased to 25°C until control of the graft is achieved. After antegrade cardioplegia has been given for 2 to 3 minutes, we shift to retrograde induction for another 2 to 3 minutes. Giving any antegrade cardioplegia does risk embolization from atherosclerotic vein grafts, but if these grafts have not yet been manipulated, that danger is relatively small. Once the adequacy of retrograde cardioplegia delivery has been established, it is often possible to use that route predominantly for maintenance doses.

Intrapericardial Dissection

When the heart has been arrested completely, intrapericardial dissection of the left ventricle is undertaken, starting at the diaphragm and extending out to the left of the apex of the heart. After the apex is identified, the surgeon divides the pericardium in a cranial direction on the left side of the LAD artery (Fig. 27-15). A patent LITA-to-LAD graft will be contained within the strip of pericardium that lies over the LAD artery. Dissection of this pedicle from the anterior aspect of the pulmonary artery will allow an atraumatic clamp to be placed across the patent ITA graft and also will allow the passage of new bypass grafts from the aorta underneath the patent ITA graft to left-sided coronary arteries. The advantages of waiting until after aortic clamping and arrest to dissect out the left ventricle are that dissection is more accurate, there is less damage to the epicardium and less bleeding, manipulation of atherosclerotic vein grafts is less likely to cause coronary embolization, and the dissection of patent ITA grafts is safer.

After the heart is dissected out completely, the coronary arteries to be grafted can be identified, the lengths that

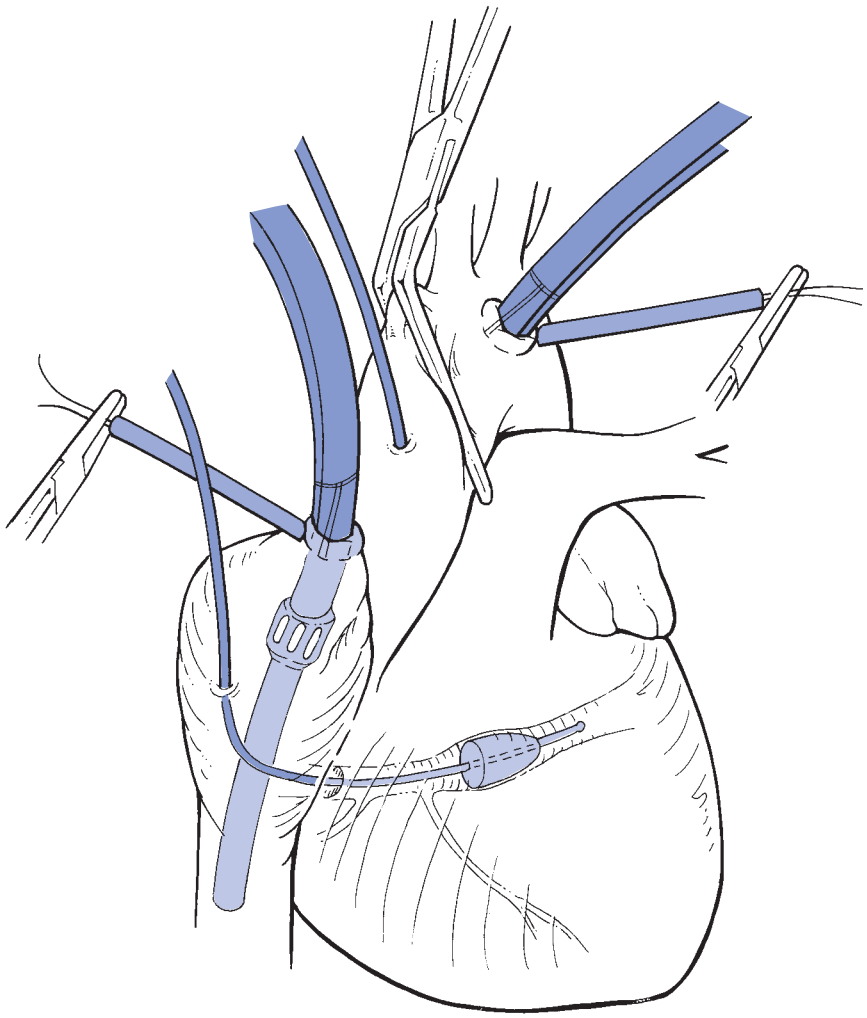

Figure 27-14. Standard cannulation for coronary artery reoperation includes aortic arterial cannulation, an aortic needle for antegrade delivery of cardioplegia and aortic root venting, a single two-stage venous cannula, and a transatrial coronary sinus catheter with a self-inflating balloon for delivery of retrograde cardioplegia. Cannulation is accomplished prior to dissection of the left ventricle.

bypass conduits need to reach those vessels may be assessed, and the final operative plan can be established. The old grafts and epicardial scarring that are present during reoperations make the preoperative prediction of the lengths of conduits needed for bypass grafts quite difficult, particularly the lengths of arterial grafts, and it is wise to have some flexibility in the operative plan. Prior to the construction of the anastomoses, those patent but atherosclerotic vein grafts that are going to be disconnected are identified and are disconnected with a scalpel. The order of anastomosis construction that is used by the authors is (1) distal vein graft anastomoses, (2) distal free arterial graft anastomoses, (3) distal in situ arterial graft anastomoses, and (4) proximal (aortic) anastomoses.

Stenotic Vein Grafts

When should patent or stenotic vein grafts be replaced, and what should they be replaced with? Atherosclerosis in vein grafts is common if those grafts are more than 5 years old, and leaving them in place risks embolization of atherosclerotic debris at the time of reoperation and subsequent development of premature graft stenoses or occlusions after reoperation. On the other hand, replacement of all vein grafts extends the operation and may use up available bypass conduits.

In the past, our general rule has been to replace all vein grafts that are more than 5 years old at the time of reoperation, even if those grafts are not diseased angiographically. However, this strategy assumes that conduits are available that can replace these old grafts. Today, many patients have very limited conduits at reoperation because of the large numbers of vein grafts used at primary surgery or because of multiple previous operations. Thus, graft replacement must be individualized. Inspection of vein grafts at reoperation occasionally will identify a graft that looks normal angiographically and does not appear to have any thickening or atherosclerosis on visual inspection. Often such vein grafts will be left alone.

Replacing old vein grafts with new vein grafts is best accomplished by creating the new vein-to-coronary-artery anastomosis at the site of the previous distal anastomosis, leaving only 1 mm or so of the old vein in place (Fig. 27-16). If significant native-vessel stenoses have developed distal to the old vein graft, it is often best to place a new graft to the distal vessel in addition to replacing the vein graft. Many reoperative candidates have proximal occlusions of

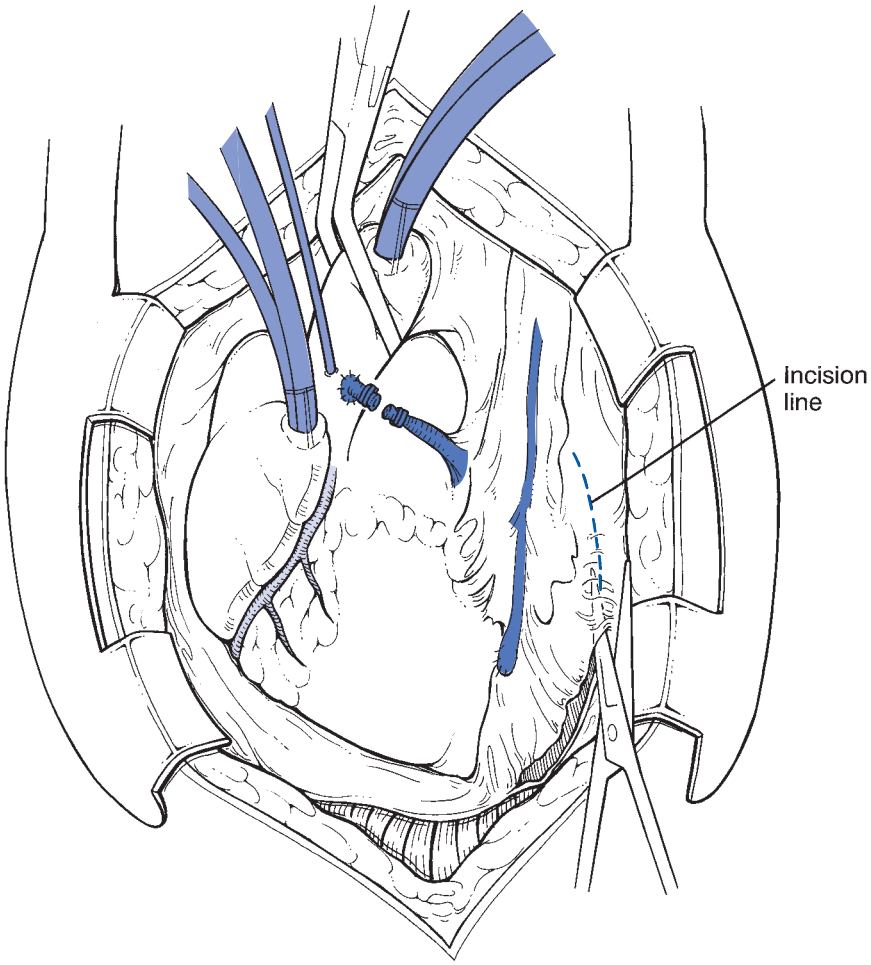

Figure 27-15. Division of the pericardium along the diaphragm allows the surgeon to reach a point to the left of the cardiac apex. From that point, the pericardium can be divided in a cranial direction to the left of the LAD artery, leaving a patent ITA graft in the strip of tissue overlying the LAD artery. Atherosclerotic vein grafts that are going to be replaced may be divided once a dose of antegrade cardioplegia is given.

the native coronary artery system and multiple stenoses throughout the vessel, and if only new distal grafts are constructed, the proximal segments of coronary arteries and their branches that are supplied by atherosclerotic vein grafts may be jeopardized. More than one graft to a major coronary artery may be desirable during reoperation (Fig. 27-17).

Sequential vein grafts often are very helpful during reoperation because they allow more distal anastomoses and fewer proximal anastomoses. Sites for proximal anastomoses are often at a premium in the scarred reoperative aorta.

Artery-to-coronary-artery bypass grafts have many advantages during reoperations. First, they are often available. Second, the tendency of arteries to remain patent even

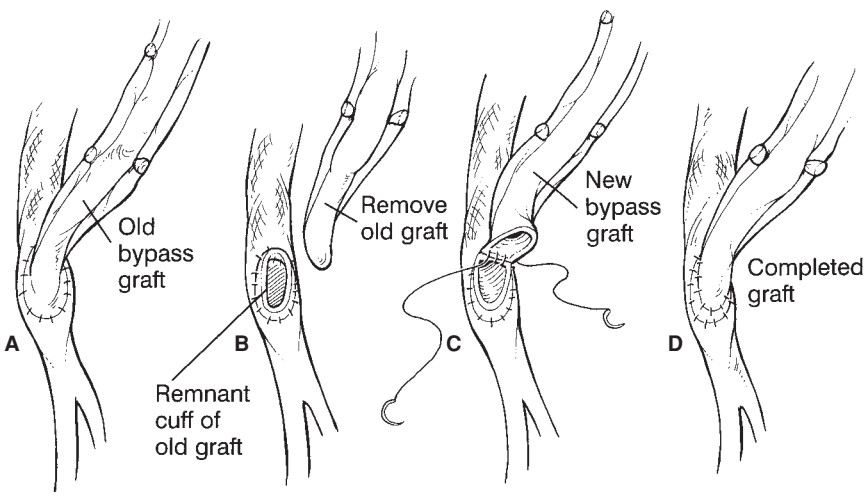

Figure 27-16. For patients with extensive native coronary atherosclerosis, the distal anastomotic site of an old vein graft is often the best spot for the distal anastomosis of a new graft. Only a small rim of the old graft should be left in place.

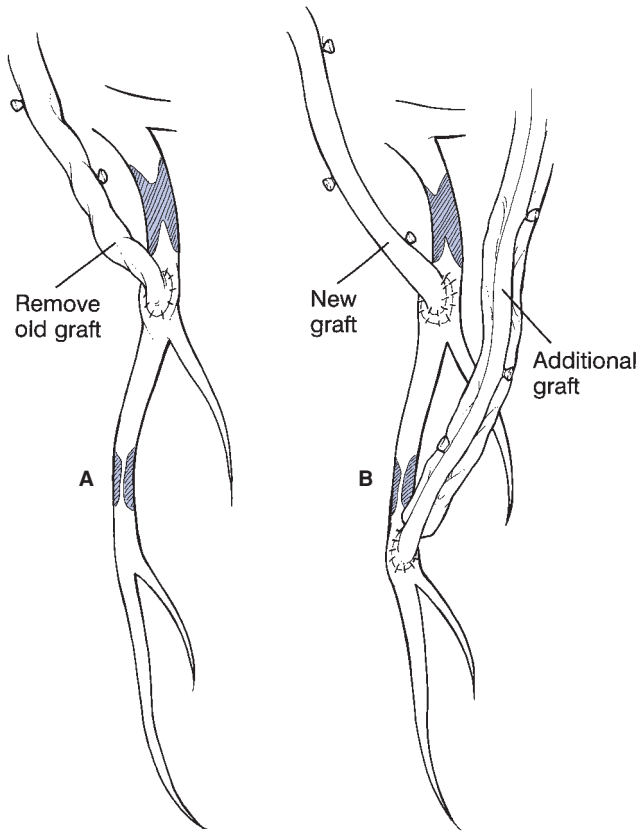

Figure 27-17. Extension of native-vessel coronary artery disease may indicate the placement of new distal grafts as well as replacement of diseased vein grafts supplying proximal coronary artery segments.

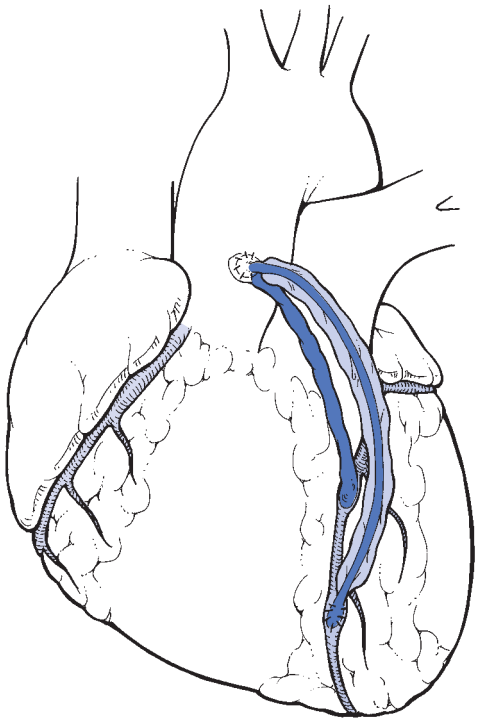

Figure 27-18. The hood of new or old vein grafts is often the best spot for the aortic anastomosis of free arterial grafts. Atherosclerosis rarely occurs in that "bubble" of vein.

when used as grafts to diffusely diseased coronary arteries makes them particularly applicable to reoperative candidates. Third, in situ arterial grafts do not require a proximal anastomosis. If the left ITA has not been used as a graft at a previous operation, a strong attempt should be made to use it as an in situ graft to the LAD artery. During primary operations, the right ITA usually can be crossed over as an in situ graft to left-sided vessels, but such a plan is more difficult during repeat surgery, so the right ITA is often used as a free graft.

Arterial graft proximal anastomoses are a problem at reoperation because the scarring and thickening of the reoperative aorta often make direct anastomoses of arterial grafts to the aorta unsatisfactory. However, when old vein grafts become occluded, there is usually a "bubble" of the hood of the old vein graft that is not atherosclerotic and that often is a good spot for construction of a free (aorta-to-coronary-artery) arterial graft anastomosis (Fig. 27-18). In addition, if new vein grafts are performed, the hood of that new vein graft represents a favorable location for an arterial graft anastomosis. Late angiographic data regarding this strategy are not available, but the relative freedom of the hood of vein grafts from the development of atherosclerosis means these grafts are likely to be successful.

Another effective strategy is to use either an old arterial graft or a newly constructed arterial graft for the proximal anastomosis of a free arterial graft (Fig. 27-19). Composite arterial grafts, usually using a new in situ left ITA graft at the proximal anastomotic site for a free right ITA graft, have been employed with increasing frequency, and early outcomes have been favorable.[48,49] This method is particularly useful during reoperations because it may avoid an aortic anastomosis, and less right ITA graft length is needed to reach distal circumflex arteries. Other advantages of using a previously performed patent ITA graft for the proximal anastomosis of a new arterial graft are that the old left ITA graft often has increased in size, and the preoperative angiogram has demonstrated its integrity. In situations where the effectiveness of an LITA-to-LAD graft has been jeopardized by a distal LAD lesion, a short segment of a new arterial graft can be used to bridge that stenosis from the old arterial graft to the distal LAD artery (see Fig. 27-18).

Can an ITA graft be used to replace a vein graft during reoperation? When faced with replacing a stenotic or patent vein graft during reoperation, the surgeon has a number of options, all of which have some potential disadvantages:

1. The surgeon may leave the old vein graft in place and add an arterial graft to the same coronary vessel. The dangers of this approach are that atherosclerotic embolization from the old vein may occur during the reoperation, and competitive flow

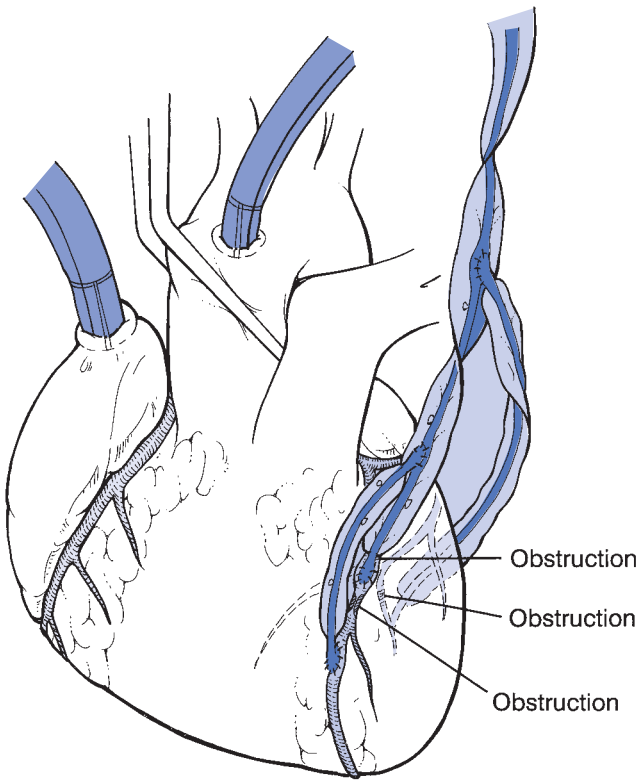

Figure 27-19. Composite arterial grafts can be constructed using a new or old left ITA graft as the inflow source. With its proximal anastomosis to the left ITA, a right ITA graft will easily reach the circumflex branches. Furthermore, a shorter segment of inferior epigastric artery or radial artery can be used to reach the distal LAD artery if intervening native LAD stenoses have limited the effectiveness of an old ITA graft.

between the vein graft and the arterial graft may jeopardize the ITA graft after reoperation.

2. The surgeon may remove the old vein graft and replace it with an ITA graft. This decreases the likelihood of atherosclerotic embolization and competitive flow but risks hypoperfusion during reoperation if the arterial graft cannot supply all the flow that had been generated previously by the vein graft.
3. The surgeon may replace the old vein graft with a new vein graft. The disadvantage of this approach is a long-term one: The coronary vessel is left dependent on a vein graft.

When we examined these choices in a retrospective study of operations for patients with atherosclerotic vein grafts supplying the LAD artery, we found that the worst outcomes resulted from removing a patent (although stenotic) vein graft and replacing it with only an ITA graft.[39] This strategy was associated with a significant incidence of hypoperfusion and severe hemodynamic difficulties during reoperation that were treated effectively only by adding a vein graft to the same coronary artery. The incidence of myocardial infarction associated with leaving a stenotic vein graft in place was low. Thus, atherosclerotic embolization from an atherosclerotic vein graft is a danger, but it appears that with the use of retrograde cardioplegia, it is not commonly a major catastrophe.

Another potential disadvantage of the strategy of adding an ITA graft to a stenotic vein graft is that competition in flow from the stenotic vein graft may lead to failure of the new ITA graft. However, this is unlikely to occur as long as the stenosis in the SVG is severe.[50] Our usual approach, therefore, is to remove atherosclerotic vein grafts when replacing them with a new vein graft but leave stenotic vein grafts in place when grafting the same vessel with an arterial graft (Fig. 27-20).

Alternative arterial grafts often are very useful during reoperation. The radial artery has particular advantages during repeat surgery because it is larger and longer than other free arterial grafts. These qualities increase the range of coronary arteries that can be grafted. Early studies of radial artery grafts have shown favorable patency rates, but few long-term data currently exist. If the high patency rates that have been documented by early studies are confirmed by the tests of time, the radial artery will be used extensively during reoperations. The inferior epigastric artery often is too short to function as a separate aorta-to-coronary-artery graft during

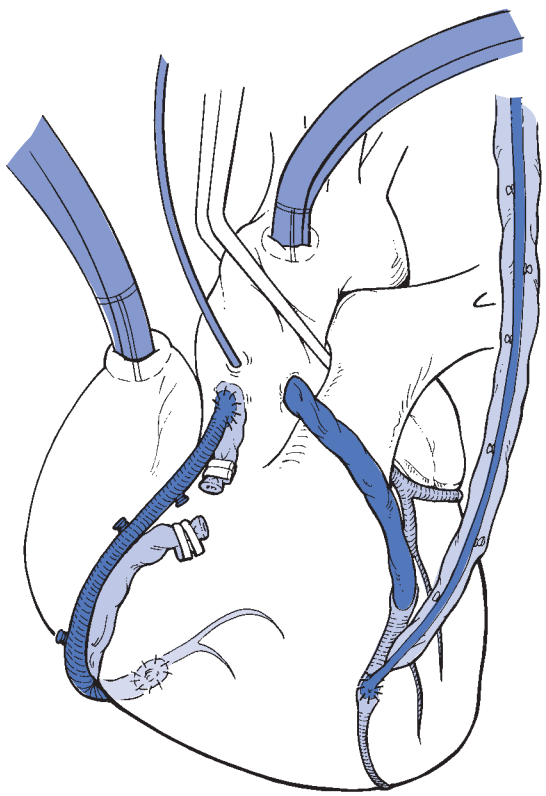

Figure 27-20. In this example, an atherosclerotic right coronary artery vein graft is disconnected and is replaced with a new vein graft. However, the stenotic vein graft to the LAD artery is left in place to avoid hypoperfusion, and a new ITA graft is added to the LAD artery.

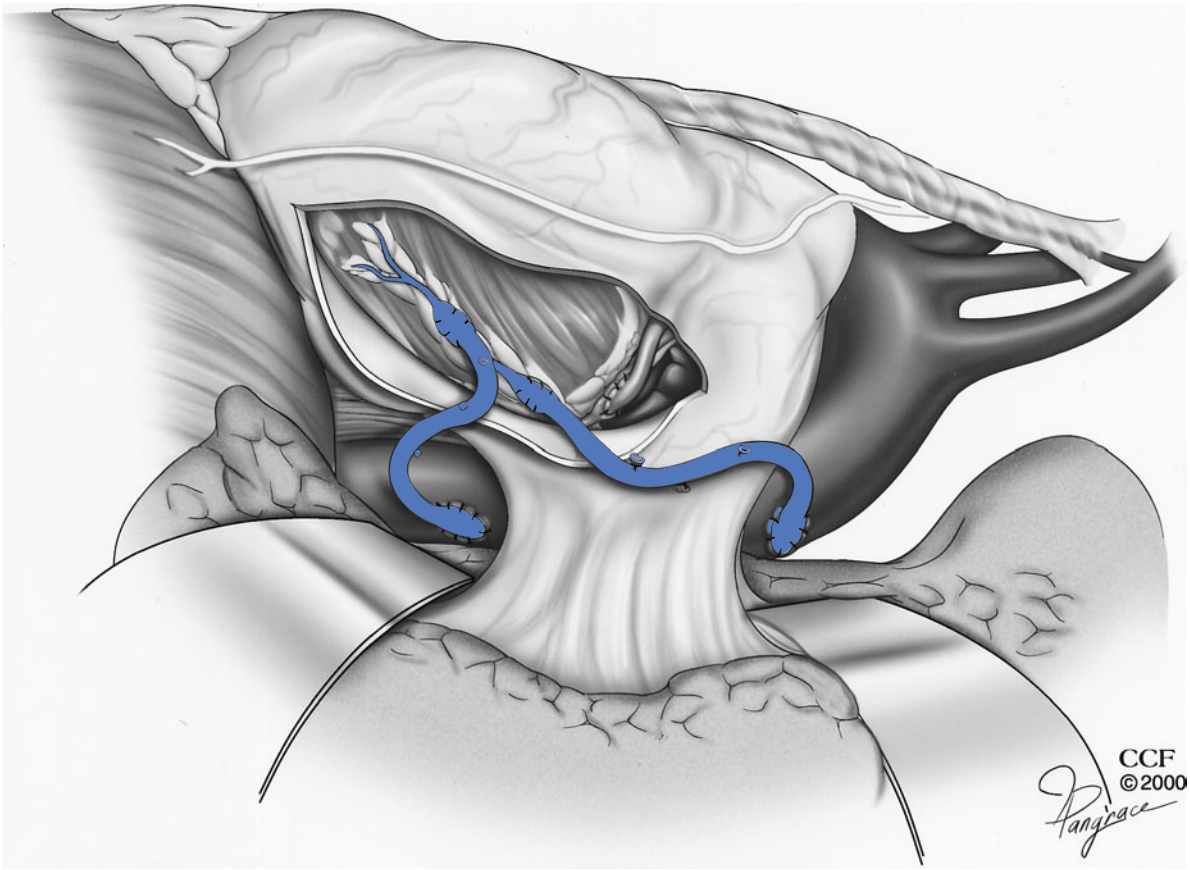

Figure 27-21. Circumflex vessels may be grafted through a left thoracotomy incision without cardiopulmonary bypass.

reoperation but can be extremely useful as a short composite arterial graft, as illustrated in Fig. 27-19.

The right gastroepiploic artery (RGEA) has established a good midterm graft patency rate record and often is useful during reoperation because it is an in situ graft.[51] Furthermore, it can be prepared prior to the median sternotomy. It is effective most often as an in situ graft to the posterior descending branch of the right coronary artery or to the distal LAD artery (Fig. 27-21).

The aortic anastomoses of the vein and arterial grafts are performed last during the single period of aortic cross-clamping. Sites for aortic anastomoses are often at a premium owing to previous scarring, atherosclerotic disease, or the use of Teflon felt during the primary operation, and often the locations of the previous vein graft proximal anastomoses are the best locations for the new ones. The advantages of constructing aortic anastomoses during a single period of aortic cross-clamping are that it minimizes aortic trauma and allows excellent visualization of the proximal anastomoses. In addition, if patent or stenotic vein grafts have been removed and replaced, reperfusion is not accomplished by aortic declamping until the aortic anastomoses have been completed.

The disadvantage of this approach is that it prolongs the period of aortic cross-clamping. However, our strategies for reoperation are not based on trying to minimize myocardial ischemic time. If cardioplegia can be delivered effectively, its metabolic concepts are valid, and myocardial protection is secure. Failure of myocardial protection usually is caused by anatomic events, not by metabolic failure. Once the proximal anastomosis has been constructed, a "hot shot" of substrate-enhanced blood cardioplegia is given, and the aortic cross-clamp is removed.

Other Options

Although most reoperations are performed through a median sternotomy with the use of cardiopulmonary bypass, the strategies of small-incision surgery and off-pump surgery that have been gaining increasing use for primary coronary artery operations also can be helpful during reoperations. Reoperations in situations in which a limited area of myocardium needs revascularization often can be accomplished through a limited incision and without the use of cardiopulmonary bypass [known as the *minimally invasive direct coronary artery bypass* (MIDCAB) *operation*]. The distal LAD artery may be exposed with a small anterior thoracotomy, and the LAD or diagonal artery may be grafted with a left ITA graft. A stabilizing device usually is employed for anastomotic construction, although the intrapericardial

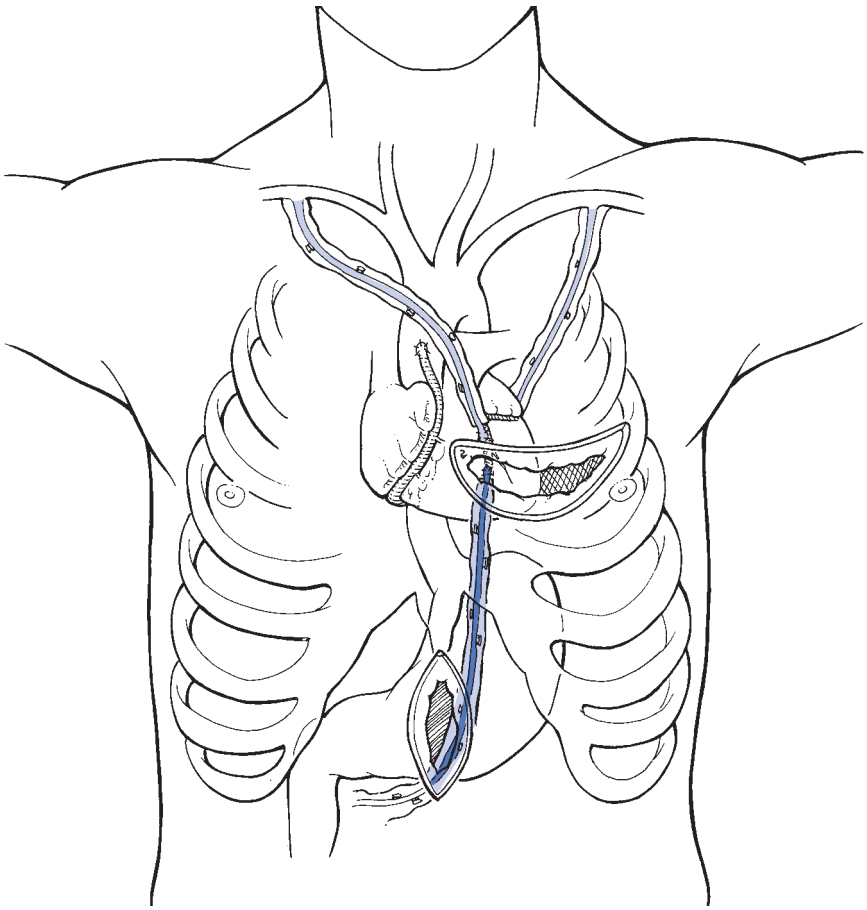

Figure 27-22. An in situ gastroepiploic artery (GEA) graft may be used for an on- or off-pump anastomosis to the distal LAD artery.

adhesions provide some stability during reoperations. If the left ITA is not available, a segment of saphenous vein can be anastomosed to the subclavian artery and routed in a transthoracic path to the LAD artery. If the right ITA is to be used as an in situ graft to the LAD artery, a median sternotomy is indicated, but if this is the only graft, off-pump surgery usually is possible.

The lateral wall of the heart can be exposed through a left lateral thoracotomy (Fig. 27-22), and the circumflex and distal right coronary artery branches can be grafted with this approach. Often the LITA already has been used for a graft, but the descending thoracic aorta may be used as a site for the proximal anastomosis of a vein graft or a radial artery graft using a partial occluding clamp. The disadvantages of this approach are that the right ITA is difficult to use as an in situ graft, and if the circumflex vessels are deeply intramyocardial, they may be difficult to expose and isolate with the off-pump strategy.

In addition to avoiding potential complications of cardiopulmonary bypass, the "limited-area, off-pump" approach also avoids extensive dissection of the heart and possible manipulation of atherosclerotic vein grafts. The disadvantage of this approach is that most patients who are candidates for reoperation need grafts to multiple vessels in multiple myocardial areas.

Use of a median sternotomy and the off-pump strategy to graft multiple myocardial areas is now a standard approach to primary coronary revascularization and also can be used during reoperation. However, because of the need to access all areas, extensive dissection sometimes is necessary for lysis of adhesions to be able to mobilize the heart. If patients have atherosclerotic vein grafts, dissection and manipulation create the dangers of embolization of atherosclerotic debris and myocardial infarction. This problem was encountered during the early years of bypass surgery when the risks of atherosclerotic embolization were less recognized. Another disadvantage of off-pump reoperative strategies is that reoperative candidates often have very distal and diffuse CAD, which leaves intramyocardial segments as the best areas for grafting. These characteristics stress off-pump isolation and immobilization techniques. In addition, the aortic anastomoses of vein or free arterial grafts may be difficult because of aortic atherosclerosis, adhesions, or previous aortic anastomoses that may limit the application of a partial occluding clamp. On the other hand, the use of off-pump techniques may minimize aortic trauma, particularly if in situ arterial grafts can be employed to provide inflow to new grafts.

In an individual case, the disadvantages of off-pump surgery may be important or irrelevant. Surgeons who perform

reoperative coronary artery surgery in a wide spectrum of situations will find both on- and off-pump strategies helpful.

RESULTS OF CORONARY ARTERY REOPERATIONS

Coronary artery reoperations are riskier than primary operations. A study from the Society of Thoracic Surgeons (STS) database reported an in-hospital mortality rate of 6.95% associated with reoperations for the years 1991–1993, and in a multivariate analysis of all isolated coronary artery bypass surgery, "previous operation" was identified as a factor that increased the mortality rate.[12] At the Cleveland Clinic Foundation, the in-hospital mortality rate of a first reoperation ranged between 3 and 4% from 1967 through 1991, and the rate was 3.7% for 1663 patients having repeat surgery from 1988 through 1991.[1–3] Progress during the last decade has continued to lower this risk. In a recent report by Sabik and colleagues, the hospital mortality rate for patients undergoing reoperative CABG was reduced to 2.5% in 2002, and risk adjustment identified the comorbidity burden carried by reoperative patients as a factor that increased risk, not reoperative status itself.[14]

Recent mortality rates from other large series range from 4.2 to 11.4%, most being around 7%.[4–9,52] All these figures are two to five times higher than the rates we would expect for the risk of primary CABG.

Coronary artery reoperations have been associated with a higher in-hospital mortality mostly because of an increased risk of perioperative myocardial infarction. In the Cleveland Clinic Foundation series, the cause of perioperative death was cardiovascular in 85% of cases in the most recent cohort of patients undergoing reoperation, a figure that contrasts with recent studies of primary operations, in which noncardiac causes of death have been increasingly important.[3,15] Furthermore, in the reoperative series, in-hospital mortality was associated with new perioperative myocardial infarction in 67% of cases. Multiple causes of myocardial infarction have been identified, including incomplete revascularization owing to distal CAD, vein graft thrombosis, ITA graft failure, atherosclerotic embolization from vein grafts, injury to bypass grafts, hypoperfusion from arterial grafts, preoperative myocardial infarction, and complications of PTCA.

Multiple studies of patients undergoing reoperation have identified increased age, female gender, and emergency operation as clinical variables that have a high association with in-hospital mortality. Emergency operation is a particularly strong factor. Although there is not a standard definition of *emergency,* mortality rates after emergency reoperations that have been reported range from 13 to 40%.[3,5–8] Data from the STS for the year 1997 documented a risk of 5.2% for elective reoperations, 7.4% for urgent reoperations, 13.5% for emergency reoperations, and 40.7% for "salvage" reoperations. There is clearly a major increment in risk associated with emergency reoperations, a larger increment than has existed for patients undergoing primary surgery.

Advanced age, by itself, does not increase the risk of reoperation substantially but does so when combined with other variables. In a review of 739 patients aged 70 years or older undergoing reoperation, we noted an overall in-hospital mortality rate of 7.6% and identified emergency operation, female gender, left ventricular (LV) dysfunction, creatinine concentration greater than 1.6 μg/dL, and left main coronary artery stenosis as specific factors increasing risk. For patients with none of these characteristics, the in-hospital mortality rate was only 1.5%.[53]

Specific anatomic situations, in particular, the presence of patent ITA grafts and atherosclerotic vein grafts, can increase the risk of reoperation, but with experience, these technical factors largely have been neutralized. We have never documented an increased mortality rate for patients with patent ITA grafts but have noted that the risk of ITA damage has dropped from 8% in our early experience to 3.7% more recently, an improvement almost entirely related to increased surgical experience. With proper positioning of an ITA graft at primary operation, a patent LITA-to-LAD-artery or LITA-to-circumflex-artery graft should not represent an impediment to reoperation. Situations in which a patent in situ right ITA graft crosses the midline to supply the LAD or circumflex system are more difficult and require extreme care in reoperating using a median sternotomy incision. Although these situations are uncommon and provide difficult technical challenges, the risks for these patients have not been increased.

Studies from the past noted that the presence of atherosclerotic vein grafts did increase perioperative risk. Perrault and colleagues documented mortality rates of 7, 17, and 29% for patients with one, two, or three stenotic vein grafts, respectively, and in a previous study of patients with atherosclerotic vein grafts, we noted that the presence of an atherosclerotic vein graft to the LAD artery increased in-hospital risk.[30,36] However, in our more recent study we found that atherosclerotic vein grafts did not increase mortality, although there was a nonsignificant trend toward increased risk for patients with multiple stenotic grafts.[3] The favorable results for these patients have been based on a combination of improved technology, the use of retrograde cardioplegia delivery, and increased surgeon experience.

Although arterial grafts may offer advantages at reoperation, their use may prolong an already complex operation, and the influence of arterial grafting on perioperative risk has been a concern. However, we have specifically studied this issue and found that the use of single or double ITA grafts at reoperation does not increase perioperative risk, and in fact, not having an ITA graft at either the first or second operation appeared to be a factor associated with increased in-hospital mortality.[3] Graft selection in that study was not randomized, and it is certainly possible that the increased risk for patients receiving only vein grafts was related to patient-related variables rather than surgical strategy. It does appear, however, that the use of arterial grafts does not increase risk. Except for an increased incidence

of perioperative myocardial infarction, in-hospital morbidity does not seem to be increased for patients undergoing reoperation. One important observation relates to wound complications. Multiple groups, including ours, have noted an increased risk of wound complications when diabetic patients have received bilateral (simultaneous) ITA grafts. However, there does not appear to be an increased risk of wound complications for diabetic patients who receive staged ITA grafts, one at the first and another at a second operation.

It is important to note that only the variables that can be identified and quantified are included in studies consistent enough to be identified as risk factors. For example, experience and logic dictate that severe atherosclerosis of the ascending aorta is a major risk factor, but this is rarely identified in large studies because patients do not routinely undergo echocardiography to identify the presence of aortic atherosclerosis.

Late Results

Patients who are undergoing reoperation are at a later stage in the progression of their native coronary atherosclerosis compared with the point when they underwent primary surgery, and the anatomic corrections achieved at reoperation are less perfect. Although the definition of *complete revascularization* varies widely, few reoperative candidates undergo an operation in which all diseased segments of all arteries receive bypass grafts. It is not surprising that the long-term results of reoperation have not been as favorable as the long-term results of primary operations.

The likelihood of recurrent angina after any bypass operation is related to time, but angina symptoms are more common after repeat surgery than they are after primary operation. Follow-up of our reoperative patients at a mean interval of 72 months after reoperation showed that 64% of patients were in New York Heart Association (NYHA) functional class I, although only 10% of patients had class III or class IV symptoms.[2] Weintraub and colleagues also noted at a 4-year follow-up that 41% of reoperative patients had experienced some angina.[6]

Late survival rates after reoperation are also inferior to those after primary surgery. Weintraub and colleagues noted 76% 5-year and 55% 10-year survival rates, and our most recent follow-up study found a 10-year survival rate of 69% for in-hospital survivors[2,6] (Fig. 27-23). The predictors of late survival have varied among studies, but LV dysfunction, advanced age, and diabetes consistently have been associated with a decreased late survival rate. The variables identified by multivariate testing as decreasing the late survival for 2429 hospital survivors of a first reoperation are listed in Table 27-3. The influence of ITA grafts on late survival has been difficult to determine for reoperations. We found a positive influence of a single ITA graft on late survival, as have others,[54] but the effect was not as dramatic as has been noted after primary operations. Weintraub and colleagues did not document an improved survival associated with ITA grafting.[6]

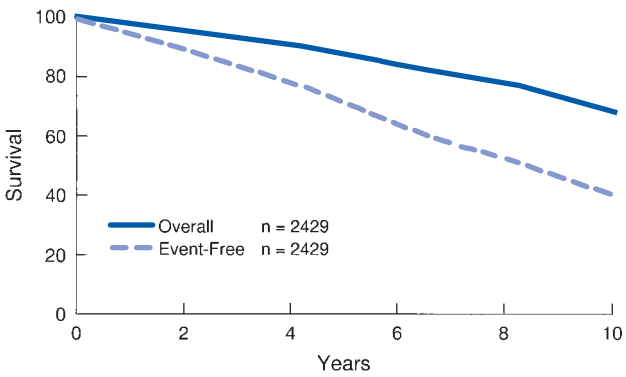

Figure 27-23. For 2429 hospital survivors who underwent reoperation between 1967 and 1987, the 10-year survival was 69%, and event-free survival was 41%. (*Reprinted with permission from Loop FD, Lytle BW, Cosgrove DM, et al: Reoperation for coronary atherosclerosis: Changing practice in 2509 consecutive patients. Ann Surg 1990; 212:378.*)

Multiple Coronary Artery Reoperations

Patients who have had more than one previous coronary artery operation are like patients undergoing first reoperations, only more so. Many patients undergoing multiple reoperations had their first procedure more than 15 years ago, and severe native-vessel disease and lack of bypass conduits are a common combination of problems. Selection

Table 27–3.

Factors Decreasing Late Survival After Reoperation: 1967–1987[2]

Factor	*p*-Value	Relative risk
LV dysfunction	.0001	1.9
Age	.0001	1.04
Current cigarette smoking	.0001	1.6
Hypertension	.0002	1.4
Left main ≥50%	.0001	2.0
Triple-vessel disease	.0001	1.6
NYHA III/IV symptoms	.003	1.4
Peripheral vascular disease	.001	1.5
Interval >60 months	.006	1.003
No ITA at first operation	0.03	1.5

LV = left ventricular.

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criteria vary widely among institutions, but in-hospital mortality rates are increased relative to first reoperations.[10,11] Through 1993, we reoperated on 392 patients who had more than one previous bypass operation, with an in-hospital mortality rate of 8%. Over the next 10 years, this mortality rate has decreased to 5.8%.[14] Follow-up of the in-hospital survivors in the former group found late survival rates of 84% at 5 and 66% at 10 postoperative years. Thus, although the in-hospital risks were increased for these patients, the long-term outcome has been relatively favorable. Age was a major determinant of outcome. Recently, in-hospital mortality for patients younger than 70 years of age has decreased to 1 to 2%, but for patients over age 70, it has remained higher than 10%. Furthermore, patients over age 70 who did survive operation in our series had only a 50% 5-year late survival.

CONCLUSION

Coronary artery reoperations continue to present adult cardiac surgeons with their most difficult challenges in part because of the many technical pitfalls that exist but also because coronary artery reoperations are so common. The population of patients who have had previous bypass surgery is huge, and patients who develop recurrent ischemic syndromes expect that they will be treated effectively. Although we now understand the long-term implications of using vein grafts, technical and operative time considerations make it unlikely that a wave of total arterial revascularization will engulf primary coronary artery surgery. Thus, the numbers of reoperations are likely to continue to increase, and improvement over the principles outlined in this chapter will continue to be an important goal.

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CHAPTER 28

Transmyocardial Laser Revascularization and Extravascular Angiogenetic Techniques to Increase Myocardial Blood Flow

Keith A. Horvath • Yifu Zhou

TRANSMYOCARDIAL LASER REVASCULARIZATION (TMR) HISTORY

Despite the success of medical therapy, percutaneous coronary interventions (PCIs), and coronary artery bypass grafting (CABG) in the treatment of coronary artery disease (CAD), there are a significant number of patients with refractory angina owing to diffuse CAD that is not amenable to PCI or CABG. This severe CAD can lead to incomplete revascularization following CABG and is noted to occur in up to 25% of CABG surgery.[1] This incomplete revascularization is a powerful independent predictor of operative mortality and perioperative adverse events.[1–3] Additionally, the presence of diseased but nongrafted arteries carries a poor prognosis and poses a significant negative influence leading to an increased incidence of death, recurrent angina, myocardial infarction (MI), and the need for repeat CABG.[4–6]

Strategies to treat patients with end-stage coronary disease have sought to create or enhance myocardial angiogenesis. Such techniques include TMR as well as protein-, gene-, and cell-based therapies. TMR was founded, in part, on previous methods of providing direct perfusion to the myocardium. Prior attempts at direct perfusion were based on Wearn's description of sinusoids that allowed blood to flow directly from the ventricle into the myocardium.[7] These arterioluminal connections provide perfusion in more primitive vertebrate hearts and occur clinically in children with pulmonary atresia, an intact ventricular septum, and proximal obstruction of the coronary arteries. Sen and colleagues[8] used myocardial acupuncture to establish direct perfusion and theoretically to recreate a coronary microcirculation similar to that of the reptilian heart. Additional methods of attempting to improve myocardial blood flow include Beck's creation of a form of superficial angiogenesis as a response to epicardial and pericardial inflammation.[9] Combining the acupuncture, implantation, and inflammation techniques, Boffi[10] and Borst[11] used hollow tubes implanted in the myocardium to establish direct perfusion. Results from all these procedures yielded limited success. The angina relief obtained was not long-lasting, was difficult to replicate, and most important, eventually was overshadowed by the ability to perform CABG. The mechanical trauma that resulted in poor long-term patency of myocardial acupuncture was overcome in theory by using a laser to create the channels. Although Mirhoseini and colleagues[12,13] and Okada and colleagues[14,15] pioneered the use of a laser to perform this type of revascularization in conjunction with CABG in the early 1980s, the use of a laser as sole therapy to establish its efficacy required advancements in the technology. The carbon dioxide (CO_2) laser used by Mirhoseini had a peak output of 80 W and therefore required a significant amount of time to complete a transmural channel. As a result, to perform TMR optimally, the heart had to be chilled and still. Increasing the output of the laser to 800 W allowed TMR to be performed on a beating heart. This breakthrough led to the widespread clinical application of TMR. Since then, over 25,000 patients have been treated with TMR around the world, and results from individual institutions, multicenter studies, and prospective, randomized, controlled trials have been reported.[16–29]

CLINICAL TRIALS

The early nonrandomized trials demonstrated that sole-therapy TMR could be performed safely on patients with

severe CAD who previously had no options. The significant angina relief seen in such patients led to prospective, randomized, controlled studies to further demonstrate the efficacy of TMR. In these pivotal trials, over 1100 patients were enrolled and randomized to receive either TMR or medical management as treatment for their severe angina.[23–28] The trials employed a 1:1 randomization in which half the patients were treated with laser and patients in the control group continued on maximal medical therapy. All patients were followed for 12 months.

TMR AS SOLE THERAPY

Patients

The entry criteria for these studies and for sole-therapy TMR in general are as follows: Patients had refractory angina that was not amenable to standard methods of revascularization, as verified by a recent angiogram. They had evidence of reversible ischemia based on myocardial perfusion scanning, and their left ventricular ejection fractions were greater than 25%.

The typical patient profiles of TMR patients in the randomized, controlled trials are listed in Table 28-1. Because the patients were equally randomized to the medical management group, there were no significant demographic differences between the TMR and control groups for any of these trials. Two different wavelengths of laser light were used. Three studies[23–25] employed a holmium:yttrium-aluminum-garnett (Ho:YAG) laser, and three[20–28] used a carbon dioxide (CO_2) laser. The average patient age was 62 years, and most were male (86%). While there were significant differences in the baseline distribution of patients according to Canadian Cardiovascular Society (CCS) angina class, the majority of the patients were in angina class IV (61%). The ejection fractions for all the patients were mildly diminished at 48 ± 10%. Many of the patients had suffered at least one previous MI, and most had some prior revascularization, CABG and/or PCI. Two of the trials[23,26] permitted a crossover from the medical management group to laser treatment for the presence of unstable angina that necessitated intravenous antianginal therapy for which they were unweanable over a period of at least 48 hours. By definition, these crossover patients were less stable than and significantly different from those who had been randomized initially to TMR or medical management alone.

Operative Technique

For sole-therapy TMR, the patient is placed in a supine position with his or her left side slightly elevated. General

Table 28–1.

Patient Characteristics in RCTS of Sole-Therapy TMR

Characteristic	Allen	Frazier	Burkhoff	Schofield	Aaberge
Patients (*N*)	275	192	182	188	100
Age (years)	60	61	63	60	61
Male gender (%)	74	81	89	88	92
EF (%)	47	50	50	48	49
CCS class III/IV (%)	0/100	31/69	37/63	73/27	66/34
CHF (%)	17	34	NR	9	NR
Diabetes (%)	46	40	36	19	22
Hyperlipidemia (%)	79	57	77	NR	76
Hypertension (%)	70	65	74	NR	28
Prior MI (%)	64	82	70	73	70
Prior CABG (%)	86	92	90	95	80
Prior PCI (%)	48	47	53	29	38

Baseline patient demographics from prospective, randomized, controlled trials of TMR.
CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular System angina class; CHF = congestive heart failure; EF = ejection fraction; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention.

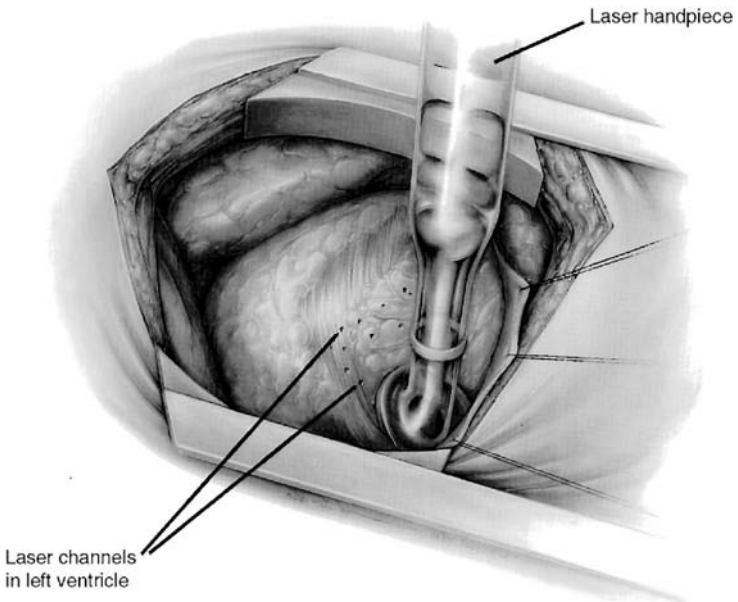

Figure 28-1. For TMR, channels of 1 mm diameter are created in a distribution of one per square centimeter starting inferiorly and then working superiorly to the anterior surface of the heart. The number of channels created depends on the size of the heart and on the size of the ischemic area.

anesthesia is established using a double-lumen endotracheal tube or a bronchial blocker to isolate the left lung. While not mandatory, this facilitates the operation, particularly because most of the patients have pleural and mediastinal adhesions from previous bypass surgery. Additionally, a thoracic epidural catheter can be employed to provide postoperative pain control.

A left anterior thoracotomy in the fifth intercostal space is the usual incision site. Once the ribs are spread by a retractor, the pericardium is opened to expose the epicardial surface of the heart (Fig. 28-1). Care must be taken to avoid previous bypass grafts. The left anterior descending (LAD) artery is identified and used as a landmark for the location of the septum. The inferior and posterolateral portions of the heart can be reached through this incision with a combination of manual traction, placement of packing behind the heart, and as illustrated, with the use of a right-angled laser handpiece. Channels are created starting near the base of the heart and then serially in a line approximately 1-cm apart toward the apex, starting inferiorly and working superiorly to the anterior surface of the heart. Since there is some bleeding from the channels, commencement of the TMR inferiorly keeps the anterior area clear and expedites the procedure. The number of channels created depends on the size of the heart and the size of the ischemic area. Myocardium that is thinned by scar, particularly when the scar is transmural, should be avoided because TMR will be of no benefit in these regions, and bleeding from channels in these areas may be problematic. The thoracotomy then is closed after placement of a chest tube, and in the majority of the cases, the patient is extubated in the operating room.

The handpiece in Fig. 28-2 is from a CO_2 laser and illustrates one of the differences between the two lasers employed for TMR. The CO_2 laser energy is delivered via hollow tubes and is reflected by mirrors to reach the epicardial surface. One-millimeter channels are made with a 15- to 20-J pulse. Firing of the laser is synchronized to occur on the R wave of the electrocardiogram (ECG) to avoid arrhythmias. The transmural channel is created by a signal pulse in 40 milliseconds and can be confirmed by transesophageal echocardiography (TEE). The vaporization of blood by the laser energy as the laser beam enters the ventricle creates an obvious and characteristic acoustic effect on TEE. The Ho:YAG laser achieves a 1-mm channel by manually advancing a fiber

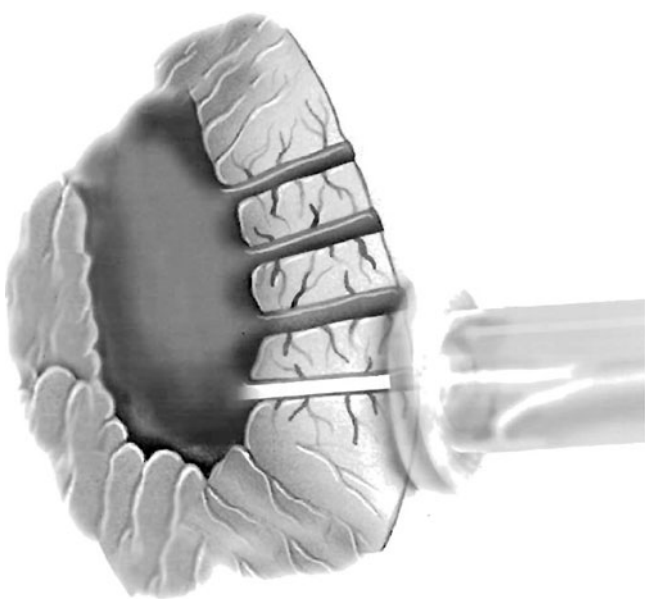

Figure 28-2. The CO_2 laser creates a transmural channel in a single 20-J pulse. Conceptually, direct perfusion may occur via the channel. Evidence indicates the laser stimulates angiogenesis in and around the channel that leads to improved perfusion.

bundle through the myocardium while the laser fires. Typical pulse energies are 2 J for this laser at a rate of 5 pulses per second; 10 to 20 pulses are required to traverse the myocardium. Detection of transmural penetration is done primarily by tactile and auditory feedback.

Endpoints

The principal subjective endpoint for all the trials was a change in angina symptoms. This was assessed by the investigator and/or a blinded independent observer. In addition to assigning an angina class, standardized questionnaires such as the Seattle Angina Questionnaire, the Short Form Questionnaire 36 (SF-36), and the Duke Activity Status Index were employed. These tests were used to detect changes in symptoms and quality of life. Objective measurements consisted of repeat exercise tolerance testing as well as repeat myocardial perfusion scans. Patients were reassessed at 3, 6, and 12 months after randomization.

RESULTS

Mortality

Prior to the randomized studies, mortality rates in the 10 to 20% range[16–22] were reported for TMR patients. In the randomized trials, lower perioperative mortality rates were reported ranging from 1 to 5%.[23–28] One of the important lessons learned from these controlled trials that differs from the earlier studies was a decrease in the mortality when patients taken to the operating room were stable, specifically not on intravenous (IV) heparin or nitroglycerin. When patients were allowed to recover from their most recent episode of unstable angina and were able to be weaned from intravenous medications such that their operation could be performed 2 weeks later, the mortality dropped to 1%.[26] The 1-year survival for TMR patients was 84 to 95% and for medical management patients was 79 to 96%. Meta-analysis of the 1-year survival demonstrated no statistically significant difference between the patients treated with a laser and those who continued with their medical therapy.[30] Long-term survival of the randomized patients from two of these studies has been reported. Four-year follow-up from Aaberge and colleagues, in which both the TMR and medical management groups were kept intact, demonstrated a 78% survival for TMR versus 76% for medical management (p = ns).[31] In a 5-year follow-up using an intent-to-treat analysis, Allen reported a survival for TMR patients at 65% versus 52% for medical management patients ($p = .05$).[32]

Morbidity

Unlike mortality, the exact definition of various complications varied from one study protocol to the next, and therefore, morbidity data are difficult to pool. Nevertheless, the typical TMR patient's postoperative course had a lower incidence of MI, heart failure, and arrhythmias than what has been documented in a similar cohort of patients, those who have reoperative CABG.[23–28]

Angina Class

The principal reason for performing TMR is to reduce the patient's anginal symptoms. This can be quantified by assessing the angina class before and after the procedure. Angina class assessment was performed by a blinded independent observer in all studies. This was done as the only angina assessment or as comparison with the investigators' assessment. Significant symptomatic improvement was seen in all studies for patients treated with the laser. Using a definition of success as a decrease of two or more angina classes, all the studies demonstrated a significant success rate after TMR, with success rates ranging from 25 to 76% (Fig. 28-3). A meta-analysis of this angina reduction yielded a summary odds ratio of 9.3 [95% confidence interval (CI) 4.6–18.5; $p < .000001$]. Significantly fewer patients in the medical management group experienced symptomatic improvement, and the success rate for these patients ranged from 0 to 32%. The seemingly broad range of success is due to differences between the baseline characteristics of the studies. It is more difficult to achieve a two-angina-class improvement if the baseline angina class is III. Studies that started with most of their patients in angina class III, not surprisingly, showed the lowest success rate. In contrast, the largest success rate for TMR was seen in the trial in which all the patients were in CCS class IV at enrollment. Of note, the medical management group in this study also showed the largest success rate.[23] This underscores some of the baseline differences between the studies.

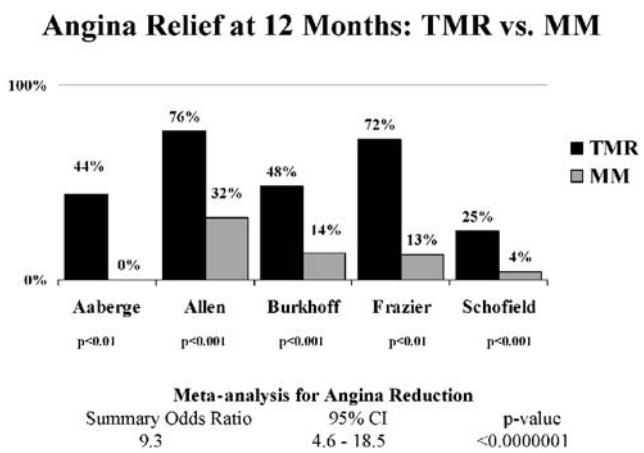

Figure 28-3. Summary of the angina relief results from five prospective, randomized, controlled trials comparing transmyocardial laser revascularization (TMR) and medical management (MM). Graph illustrates success rate for TMR or MM as measured by the percentage of patients that had a decrease of two or more angina classes. Meta-analysis of these results documents the significant advantage seen with TMR over MM.

Quality of Life and Myocardial Function

Quality-of-life indices as assessed by the Seattle Angina Questionnaire, the SF-36, and the Duke Activity Status Index demonstrated significant improvement for TMR-treated patients versus medical management in every study. Global assessment of myocardial function by ejection fraction using echocardiography or radionuclide multigated acquisition scans showed no significant change in overall ejection fraction for any of the patients regardless of group assignment or study.

Hospital Admission

Another indicator of the efficacy of TMR was demonstrated in a reduction in hospital admissions for unstable angina or cardiac-related events postprocedure. A meta-analysis of the data provided indicates that the 1-year hospitalization rate of patients in the laser-treated group was statistically significantly less than for those treated medically. Medical management patients were admitted four times more frequently than TMR patients over the year of follow-up.[30]

Exercise Tolerance

Additional functional test assessment using exercise tolerance also was performed in three of the trials.[24,27,28] While the method of treadmill testing differed between the trials, the results demonstrate an improvement in exercise tolerance for TMR-treated patients. Two studies showed an average of 65 to 70 second improvement in the TMR group at 12 months compared with their baseline, whereas the medical management group had either an average of 5 second improvement or a 46 second decrease in exercise time over the same interval.[27,28] One additional trial demonstrated that the time to chest pain during exercise increased significantly, and fewer patients were limited by chest pain in the TMR group, whereas the medical management group showed no improvement.[28]

Medical Treatment

All the studies employed protocols that continued all the patients on maximal medical therapy. For each study, the frequencies and dosages of antianginal and cardiovascular drugs were similar between the two groups at baseline. TMR patients, as a result of their symptomatic improvement, had a reduction in their medication use over the year of follow-up. Since many of these patients used a combination of short- and long-acting nitrates preoperatively, the trials demonstrated a significant decrease in the use of nitrates in TMR-treated patients, whereas the medical management patients showed a slight increase in their nitrate usage. At 1 year, the overall medication use decreased or remained unchanged in 83% of the TMR patients, and conversely, the use of medications increased or remained unchanged in 86% of the medical management patients.[26] The significant angina relief seen following TMR was not due to medication changes or increases for the TMR-treated patients.

Myocardial Perfusion

As stated previously, myocardial perfusion scans were obtained preoperatively to verify the extent and severity of reversible ischemia. The four largest randomized trials included follow-up scans as part of the study.[23,24,26,27] These results reflect over 800 of the patients randomized. The methodology of recording and analyzing these results differed in each study, so it is difficult to pool the data. Nevertheless, review of the results demonstrated an improvement in perfusion for CO_2 TMR-treated patients. Fixed (scar) and reversible (ischemic) defects were tallied for both the TMR-treated patients and the medical management groups. One study demonstrated a significant decrease in the number of reversible defects for both the TMR and the medical management patients.[27] This improvement in the reversible defects in the TMR group was seen without a significant increase in the fixed defects at the end of the study. However, the number of fixed defects in the medical management group had nearly doubled over the same 12-month interval. Similarly, there was a 20% improvement in the perfusion of previously ischemic areas in the CO_2 TMR group of another trial, and in that same trial there was a 27% worsening of the perfusion of the ischemic areas in the medical management group at 12 months.[26] There was no difference in the number of fixed defects between the groups at 12 months, nor was there a significant change in the number of fixed defects for each patient compared with his or her baseline scan. The remaining two Ho:YAG studies that obtained follow-up scans showed no significant difference between the TMR and medical management groups at 12 months and no significant improvement in perfusion in the TMR-treated patients over the same interval.[23,24]

Nonrandomized data previously had demonstrated an improvement in perfusion using dual isotope scanning at 1 and 2 years after CO_2 TMR.[33] Additionally, using N-13 ammonia position-emission tomographic (PET) assessment, subendocardial perfusion improved significantly compared with subepicardial perfusion after CO_2 TMR treatment.[34,35]

Long-Term Results

Two reports of long-term follow-up of prospectively randomized patients are available. Similar to the 1-year results, intention-to-treat analyses determined that significantly more TMR than medical management patients continued to experience at least two-class angina improvement from baseline (88% versus 44%; $p < .001$) or were free from angina symptoms altogether (33% verssu 11%; $p = .02$) at a mean of 5 years.[32] In long-term follow-up of the randomized trial that kept both the TMR and medical management groups intact (i.e., no crossover), it was shown that angina symptoms still were improved significantly (24% versus 3%, TMR versus medical management; $p = .001$), and unstable angina hospitalizations were reduced significantly ($p < .05$) at a mean follow-up of 43 months.[31] Follow-up of a series of nonrandomized patients who received TMR and survived

long term support these findings.[36] At a mean of 5 years and up to 7 years postprocedure, 81% of these patients improved to class II or better, 68% were found to have improved at least two angina classes from baseline, 17% were angina-free, and quality of life remained significantly improved. These last two reports reflect the sustained angina relief seen with CO_2 TMR because these patients had no additional procedures to account for their symptom improvement over the long term.

Based on an assessment of the cumulative results from these multiple randomized trials, the recently updated American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines[37] and the Society of Thoracic Surgeons (STS) practice guidelines[38] have determined that the weight of the evidence favors the use of TMR in the treatment of stable, medically refractory angina patients.

TMR AS AN ADJUNCT TO CABG

Clinical Trials

Owing to its success as sole therapy, TMR has been evaluated in conjunction with CABG in patients with diffuse CAD who would be incompletely revascularized by CABG alone. The safety and effectiveness of adjunctive TMR have been somewhat difficult to assess owing to the influence of coronary bypass grafts and the lack of randomized control arms in some studies.[39–41]

Two prospective, randomized, controlled multicentered trials have been performed using TMR adjunctively with CABG in patients. In these studies, patients with one or more viable myocardial target areas served by coronary vessels that were not amenable to bypass grafting received either CABG plus TMR or CABG alone.[42,43] Baseline and operative characteristics were similar between groups, including the location and number of bypass grafts placed (3.1 ± 1.2, CABG + TMR; 3.4 ± 1.2, CABG alone; $p = .07$). Patients were blinded to their treatment group through 1-year follow-up.

RESULTS

Mortality

Improved outcomes following TMR + CABG versus CABG alone in terms of a reduced operative mortality rate (1.5% versus 7.6%; $p = .02$), reduced postoperative inotropic support requirements (30% versus 55%; $p = .001$), increased 30-day freedom from major adverse cardiac events (97% versus 91%; $p = .04$), and improved 1-year Kaplan-Meier survival (95% versus 89%; $p = .05$) have been reported.[42] Multivariable predictors of operative mortality were CABG alone [odds ratio (OR) 5.3; $p = 0.04$] and increased age (OR 1.1; $p = .03$).[42] A similar trend in operative mortality following TMR + CABG versus CABG alone (9% versus 33%; $p = .09$) was reported in a study of high-risk patients.[43]

Efficacy

The use of TMR adjunctively with CABG has been shown to decrease intensive-care-unit (ICU) times and length of hospitalization stay.[41] In a long-term follow-up of the randomized, controlled trial, the effectiveness of TMR + CABG versus CABG alone has been reported.[44] At a mean of 5 years, both groups experienced significant angina improvement from baseline; however, the TMR + CABG group had a lower mean number of angina-free patients (78% versus 63%; $p = .08$) compared with the CABG-alone group. Long-term survival was similar between randomized groups.

Observational data on the practice of TMR + CABG have been collected in the STS National Cardiac Database.[45,46] From 1998 to 2003, 5618 patients underwent TMR + CABG. These were compared with 932,715 patients who underwent CABG-only operations. The TMR + CABG patients therefore account for 0.6% of the surgical revascularization practice in the database. Table 28-2 outlines the significant baseline differences between the CABG-only patients and the TMR + CABG patients. The TMR + CABG patients have an increased incidence of every surrogate marker of diffuse arterial disease, and therefore, it is not surprising that their observed mortality was higher at 3.8% (versus 2.7% for CABG-only patients; $p < .001$). When unstable angina patients were removed, the observed mortality for TMR + CABG was decreased to 2.7%, and the observed:expected (O/E) ratio was 0.87. Comparison of use and outcomes from sites that have a TMR laser versus those that showed no evidence of overuse of TMR or difference in outcomes.[46]

MECHANISMS

Laser-Tissue Interactions

Understanding the mechanism of TMR starts with understanding the laser-tissue interaction. While numerous devices,[47,48] including ultrasound,[49] cryogenic ablation,[50] radiofrequency revascularization,[51,52] heated needles,[53,54] and the aforementioned hollow and solid needles have been used; none has engendered the same response that is seen with a laser. Additionally, numerous wavelengths of laser light also have been employed. These include xenon-chloride (XCl),[55,56] neodymium:YAG (Nd:YAG),[57] erbium:YAG (Er:YAG),[58] and thulium-holmium-chromium:YAG lasers (THC:YAG).[59] All these devices have been explored experimentally but have not been pursued on a significant scale clinically. Only CO_2 and Ho:YAG lasers are used for TMR. The result of any laser-tissue interaction depends on both laser and tissue variables.[33,58–60] A CO_2 laser has a wavelength of 10,600 nanometers, whereas a Ho:YAG laser has a wavelength of 2120 nanometers. These infrared wavelengths are absorbed primarily in water and therefore rely on thermal energy to ablate tissue. One significant difference, however, is that the Ho:YAG laser is pulsed, and the arrival of two successive pulses must be separated by time to allow for thermal dissipation. Otherwise, the accumulated heat will cause the

Table 28–2.

Comparison of CABG Only versus TMR + CABG Patients, STS Adult Cardiac Database 1998–2003

Characteristic	CABG only	TMR + CABG	*p*-Value
N	932, 715	5, 618	
Body surface area, m^2 (SD)	1.96 (0.24)	1.99 (0.23)	<.001
Diabetes (all types)	34%	50%	<.001
Insulin-dependent diabetes	10%	19%	<.001
Renal failure	5%	7%	<.001
Dialysis	1%	2%	<.001
CVA	7%	9%	<.001
Chronic lung disease	14%	17%	<.001
Peripheral vascular disease	16%	20%	<.001
Cerebral vascular disease	12%	17%	<.001
MI	46%	49%	<.001
Reoperation	9%	26%	<.001
Three-vessel CAD	71%	80%	<.001
Hypercholesterolemia	62%	73%	<.001
Hypertension	72%	80%	<.001

Baseline demographics of TMR combined with CABG patients enrolled in the Society of Thoracic Surgeons (STS) National Adult Cardiac Database. CAD = coronary artery disease; CVA = cerebral vascular accident; MI = myocardial infarction.

tissue to explode under pressure. Such explosions create acoustic waves that travel along the planes of lower resistance between muscle fibers and cause structural trauma as well as thermocoagulation.[60] The standard operating parameters for the Ho:YAG laser are pulse energies of 1 to 2 J and 6 to 8 W/pulse. The energy is delivered at a rate of 5 pulses per second through a flexible 1 millimeter optical fiber bundle. Despite the low energy level and short pulse duration, very high levels of peak power are delivered to the tissue so that with each pulse there is an explosion (Fig. 28-4). Additionally, the fiber is advanced manually through the myocardium, and it is therefore impossible to know whether the channel is being created by the kinetic energy delivered via the mechanical effects of the fiber or whether there has been enough time for thermal dissipation prior to the next pulse.

In contrast, the CO_2 laser was used at an energy level of 15 to 20 J/pulse with a pulse duration of 25 to 40 milliseconds. At this level, the laser photons do not cause explosive ablation, and the extent of structural damage is limited. Additionally, a transmural channel can be created with a single pulse (see Fig. 28-4). Confirmation of this transmurality is obtained by observing the vaporization of blood within the ventricle using TEE.

Finally, the CO_2 laser is synchronized to fire on the R wave, and with its short pulse duration, arrhythmic complications are minimized. The Ho:YAG device is unsynchronized and, owing to the motion of the fiber through the myocardium over several cardiac cycles, is more prone to produce ventricular arrhythmias.

Patent Channels

As noted earlier, the original concept of TMR was to create perfusion via channels connecting the ventricle with the myocardium. Clinical work has demonstrated some evidence of long-term patency.[61,62] Additional experimental work showed some evidence of patency as well.[63–66] There are also significant reports from autopsy series and laboratories that indicate that the channels do not remain patent.[67–71] The consensus is that while channels occasionally may remain patent, this is not the principal mechanism of TMR.

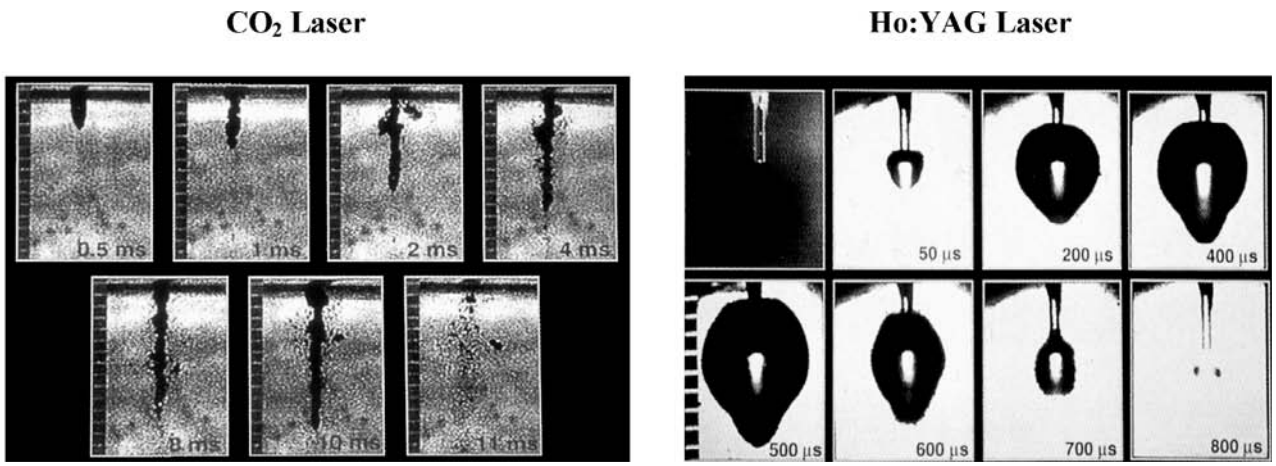

Figure 28-4. Sequential photography of the firing of a single pulse from a CO_2 laser and a HO:YAG laser into water. The pulse duration and energy levels are the same as those employed clinically.

Denervation

In contrast to the open-channel mechanism, damage to the sympathetic nerve fibers may explain the angina relief noted in clinical trials. The nervous system of the heart can function independent of inputs from extracardiac neurons to regulate regional cardiac function by reflex action. This intrinsic system contains afferent neurons, sympathetic efferent postganglionic neurons, and parasympathetic efferent postganglionic neurons. Because of this complex system, it is difficult to demonstrate true denervation. However, several experimental studies have demonstrated that denervation indeed may play a role in Ho:YAG TMR.[72–74] Experimental evidence to the contrary was performed in a nonischemic animal model.[75] Although the studies were carried out carefully, it is difficult to isolate the sympathetic afferent nerve fibers, and the experiments were in the acute setting and only address short-term effects. Regardless of the methodology employed in the laboratory, there is significant evidence of sympathetic denervation following PET scanning of Ho:YAG TMR–treated patients.[76]

Angiogenesis

The likely underlying mechanism for the clinical efficacy of TMR is the stimulation of angiogenesis. This mechanism fits the clinical picture of significant improvement in symptoms over time, as well as a concomitant improvement in perfusion, as seen with the CO_2 laser. Numerous reports have demonstrated a histologic increase in neovascularization as a result of TMR channels.[68,70,77–83] More molecular evidence of this angiogenic phenomenon was derived from work that demonstrated an upregulation of vascular endothelial growth factor (VEGF) messenger RNA, expression of fibroblast growth factor 2 (FGF2), and matrix metalloproteinases following TMR.[84–86] Histologically, similar degrees of neovascularization have been noted after mechanical injury of various types. Needle injury has been demonstrated by immunohistochemistry to also stimulate growth factor expression and angiogenesis. The conclusion is that TMR-induced angiogenesis is a nonspecific response to injury.[87–89] Investigation of this using hot and cold needles, radiofrequency energy, and laser energy to perform TMR clearly demonstrates a spectrum of tissue response to the injury.[53] The results in a model of chronic myocardial ischemia to mimic the clinical scenario indicate that indeed neovascularization can occur after mechanical TMR, but if these new blood vessels grow in the midst of a scar, there will be little functional contribution from blood flow through these new vessels. The recovery of function with laser TMR was due to a minimization of scar formation and a maximization of angiogenesis.

This then becomes a critical question: If TMR induces angiogenesis, is there an ensuing improvement in function? Clinically, this has been demonstrated subjectively with quality-of-life assessments, but more important, it has been demonstrated objectively with multiple techniques, including dobutamine stress echocardiography,[90] PET scanning,[34] and cardiac magnetic resonance imaging (MRI).[91,92] As further evidence of the angiogenic response, experimental data have mirrored the clinical perfusion results noted, with improvements in perfusion in porcine models of chronic ischemia where the ischemic zone was treated with CO_2 TMR.[93–96] This improved perfusion did lead to an improvement in myocardial function as well.

PERCUTANEOUS MYOCARDIAL LASER REVASCULARIZATION

Myocardial laser revascularization has been performed percutaneously,[97–99] thoracoscopically,[100] via thoracotomy,[23–29] and via sternotomy.[39–42] Aside from the PMR approach, any of the other surgical approaches have yielded similar

symptomatic improvement. Several percutaneous trials have attempted to demonstrate a symptomatic improvement with the creation of 2 to 3 millimeter-deep subendocardial divots achieved with a laser fiber fed via a peripheral artery into the left ventricle.[97–99] Even with the use of electromechanical mapping to verify the position of the fiber and creation of the channel, the results from PMR have been less favorable than those seen with TMR. A double-blinded, randomized, controlled trial showed no benefit to the laser-treated patients compared with the untreated control group.[99] Since the patients were blinded to their treatment, the possibility of a significant placebo effect for PMR has been raised. Of note, the morbidity and mortality of PMR reportedly are similar to those seen with TMR. As a result, the U.S. Food and Drug Administration (FDA) rendered PMR unapprovable.

The failure of PMR to achieve the same clinical results that have been seen with TMR may be due to several significant limitations, the first of which is the partial-thickness treatment of the left ventricle. Even at the maximal estimated depth of 6 millimeters that has been reported with PMR, this is significantly less than the full-thickness treatment of the myocardium that is achieved with an open TMR approach. Furthermore, typically fewer of these partial-thickness channels are created with PMR. The exact location of the channel and the establishment of a wide distribution of the channels from inside a moving ventricle are also problematic. Finally, the limitations of Ho:YAG TMR are also applicable to PMR because that is the wavelength of light that has been employed.

FUTURE USES OF TMR

Other potential applications include the use of TMR in the treatment of cardiac transplant graft atherosclerosis. While the procedure has been performed on a small number of patients, the results have indicated a benefit.[101,102] Finally, the combination of TMR plus other methods of angiogenesis may provide an even more robust response. Experimental work investigating these combinations has verified a synergistic effect with regard to histologic evidence of significant angiogenesis and, perhaps more important, an improvement in myocardial function with a combination of TMR and gene therapy versus either therapy alone.[103–107]

Cardiothoracic surgeons increasingly are faced with a more complex patient who has developed a pattern of diffuse CAD and has exhausted nonsurgical options. Results replicated in multiple randomized, controlled trials augmented by recently available long-term results have validated the safety, effectiveness, and substantially improved health outcomes achieved through application of TMR for the treatment of selected patients with severe angina owing to diffuse disease when used alone and as adjunctive therapy to achieve a more complete revascularization.

EXTRAVASCULAR ANGIOGENETIC TECHNIQUES

Prior to TMR, investigators have been trying different mechanical strategies to increase blood flow in ischemic hearts since the 1930s by obliterating the pericardial sac with mechanical abrasion and the addition of asbestos powder,[108] tacking omentum to ischemic hearts,[109,110] removing the epicardium,[111] or combining several of these with the addition of implanting the internal mammary artery into the myocardium.[112] Subsequently, pharmacologic strategies were employed in both experimental and clinical studies in an attempt to revascularize ischemic hearts by using heparin[113–115] and growth factors such as VEGF in the late 1970s and 1980s[116–120] and basic fibroblast growth factor (bFGF, or FGF2) and acidic FGF (aFGF, or FGF1) in the 1980s.[121–125] The angiogenic growth factors were first applied via direct delivery of specific proteins, and subsequently, owing to the development of DNA technology and gene delivery techniques, gene therapy studies were performed in both experimental and clinical studies. In the late 1990s, cell-based therapy was introduced in therapeutic angiogenesis for ischemic heart diseases and has been the most rapidly progressing and hot research field over the past 5 years. In this section we will discuss the topic of protein-, gene-, and cell-based therapeutic angiogenesis for the treatment of ischemic cardiovascular diseases.

Proteins

Experimental studies

Several early studies were published demonstrating that VEGF, aFGF (FGF1), and bFGF (FGF2) proteins produced in vitro changes compatible with their having angiogenesis potential.[126–131] These studies were followed by in vivo work showing that these factors actually do stimulate the growth of new vessels.[126,132,133] The more recent elegant genetic studies of vasculogenesis occurring during embryogenesis in the mouse add to the now unequivocal evidence documenting the critical importance of many molecules, including major contributions of VEGF and angiopoietin-1, to the development of mature, branching blood vessels.[134–136]

That bFGF and VEGF proteins actually could stimulate the development of collaterals to tissues supplied by an obstructed artery and in the process augment tissue blood flow was first demonstrated in the early 1990s. In experiments on myocardial ischemia, a portion of the left ventricle of dogs was made ischemic by gradual occlusion of the circumflex coronary artery. The intracoronary or left atrial administration of bFGF or intracoronary administration of VEGF proteins daily for 28 days significantly increased collateral flow.[137–139] Likewise, studies in the rabbit ischemic hind limb model demonstrated that intramuscular administration of bFGF protein daily for 2 weeks improved limb perfusion significantly.[140]

Although such studies demonstrated proof of concept, additional studies also raised issues that still have not been resolved. For example, in attempts to determine a clinically feasible strategy for delivery of protein to enhance collateral flow, different durations of intra-arterial protein administration were studied in the canine myocardial ischemia model. While 28 days of administering boluses of VEGF into the left atrium improved collateral flow, 7 days of administration did not,[141] and while 7 and as few as 2 days of intracoronary administration of bFGF improved collateral flow, a single bolus injection did not.[142] These results demonstrated, at least in this model of myocardial ischemia, that the duration of exposure of the vessels supplying the ischemic tissue to angiogenesis factors is critical for a therapeutically relevant effect.

Additional studies employing ^{125}I-labeled bFGF demonstrated that route of administration is another critical factor in determining local tissue uptake[143] and, potentially, therapeutic response. Thus, whereas 3 to 5% of an intracoronary dose of bFGF was recovered in the myocardium, only 0.5% of an intravenous dose was. The most plausible explanation of these findings derives from the fact that myocardial uptake depends on peak serum concentration; because bFGF has a heparin-binding domain, considerable first-pass uptake in the lungs will occur following intravenous administration (the lungs contain large amounts of heparin sulfates), resulting in a blunted peak serum concentration presented to the myocardium when compared with the very high concentrations presented to the myocardium with bolus injection directly into the coronary artery.

The biologic consequences of these differences were demonstrated in angiogenesis studies of the same canine ischemia model. Collateral flow improved with intracoronary administration of bFGF but did not increase when the drug was given intravenously, despite its being given for 1 week.[142] Although similar uptake studies have not been performed with VEGF, its 165 isoform ($VEGF_{165}$) also has a heparin-binding domain (whereas $VEGF_{121}$ does not), suggesting that similar results would be seen.

Animal studies that appear to be at variance with these results also have been reported. Thus, Lopez and colleagues[144] delivered $VEGF_{165}$ to a porcine model of myocardial ischemia (ameroid occlusion of the circumflex coronary artery) by three different local intracoronary delivery systems (via an InfusaSleeve catheter, via intracoronary bolus infusion, and via epicardial implantation of an osmotic delivery system). VEGF was administered 3 weeks after ameroid placement, and indices of collateral function were assessed at that time (baseline) and 3 weeks later. Whereas there was no significant improvement in circumflex territory perfusion in control pigs, improved circumflex perfusion was demonstrable within each VEGF-treated group using paired *t*-tests to compare pre- and posttreatment perfusion values. Although these data are suggestive of a VEGF treatment effect, they are not convincing. First, ongoing collateral development has been observed in pigs throughout the 6-week period following circumflex ameroid placement.[145] In the Lopez study, however, the control group did not exhibit the expected increase in circumflex territory perfusion during that interval. Second, direct comparisons between individual VEGF treatment groups and the control group were not statistically significant. Only when all three VEGF treatment groups were combined in a post hoc analysis was a statistically significant difference demonstrable between VEGF groups and the control group. Third, there were three deaths in VEGF-treated animals during the investigation. Elimination of three animals in a small study such as this could have an important effect on the results through selection bias. Thus, while suggestive, the data from this experiment do not demonstrate unequivocally that a *single* bolus intracoronary injection of VEGF is capable of increasing collateral flow to a greater extent than that which occurs in the absence of therapy.

Hariawala and colleagues[146] also reported improved flow in a similar model. However, this study is flawed by the fact that intracoronary bolus administration of VEGF (2 mg) caused severe hypotension that led to the acute death of 4 of 8 animals in the treated group; hence the surviving animals, which were found to have greater collateral flow than the untreated controls, may have survived only *because* they had greater intrinsic collateral flow. These investigators also demonstrated in the rabbit hind limb model of ischemia that a single dose of intrafemoral bFGF or $VEGF_{165}$ improves collateral flow and, surprisingly, that a single intravenous dose of $VEGF_{165}$ also improves flow.[147,148] Thus conflicting results are reported in the literature relating to whether a *single* intra-arterial bolus injection of VEGF or bFGF protein improves collateral flow and whether improvement occurs following intravenous administration, at least for heparin-binding agents.

Clinical trials

The clinical trials of protein-based angiogenesis have been reported by using growth factors like FGF and VEGF families. The effect of FGF-1 on the ischemic myocardium was first performed by Schumacher and colleagues[149] in a series of 20 patients. In the study, 0.01 mg/kg of FGF-1 protein was injected directly into the ischemic myocardium along LAD while patients were undergoing bypass surgery. Three months later, neoangiogenesis, together with the development of a normal vascular appearance, was demonstrated angiographically. The first randomized, double-blind, placebo-controlled clinical trial for basic FGF was reported by the Simons' group.[150] Twenty-four patients undergoing CABG were randomized to three groups, receiving either 10 μg or 100 μg of bFGF, or placebo through delivery of microcapsules capable of sustained-release which were implanted in ischemic myocardium. During 16 months of follow-up, all patients in the 100 μg bFGF remained angina-free and a stress nuclear perfusion imaging test at baseline and 3 months showed significant improvement. The efficacy of single intracoronary infusion of FGF-2 (0, 0.3, 3, or 30 μg/kg; n=337 patients) was tested by a multicenter FIRST trial.[151] At 90 days, in all FGF-2 treated groups angina symptoms were significantly reduced compared with placebo, but not in 180 days due to the continued improvement in the

placebo. The effect of intracoronary injection of recombinant human VEGF on myocardial perfusion was first performed on 14 severe CAD patients[152], and followed by a multicenter VIVA trial on a total of 178 patients.[153] In the small patients group study, seven patients who received high-dose VEGF (0.05–0.167 μg/kg) showed improvement in resting myocardial perfusion and collateral count density at 60 days follow-up.[152] In the VIVA trial, patients were randomized to receive a 20-minute intracoronary infusion of placebo, low-dose (17 ng/kg/min)or high-dose (50 ng/kg/min) rhVEGF and followed by 4-hour intravenous infusion on days 3, 6, and 9. However, the study showed no significant differences in primary end point of the trial and ETT time compared with placebo at 60 days follow-up. At day 120, high-dose patients showed improvement in angina class and favorable trends in exercise treadmill test time and quality of life.[153]

Genes

Experimental studies

Gene therapy presents one of the solutions to the possible dosing conundrum because gene therapy can be considered a sophisticated form of a sustained delivery system. Once transfected, the target cell expresses gene product for days, weeks, or longer depending on the specific tissue transfected and the specific vector used.

Proof of concept that gene therapy can improve collateral function was demonstrated by Giordano and colleagues.[154] They found in a porcine model of myocardial ischemia (ameroid occlusion of the circumflex coronary artery) that a single-dose intracoronary administration of an adenoviral vector carrying the FGF5 transgene into the nonoccluded right coronary artery increased myocardial flow and function. Surprisingly, they found that about 95% first-pass myocardial uptake was achieved with intracoronary administration. Hammond and colleagues have since demonstrated that FGF4 produces similar effects in restoring myocardial flow and function.[155] Improvement of myocardial contractility in a porcine model of chronic ischemia has been reported recently by using a combined TMR and FGF-2 gene therapy approach.[156] In this study, adenoviral vector encoded FGF-2 was formulated in a collagen-based matrix and directly injected into ischemic myocardium. Other investigators also have performed studies employing the rabbit hind limb model of ischemia and have reported that injection into the femoral artery of the $VEGF_{165}$ transgene carried in a plasmid vector improves collateral flow.[157]

Direct intramyocardial injection

No matter how efficient first-pass uptake is, a considerable proportion of an angiogenesis factor *injected into an artery* supplying the target tissue will enter the systemic circulation and thereby expose nontarget tissues to its biologic effects.[158] While there is no definitive evidence yet that such systemic spillover will produce serious side effects, there is always that possibility (see below). It therefore would appear that if *direct intramuscular injection* of the angiogenesis factor, either by the transepicardial or transendocardial route, does result in enhanced collateral flow, such an approach might be preferable.

A protein injected once intramuscularly would be unlikely to persist in the tissue long enough to exert an important biologic effect.[158] Although multiple injections of protein might well improve collateral flow,[140] such a strategy has practical limitations. Therefore, once it was demonstrated that an adenoviral vector carrying a reporter transgene efficiently expresses its gene product after intramyocardial injection,[159] this approach to gene delivery was explored as an approach for gene therapy.

Proof of concept that intramyocardial injection could enhance collateral flow and improve impaired myocardial function was demonstrated in a porcine model of myocardial ischemia. This was achieved by the transepicardial injection of an adenoviral vector carrying the $VEGF_{121}$ transgene performed following thoracotomy.[160] The feasibility of catheter-based transendocardial delivery of angiogenesis genes has been shown recently,[161,162] demonstrating that the direct injection of angiogenesis factors into the myocardium can be accomplished without the need for thoracotomy.

However, because VEGF induces marked increases in vascular permeability and tissue edema, excessive VEGF administration could develop deleterious effects. Recent reports showed that in a chronic ischemic rabbit ear model, both adenoviral encoded VEGF and Angiopoietin-1 (Ang-1) increased flow at one week after injection. However, Ang-1-induced flow was localized to larger vessels, with no visible inflammatory response, but VEGF produced a diffuse increase in flow that was associated with pronounced swelling, vessel leakage, and inflammatory cell infiltration. At 4 weeks, the flow in the VEGF treated group decreased from pretreatment values. In contrast, the Ang-1-induced improvement was maintained.[163] Similar deleterious effects of VEGF were also reported by Masaki et al in their mouse hind limb ischemia model.[164]

Clinical trials

The first clinical trial on gene-based therapy using adenoviral vector was reported by Rosengart and colleagues.[165] In this phase I trial, 15 patients received adenoVEGF121 by direct intramyocardial injection as an adjunct to conventional CABG and six patients received gene-therapy only. Thirty days after the treatment, all patients showed improvement of wall motion in the area of vector administration by coronary angiography and stress ^{99m}Tc-sestamibi perfusion scan, as well as improvement in angina class after therapy. There was no evidence of systemic or cardiac-related adverse events related to vector administration. The effect of plasmid encoded VEGF2 on chronic myocardial ischemia was studied in 19 patients using catheter-based delivery.[166] In this small phase 1/2 study, Losordo and colleagues used an injecting catheter device guided by NOGA mapping technique and administered 200–800 μg of phVEGF2 plasmid directly into the endomyocardium. The end point analysis at

3 months disclosed improvement in angina class and strong trends favoring efficacy of phVEGF2 versus placebo in exercise duration, functional improvement, and Seattle Angina Questionnaire data. The adenoviral encoded FGF4 was studied by AGENT trial by Grines et al in a group of 79 patients with chronic stable angina pectoris.[167] In this trial, patients received one time intracoronary injection of five different doses of adenoviral encoded FGF4 (from $3.3 \times 10^8 - 10^{11}$ viral particles in half-log increments). In this first report of a randomized, double-blind and placebo-controlled trial, ad5-FGF4 showed a trend to have greater improvements in exercise time versus placebo at 4 weeks' follow-up. The same group also reported an AGENT-2 study of 52 patients with chronic stable angina using a single dose of 10^{10} viral particle of ad5FGF4 intracoronary infusion. At 8 weeks after treatment, ischemic defect size was significantly decreased in ad5FGF4 injected patients compared with placebo-treated patients and the viral vector was well tolerated and did not result in any permanent adverse sequelae.[168] Hedman et al. conducted a phase II Kuopio Angiogenesis Trial (KAT) to study the effects of VEGF on restenosis and chronic myocardial ischemia by intracoronary injection of either adenoviral or plasmid encoded VEGF165 on 103 patients who underwent PTCA and stenting.[169] At 6 months' follow-up, no difference was found in restenosis rate or minimal lumen diameter between all study groups. However, myocardial perfusion showed a significant improvement in the adenoVEGF treated group. Recently, the Euroinject One Trial was reported by Kastrup and colleagues[170] on direct intramyocardial plasmid VEGF-A_{165} gene therapy in patients with stable severe angina pectoris. In this study, 80 "no option" patients with severe stable ischemic heart disease were randomly assigned to receive either 0.5 mg of phVEGF-A_{165} or placebo plasmid in the myocardial region showing stress-induced perfusion defects under the guidance of the NOGA-MyoStar system. At three months' follow-up, the VEGF gene transfer did not significantly improve stress-induced myocardial perfusion defect compared with placebo. However, improved regional wall motion indicated a favorable anti-ischemic effect.

In summary, single protein or gene-based therapy so far has not achieved significant convincing beneficial results in improving myocardial perfusion both experimentally and clinically. More clinical studies are needed in order to determine how to achieve optimal myocardial angiogenesis. Many aspects of gene transfer, including the appropriate vector dose, formulation, and administration route, are still to be tested.

Cell-Based Therapy

Two classical concepts have been challenged in recent years by cell-based therapy using either embryonic or adult stem cells: First, vasculogenesis, which previously referred to a process that occurred only in the embryo, in which the vascular system develops from mesodermal precursor cells called *angioblasts* that invade the different embryonic organs and assemble in situ to form the primary capillary plexus. However, many investigators now believe that in adults, bone marrow–derived stem cells or endothelial progenitor cells can be recruited to and incorporated into tissues undergoing neovascularization. Second, cardiac myocytes originally were considered to be terminally differentiated cells that cannot be regenerated in adulthood. However, recent studies have shown that a limited number of cardiomyocytes may be regenerated by locally sited or recruited circulating stem cells. Therefore, stem cells, which include hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), mesenchymal stem cells/stromal stem cells (MSCs), myoblasts, and undifferentiated side population cells, have been used as an alternative therapeutic strategy for ischemic cardiovascular diseases that cannot be treated by routine interventional approaches. Theoretically, embryonic stem cells have more potential to differentiate into cardiomyocytes; however, clinical trials are now only limited to adult stem cells owing to the fact that they are relatively easier to handle, and autologous transplantation can be performed in clinical patients. Several centers around the world, specifically in Germany and Korea, had reported an improved functional status in experimental animals and clinical patients after such therapy; however, it is still unclear how bone marrow–derived stem/progenitor cells are mobilized and recruited into ischemic tissues, if the injected cells in clinical trial patients differentiated into functional cardiomyocytes, and what particular cell type is better to use compared with others. This section will focus on the progress status of clinical trials, mechanisms of involving functional improvements by stem cell therapy, limitations for applications, and potential risks.

Clinical trials

TOPCARE-AMI: Assmus and colleagues first reported cell-based therapy for 20 acute myocardial infarction (AMI) patients in 2002.[171] In this study, the authors performed intracoronary infusion of autologous bone marrow–derived mononuclear cells ($n = 9$) or circulating blood-derived progenitor cells ($n = 11$) 4 to 5 days after AMI. The circulating blood-derived progenitor cells were expanded ex vivo for 3 days before injection. The bone marrow–derived cells were extracted on the same day as injection without expansion. At 4 months following cell injection, patients' cardiac function was improved compared with 11 matched controls. The authors also reported postinfarction remodeling outcome using serial contrast-enhanced MRI.[172] A total of 28 patients with reperfused AMI who received bone marrow-derived cells or circulating blood progenitor cells were analyzed. They found that intracoronary infusion of adult progenitor cells in patients with AMI beneficially affects postinfarction remodeling processes. The migratory capacity of the infused cells is a major determinant of infarct remodeling, suggesting a causal effect of progenitor cell therapy on regeneration enhancement.[172] In 2004, the same group reported final 1-year results of 59 patients that showed similar functional improvements.[173]

Strauer and colleagues conducted a study to test the effect of autologous bone marrow-derived mononuclear cells (BMCs) on myocardial repair or regeneration. The authors first reported the data with 10 AMI patients who received BMCs by intracoronary injection and compared with 10 compatible patients treated with standard therapy alone. At 3 months following cell therapy, they found that the infarct region had decreased significantly and wall motion also significantly improved.[174] More recently, the same group reported another study using same cell therapy technique on 18 patients with chronic MI (5 months to 8.5 years old) for their effects on myocardial regeneration.[175] At 3 months, the patients with cell therapy showed that the infarct size was reduced by 30% and global left ventricular ejection fraction and infarction wall movement velocity increased significantly, whereas in the control group no significant changes were observed. The authors also found that following BMC transplantation there were improvements in maximum oxygen uptake and regional ^{18}F-fluor-desoxy-glucose uptake into infarct tissue suggesting a regeneration of myocardium after infarction.

Perin and colleagues[176] reported their results using a NOGA catheter technique to transendocardially inject autologous bone marrow stem cells for severe chronic ischemic heart failure patients. Fourteen patients who received cell injection showed significant functional improvement compared with seven controls. Similar methods also were reported by Fuchs and colleagues in Washington Hospital Center in 10 no-option patients with advanced CAD. The authors first initiated a porcine ischemic model to test the effect of freshly extracted autologous bone marrow on myocardial blood perfusion. Improved collateral flow and contractility in a treated group of animals was found.[177] Subsequently, in a pilot clinical study, the 10 no-option patients with advanced CAD autologous bone marrow direct myocardial injection induced a significant improved Canadian Cardiovascular Society angina score and stress-induced ischemia occurring within the injected territories.[177,178]

Chen and colleagues[179] were the first group to use autologous ex vivo expanded bone marrow–derived mesenchymal stem cells in patients with AMI. In their study, a total of 69 patients who received PCI 12 hours after AMI were chosen randomly for either cell injection ($n = 34$) or control ($n = 35$). The bone marrow–derived mononuclear cells were cultured in vitro for 10 days, and then patients underwent intracoronary injection of the fibroblast-like mesenchymal stem cells. Patients who received mononuclear stem cell injection showed significant improvement in left ventricular (LV) function at 3 to 6 months of follow-up.

Magic Cell

Kang and colleagues[180] reported a mobilized peripheral blood mononuclear cell study for AMI patients after coronary stenting. A total of 27 patients with AMI who underwent PCI 48 hours later were studied. Ten patients received intracoronary injection of mobilized [granulocyte colony-stimulation factor (G-CSF) 10 μg/kg for 4 days] PBMC, and 10 patients received injection of G-CSF alone, 7 as control. At 6 months, the cell infusion group showed improvement in LV function compared with the other two groups.

DIRECT MYOCARDIAL STEM CELL TRANSPLANTATION: Patel and colleagues[181] recently reported direct myocardial injection of autologous bone marrow–derived stem cells in 10 patients who underwent bypass surgery. Six months later, the cell injection patients showed improvement in LV function compared with 10 patients who received bypass surgery alone. No side effects were found with this direct stem cell injection.

Safety and Efficacy

Potential for deleterious effects

For most potent therapeutic interventions, therapeutic efficacy is rarely free of the potential for harmful effects to occur. The biologic activities of most of the angiogenesis agents currently being tested clinically are very potent, and it is likely that the same activities that lead to a therapeutic effect also could cause unwanted side effects. It is therefore probable that some side effects consequent to the cellular effects of these agents inevitably will occur. If this concept is true, then the critical question we will have to address in large clinical trials is whether the incidence of these risks is sufficiently low that they will be outweighed by the therapeutic benefits.

Among the side effects that might occur as a result of the biologic effects of these agents is the development of new blood vessels in nontargeted tissues, a complication that would be particularly devastating if it were to occur, for example, in the retina. It is possible that this particular complication may not develop unless a tissue is "primed" to respond with an angiogenesis response. That is, quiescent cells have low constitutive expression of receptors for the VEGF and FGF family of agents—thus, unless the tissue is exposed to very high doses of the ligands for prolonged periods, it is possible that normal tissue is resistant to the neovascularization effects of angiogenesis factors, a result suggested by the study by Banai and colleagues.[182] In this regard, a patient with diabetic retinopathy does have vascular cells that are "primed," insofar as it has been demonstrated that there are increased levels of one of the receptors for VEGF.[183–185]

Other VEGF-specific complications could develop as a result of the potent activity of VEGF as an inducer of vascular permeability.[117–121,186,187] Although angiogenesis and vascular permeability might be considered two separate biologic activities, it is also possible that the vascular permeability properties of VEGF are essential for angiogenesis to occur.

Whatever the interrelation between these two actions, if vascular permeability increases in tissues other than the tissue targeted for angiogenesis, serious consequences could accrue. That this could occur was demonstrated in a recent study in which the effects of overexpression of VEGF (achieved by injecting an adenovirus carrying the VEGF transgene) in adult mice was investigated.[188] The mice, as expected, developed elevated circulating levels of VEGF

following injection of the adenoviral vector. However, a high percentage died within days, developing increased vascular permeability and severe multiple-organ edema.

Other potential complications based on biologic activities are the expansion and induction of instability of atherogenic plaque and the growth of tumors. For example, Flugelman and colleagues demonstrated an association between unstable angina and the intraplaque presence of aFGF and bFGF.[189] They suggested that these agents might play a role in plaque instability. In addition, the broad range of cells on which the FGF family of agents exerts mitogenic effects could result in the growth of cells resident within plaques or of malignant cells.

Although the direct mitogenic effects of VEGF are limited largely to endothelial cells, it is of note that VEGF and its receptors, VEGFR1 and VEGFR2 (flt-1 and Flk-1), are overexpressed in atherosclerotic lesions.[190] Moreover, a number of nonendothelial tumor cells have been found to possess low levels of functional VEGFR1 and VEGFR2.[191] Also of possible relevance is the fact that the uterus possesses functional VEGF receptor tyrosine kinases[192] and that VEGF is mitogenic for uterine smooth muscle. These observations raise the possibility that the atherosclerotic lesion, certain tumors, and the common leiomyoma (fibroid) could at least theoretically respond to direct exogenous stimulation by VEGF.

There is also increasing evidence suggesting that growth of microvessels into plaque or tumors, through angiogenesis processes, is critical to growth of both tumor and plaque.[193–198] Thus, microvascular angiogenesis per se, an activity inherent in most angiogenesis factors, could predispose to plaque or tumor growth. In addition, the potent vascular permeability effect of VEGF could result in exposing a plaque or tumor to many cytokines and growth factors that normally are confined to the plasma and through this indirect mechanism stimulate their growth.

It must be emphasized that there have been *no* conclusive reports in clinical studies demonstrating that angiogenesis agents actually induce new tumor development, increase growth of in situ tumors, or increase plaque size. However, several experimental studies have demonstrated that prolonged exposure of skeletal muscle or myocardium to high local levels of VEGF or FGF family peptides can cause hemangioma-like tumors and vascular malformations[182,190,199–204] and can increase neointimal development.[205–207]

A phase I randomized, dose-escalation trial also demonstrated that high doses of bFGF can lead to the development of thrombocytopenia and renal toxicity.[208] In addition, the immune surveillance system is not normally exposed to large amounts of these proteins. It is therefore possible that antibodies can develop to these cytokines and that these could either impair the efficacy of repeated administration of the agents or even possibly lead to immunopathogenic processes. It also should be noted that one of the clinical trials in progress employs FGF2 of porcine origin[150,151]; although the high homology between the FGFs in different species makes it unlikely that recognition of nonself protein will occur, this certainly is not beyond the realm of possibility.

FGF and VEGF proteins, administered acutely, can produce hypotension through, at least in part, a nitric oxide–mediated pathway[209–211] and, in the case of FGF2, through a potassium channel–mediated mechanism.[212] The hypotensive effect has resulted in the death of pigs that had chronic myocardial ischemia and that were treated with the intracoronary injection of $VEGF_{165}$ protein[146] and in a prolonged hypotensive episode of a patient entered into a phase I study testing the safety of intracoronary administration of bFGF.[208] This complication appears to occur only when high systemic levels of bFGF and VEGF develop rapidly. Thus, it would appear to be of little or no concern if bFGF and VEGF proteins are not administered rapidly and of no concern when the factors are given as genes—which express the proteins they encode slowly.

We also need to consider, in the case of gene therapy employing viral vectors, the potential for the vectors themselves to cause deleterious effects. The administration of large amounts of virus can lead to massive immune responses that could cause serious, even fatal immunopathology. Such responses are unlikely given the amount of adenovirus administered in current clinical cardiovascular protocols. However, the foreign proteins presented by the virus, even when administered in relatively small amounts, probably will induce immune responses that conceivably could decrease subsequent sensitivity to the beneficial effects of the transgene delivered by the virus if administered repeatedly or could possibly lead to immune-mediated tissue damage.

In cell-based therapy, most of the clinical trials so far are using no ex vivo expanded or short time expanded (4 to 5 days) cells. In animal studies, stem cells potentially can transform in in vitro expansion. These transformed cells can create tumors in nude mice.[213] Similar incidents occurred occasionally in adult bone marrow–derived mesenchymal stem cells. It is still not clear which cell type is best for clinical myocardial ischemic patients; however, if it is decided to use ex vivo expanded cells, you have to be sure that they are not tumorigenic. It is absolutely necessary to test these cells for tumorigenic potential in nude mice and to perform a karyotyping test before injecting them into patients.

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CHAPTER 29

Surgical Treatment of Complications of Acute Myocardial Infarction: Postinfarction Ventricular Septal Defect and Free Wall Rupture

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Rupture of the ventricular chamber (septum or free wall) following myocardial infarction is a relatively infrequent condition with high mortality. These conditions, resulting from transmural infarction, may cause early death precluding surgical repair. Free wall rupture can result in tamponade and sudden cardiovascular collapse. In septal rupture, there is a variable amount of left-to-right shunting and it often leads to symptoms of heart failure. The clinical presentation ranges from an asymptomatic murmur to cardiogenic shock.

The first step in the evolution of surgical techniques to repair an acute postinfarction ventricular septal rupture involved differentiating the surgical treatment of these acquired lesions from the surgical approaches used to repair congenital ventricular septal defects (VSDs), which are for the most part not applicable. Next, understanding the significance of differing anatomic locations of postinfarction VSDs led to innovations in terms of the location of the cardiotomy and the type of repair necessary to achieve a successful result in any given patient. Then, the gradual appreciation of different clinical courses pursued by patients after postinfarction ventricular septal rupture, both in terms of location of the defect and the degree of right ventricular functional impairment, led to an increased urgency relative to the timing of surgical repair. More recently, improved results have been reported using the technique of endocardial patching with infarct exclusion, which may signify progress in the evolution of the surgical management of postinfarction VSDs. The incorporation of specific anatomic concepts of surgical repair and a better understanding of the physiologic basis of the disease has led to an integrated approach to the patient that has improved salvage of patients suffering this catastrophic complication of acute myocardial infarction (AMI).[1]

An *acute* postinfarction VSD is a perforation of the muscular ventricular septum occurring in an area of acutely infarcted myocardium. A ventricular septal rupture may be termed *chronic* when it has been present for more than 4 to 6 weeks. A *postinfarction ventricular rupture* is a perforation of the ventricular free wall occurring in an area of acutely infarcted myocardium.

POSTINFARCTION VENTRICULAR SEPTAL DEFECT

History

In 1845 Latham[2] described a postinfarction ventricular septal rupture at autopsy, but it was not until 1923 that Brunn[3] first made the diagnosis antemortem. Sager[4] in 1934 added the 18th case to the world literature and established specific clinical criteria for diagnosis, stressing the association of postinfarction septal rupture with coronary artery disease (CAD).

The treatment of this entity was medical and strictly palliative until 1956, when Cooley and associates[5] performed the first successful surgical repair in a patient 9 weeks after the diagnosis of septal rupture. These first patients who underwent similar repairs in the early 1960s usually presented with congestive heart failure (CHF), having survived for more than a month after acute septal perforation.[6,7] The success of operation in these patients and the precipitous, acute course of other patients with this complication[8] gave rise to the belief that operative repair should be limited to patients surviving for 1 month or longer.[6,9] This purportedly allowed for scarring at the edges of the defect, which was thought to be crucial to the secure and long-lasting closure of the septal rupture.[10,11]

In the late 1960s, more rapid recognition of septal rupture following infarction led to the recommendation that operation be attempted earlier in patients who were hemodynamically deteriorating.[1,3,12] The use of improved prosthetic materials accompanied the successful surgical repair of defects from 1 to 11 days old, as reported by Allen and Woodwark[12] in 1966, Heimbecker and colleagues[13] in 1968, and Iben and coworkers[14] in 1969. Notable among these was a superb early study by Heimbecker and associates of infarctectomy and its clinical application to patients with postinfarction VSDs. The surgical management of these patients was further refined by the inclusion of infarctectomy[13,15,16] and aneurysmectomy[17,18] and the development of techniques to repair perforations in different areas of the septum.[19–21] Over the last 15 years, it has become increasingly clear that in the majority of cases postinfarction ventricular septal rupture constitutes a surgical emergency. More recently, improved surgical techniques, newer prosthetic materials, enhanced myocardial protection, and improved perioperative mechanical and pharmacologic support have led to more favorable results in the surgical management of patients with postinfarction septal rupture.[22,23]

Incidence

Postinfarction ventricular septal defects complicate approximately 1 to 2% of cases of AMIs and account for about 5% of early deaths after MI.[24,25] The average time from infarction to rupture has been reported to be between 2 and 4 days, but it may be as short as a few hours or as long as 2 weeks.[25–28] These observations correlate well with the pathologic findings, which demonstrate that necrotic tissue is most abundant and ingrowth of blood vessels and connective tissue is only beginning 4 to 21 days following an MI.[29,30] Postinfarction ventricular septal defects occur in men more often than women (3 to 2), but more women experience rupture than what would be expected from the incidence of CAD in women.[8] The age of patients with this complication ranges from 44 to 81 years, with a mean of 62.5 years. However, there is some evidence that the average age is increasing.[23,25,31,32] The vast majority of patients who experience ventricular septal rupture do so after their initial infarction.[25,32] The overall incidence of postinfarction ventricular septal rupture may have decreased slightly during the past decade as a result of aggressive pharmacologic treatment of ischemia and thrombolytic and interventional therapy in patients with evolving MI, as well as the prompt control of hypertension in these patients.[32]

Angiographic evaluation of patients with postinfarction ventricular rupture indicates that septal rupture is usually associated with complete occlusion rather than severe stenosis of a coronary artery.[33] On average, these patients have slightly less extensive CAD, as well as less developed septal collaterals than do other patients with CAD.[34] The lack of collateral flow noted acutely may be secondary to anatomic configuration, edema, or associated arterial disease. Hill and associates,[35] in reviewing 19 cases of postinfarction ventricular septal rupture, found single-vessel disease in 64%, double-vessel disease in 7%, and triple-vessel disease in 29%. However, the frequency of single-, double-, and triple-vessel CAD is more evenly distributed in other series.[28,36]

Postinfarction ventricular septal defects are most commonly located in the anteroapical septum as the result of a full-thickness anterior infarction (in approximately 60% of cases). These anterior septal ruptures are caused by anteroseptal MI following occlusion of the left anterior descending (LAD) artery. In about 20 to 40% of patients, the rupture occurs in the posterior septum following an inferoseptal infarction, which is usually due to occlusion of a dominant right coronary artery, or less frequently, a dominant circumflex artery.[37] Thus, ventricular septal perforations occur most frequently in 65-year-old men with single-vessel coronary disease and poor collateral flow who present 2 to 4 days following their first anterior MI.

Pathogenesis

The infarct associated with septal rupture is transmural and generally quite extensive, involving, on average, 26% of the left ventricular wall in hearts with septal rupture, compared with only 15% in other acute infarctions.[25] In an autopsy study, Cummings and colleagues[38] found that in patients with acute anterior or inferior infarctions, the amount of right ventricular infarction was much greater in the hearts with septal ruptures as compared to those without septal defects. Likewise, hearts with posterior septal rupture had more extensive left ventricular necrosis than did hearts with inferior infarctions and no septal defects.

Why certain hearts rupture and others do not is not fully understood. Slippage of myocytes during infarct expansion[39] may allow blood to dissect through the necrotic myocardium and enter either the right ventricle or pericardial space.[40] Hyaline degeneration of cardiomyocytes with subsequent fragmentation and enzymatic digestion may allow fissures to form, predisposing to rupture.[41]

There are two types of rupture: simple, consisting of a direct through-and-through defect usually located anteriorly; and complex, consisting of a serpiginous dissection tract remote from the primary septal defect, which is usually located inferiorly.[42] Multiple defects, which may develop within several days of each other, occur in 5 to 11% of cases and are probably due to infarct extension. Since a successful surgical outcome is related to adequacy of closure of septal defects, multiple defects must be sought preoperatively if possible, and certainly at the time of operative repair.

Of the small number of patients who survive the early period of ventricular septal rupture, 35 to 68% go on to develop ventricular aneurysms[26,35] through the process of ventricular remodeling.[43] This compares with a 12% incidence of aneurysm formation in patients suffering an infarction but no septal rupture,[44] and probably relates to the size

and transmural nature of the infarction associated with septal rupture. Postinfarction septal rupture, especially in the posterior septum, may be accompanied by mitral valve regurgitation due to papillary muscle infarction or dysfunction. In approximately one-third of cases of septal rupture, there is a degree of mitral insufficiency, usually functional in nature, secondary to left ventricular (LV)dysfunction with mitral annular dilation, which usually resolves with repair of the defect.[34]

Pathophysiology

The most important determinant of early outcome following postinfarction ventricular septal rupture is the development of heart failure (left, right, or both). The associated cardiogenic shock leads to end-organ malperfusion, which may be irreversible. The degree to which heart failure develops depends on the size of the ventricular infarction and the magnitude of the left-to-right shunt. Left ventricular dysfunction due to extensive necrosis of the left ventricle is the primary determinant of CHF and cardiogenic shock in patients with anterior septal rupture, while right ventricular dysfunction secondary to extensive infarction of the right ventricle is the principal determinant of heart failure and cardiogenic shock in patients with posterior septal rupture.[36,45,46] However, the development of CHF and cardiogenic shock in a patient with postinfarction VSDs is not explained solely by the degree of damage sustained by the ventricle.[47]

The magnitude of the left-to-right shunt is the other key variable in the development of hemodynamic compromise. With the opening of a VSD, the heart is challenged by an increase in pulmonary blood flow, and a decrease in systemic blood flow, as a portion of each stroke volume is diverted to the pulmonary circuit. As a consequence of the sudden increase in hemodynamic load imposed upon a heart already compromised by acute infarction, and possibly by a ventricular aneurysm, mitral valve dysfunction, or a combination of these problems, a severe low cardiac output state results. The normally compliant right ventricle is especially susceptible to failure in this circumstance.[48,49] Patients with posterior ventricular septal rupture and right ventricular dysfunction may display shunt reversal during diastole because the end-diastolic pressure in the right ventricle can be higher than in the left.[40,50] Ultimately, persistence of a low cardiac output state results in peripheral organ failure.

Diagnosis

The typical presentation of a ventricular septal rupture is that of a patient who has suffered an AMI, and who after convalescing for a few days develops a new systolic murmur, recurrent chest pain, and an abrupt deterioration in hemodynamics. The development of a loud systolic murmur, usually within the first week following an AMI, is the most consistent physical finding of postinfarction ventricular septal rupture (present in over 90% of cases). The murmur is usually harsh, pansystolic, and best heard at the left lower sternal border. The murmur is often associated with a palpable thrill. Depending on the location of the septal defect, the murmur may radiate to the left axilla, thereby mimicking mitral regurgitation.[27] Up to one-half of these patients experience postinfarction chest pain in association with the appearance of the murmur.[25] Coincident with the onset of the murmur, there is usually an abrupt decline in the patient's clinical course, with the onset of congestive failure and often cardiogenic shock. The findings of cardiac failure that occur acutely in these patients are primarily the result of right-sided heart failure, with pulmonary edema being less prominent than that occurring in patients with acute mitral regurgitation due to ruptured papillary muscle.[51]

The electrocardiographic (ECG) findings in patients with acute septal rupture relate to the changes associated with antecedent anterior, inferior, posterior, or septal infarction. The localization of infarction by ECG correlates highly with the location of the associated septal perforation. In our review[32] of 55 patients with postinfarction septal rupture, the location of the defect corresponded to the territory of transmural infarction as determined by ECG in all but three patients. Up to one-third of patients develop some degree of atrioventricular conduction block (usually transient) that may precede rupture,[52] but there is no pathognomonic prognostic indicator of impending perforation. The chest radiograph usually shows increased pulmonary vascularity consistent with pulmonary venous hypertension.

It is important to realize that the sudden appearance of a systolic murmur and hemodynamic deterioration following infarction may also result from acute mitral regurgitation due to ruptured papillary muscle. Distinguishing these two lesions clinically is difficult, but a number of points may help. First, the systolic murmur associated with a septal rupture is more prominent at the left sternal border, whereas the murmur resulting from a ruptured papillary muscle is best heard at the apex. Second, the murmur associated with septal perforation is loud and associated with a thrill (in over 50% of patients), whereas the murmur of acute mitral regurgitation is softer and has no associated thrill.[8] Third, septal rupture is often associated with anterior infarctions and conduction abnormalities, whereas papillary muscle rupture is commonly associated with an inferior infarction and no conduction defects.[53] Finally, it should be noted that septal rupture and papillary muscle rupture may coexist following infarction.[20,54,55]

Until recently, the mainstay of differentiating septal rupture from mitral valve dysfunction has been right heart catheterization using the Swan-Ganz catheter.[56] With septal rupture, there is an oxygen saturation step-up between the right atrium and pulmonary artery. Step-up in oxygen saturation greater than 9% between the right atrium and pulmonary artery confirms the presence of a shunt.[57] The pulmonary-to-systemic flow ratios (Qp:Qs) obtained from oxygen saturation samples range from 1.4:1 to greater than 8:1 and roughly correlate with the size of the defect.[58] In contrast, with acute mitral regurgitation secondary to papillary muscle rupture,

there are classic giant V waves in the pulmonary artery wedge pressure trace. It should be noted, however, that up to one-third of patients with septal rupture also have mild mitral regurgitation secondary to LV dysfunction.[59]

Advances in transthoracic and transesophageal echocardiography, especially color flow Doppler mapping, have revolutionized the diagnosis of both the presence and site of septal rupture.[59–62] Echocardiography can detect the defect, localize its site and size, determine right and left ventricular function, assess pulmonary artery and right ventricular pressures, and exclude coexisting mitral regurgitation or free wall rupture. Smyllie and associates[61] reported a 100% specificity and 100% sensitivity when color flow Doppler mapping was used to differentiate ventricular septal rupture from acute severe mitral regurgitation following AMI. It also correctly demonstrated the site of septal rupture in 41 of 42 patients. Widespread use of this technology has, for the most part, replaced thermodilution catheter insertion, which in outlying hospitals, where patients are often seen first, may be time consuming and difficult to accomplish. Indeed, the trend toward early surgical referral and prompt operative repair is at least partially explained by the more widespread use of color Doppler echocardiography for diagnosis in peripheral centers.[23]

The necessity of preoperative left heart catheterization with coronary angiography has been a matter of debate. On one hand, left heart catheterization provides important information concerning associated CAD, left ventricular wall motion, and specifics of valvular dysfunction, which are all important in planning operative correction of postinfarction septal rupture. In most series[63] over 60% of patients with septal rupture have significant involvement of at least one vessel other than the one supplying the infarcted area. Bypassing associated CAD may increase long-term survival when compared with patients with unbypassed CAD.[63] However, left heart catheterization has disadvantages—it is time consuming and can contribute to both the mortality and morbidity of these already compromised patients.[23] Thus, some centers do not carry out preoperative left heart catheterization.[64,65] Others use it selectively, avoiding invasive studies in patients with septal rupture caused by anterior wall infarction, which is associated with a much lower incidence of multiple-vessel disease than septal defects resulting from posterior infarctions.[23] The issue of concomitant coronary bypassing is discussed in greater detail below.

Natural History

Reviews by Oyamada and Queen,[66] Sanders and colleagues,[8] and Kirklin and coworkers[67] reveal that nearly 25% of patients with postinfarction septal rupture and no surgical intervention died within the first 24 hours, 50% died within 1 week, 65% within 2 weeks, and 80% within 4 weeks; only 7% lived longer than 1 year. Lemery and associates[68] reported that of 25 patients with postinfarction VSDs treated medically, 19 died within 1 month. Thus, the risk of death following postinfarction VSD is highest immediately after infarction and septal rupture, and then gradually declines. Interestingly, there are reports of spontaneous closure of small defects, though this is so rare that it would be unreasonable to manage a patient with the expectation of closure.

Despite the many advances in the nonoperative treatment of CHF and cardiogenic shock, including the intra-aortic balloon pump and a multitude of new inotropic agents and vasodilators, these do not supplant the need for operative intervention in these critically ill patients.

Management

It has become clear that the early practice of waiting for several weeks after ventricular septal rupture before proceeding with surgery only selects out the small minority of patients in whom the hemodynamic insult is less severe and is better tolerated.[19,36,69] Likewise, it has also become clear that to manage most patients supportively, in hopes of deferring operation, is to deprive the great majority of those with postinfarction ventricular septal rupture of the benefits of definitive surgery before irreversible damage due to peripheral organ ischemia has occurred.[63,70]

While we[22] as well as others[69] have advocated early surgery since the middle of the 1970s, some continue to prefer to defer operation in patients who are easily supported and exhibit no further hemodynamic deterioration.[71,72] Persistence of CHF or marginal stabilization with rising blood urea nitrogen and borderline urine output necessitate aggressive therapy and prompt operation. The routine use of the intra-aortic balloon pump (IABP), whenever technically feasible, frequently results in *transient* reversal of the hemodynamic deterioration. This period of stability often makes it possible to complete left heart catheterization before proceeding to operation but should not significantly delay definitive surgical treatment. Patients with septal rupture rarely die of cardiac failure per se, but rather of end-organ failure as a consequence of shock. Shortening the duration of shock by operating early is the only therapeutic solution for this group of patients and can yield dramatic results.[32,73]

Our experience and the experience of others suggest that patients in cardiogenic shock represent a true surgical emergency requiring immediate operative repair. Because deaths in these patients result from multisystem failure secondary to organ hypoperfusion, delay in operative repair for patients in cardiogenic shock represents a failed therapeutic strategy. Those few patients who are completely stable, with no clinical deterioration, and who require no hemodynamic support, can undergo operative repair when convenient during that hospitalization. The large group of patients who are in an intermediate position between those with shock and those in stable condition should be operated on early (usually within 12 to 24 hours) after appropriate preoperative evaluation. Since the group of patients in stable condition constitutes 5% or less of the total population of patients with postinfarction ventricular septal rupture, the overwhelming majority of patients require prompt surgical treatment.

Rarely, because of a delayed referral, a patient will be seen for surgical therapy who is already in a state of multisystem failure or has developed septic complications. Such a patient is unlikely to survive an emergency operation and thus may benefit from prolonged support with an IABP before an attempted operative repair. We have found it necessary to treat a small number of patients (3 of 92) in this fashion. Baillot and colleagues[72] have reported individual successes with such an approach, which we consider the exception rather than the rule.

Preoperative Management

Because the natural course of the disease in unoperated patients is so dismal, the diagnosis of postinfarction ventricular septal rupture can be regarded as its own indication for operation.[70] Preoperative management is directed toward stabilization of the hemodynamic condition so that peripheral organ perfusion can be best maintained while any further diagnostic studies are obtained and while deciding on the optimal time for surgical intervention. Although the early clinical course of patients with postinfarction ventricular septal rupture can be quite variable, 50 to 60% present with severe CHF and a low cardiac output state requiring intensive therapy.[74]

The goals of preoperative management are to: (1) reduce the systemic vascular resistance, and thus the left-to-right shunt; (2) maintain cardiac output and arterial pressure to ensure peripheral organ perfusion; and (3) maintain or improve coronary artery blood flow. This is best accomplished by the IABP. Counterpulsation reduces left ventricular afterload, thereby increasing cardiac output and decreasing the left-to-right shunt, as reported by Gold and associates in 1973.[75] In addition, IABP support is associated with decreased myocardial oxygen consumption, as well as improved myocardial and peripheral organ perfusion. Although counterpulsation produces an overall improvement in the patient's condition, a complete correction of the hemodynamic picture cannot be obtained.[76] Peak improvement occurs within 24 hours and no further benefit has been observed with prolonged balloon pumping.[77] Pharmacologic therapy with inotropic agents and diuretics should be instituted promptly. The addition of vasodilators (i.e., sodium nitroprusside or intravenous nitroglycerine) makes good theoretical sense, because it can decrease the left-to-right shunting associated with the mechanical defect, and thus increase cardiac output. However, these effects are often associated with a marked fall in mean arterial blood pressure and reduced coronary perfusion, both poorly tolerated in these critically ill patients. It must be stressed that pharmacologic therapy is intended primarily to support the patient in preparation for operation and should not in any way delay urgent operation in the critically ill patient. We now admit patients with postinfarction septal rupture directly to the surgical intensive care unit rather than to the coronary care or medical intensive care unit.

Other techniques that have been tried in an effort to improve the hemodynamics of patients with interventricular septal rupture include venoarterial extracorporeal membrane oxygenation,[78] and inflation of a balloon in the right ventricular outflow tract to decrease the left-to-right shunt.[79] Neither has been proven reliable in clinical application. There are anecdotal reports of successful use of a left ventricular support device to reverse multiorgan failure prior to operation.[80] To avoid shunting across the lesion (right to left at the ventricular level), atrial cannulation is necessary. Use of a catheter-mounted axial flow pump (Hemopump) in stabilizing these patients is controversial because of the risk of acute pump failure due to catheter blockage from pieces of necrotic tissue.[81]

Operative Techniques

The first repair by Cooley and colleagues[5] of an acquired VSD was accomplished using an approach through the right ventricle with incision of the right ventricular outflow tract. This approach, which was adapted from surgical techniques for closure of congenital VSDs, proved to be disadvantageous for many reasons. Exposure of the defect was frequently less than optimal, particularly for defects located in the apical septum. It involved unnecessary injury to normal right ventricular muscle and interruption of collaterals from the right coronary artery. Finally, it failed to eliminate the paradoxical bulging segment of infarcted left ventricular wall. Subsequently, Heimbecker and associates[13] introduced, and others adopted,[16,26,82] a left-sided approach (left ventriculotomy) with incision through the area of infarction. Such an approach frequently incorporates infarctectomy and aneurysmectomy, together with repair of septal rupture.

Experience with a variety of techniques for closure of postinfarction ventricular septal rupture has led us to the evolution of eight basic principles (Table 29-1). Adherence to these principles in the closure of septal defects in different locations has led to the evolution of individualized approaches to apical, anterior, and inferoposterior septal defects.

General techniques

Patients are anesthetized using a fentanyl-based regimen. Pancuronium is selected as the muscle relaxant so as to prevent bradycardia. Pulmonary bed vasodilators such as dobutamine are avoided to minimize the left-to-right shunt fraction. Preoperative antibiotics include both cefazolin and vancomycin, given the fact that prosthetic material may be left in the patient.

Cardiopulmonary bypass is accomplished with bicaval venous drainage. Systemic cooling to 25°C is employed. Cardiac standstill is achieved with cold, oxygenated, dilute blood cardioplegia[83,84] using antegrade induction followed by retrograde perfusion via the coronary sinus. Although a number of myocardial protection strategies are currently available, we[83] and others[46,85,86] continue to use cold oxygenated, dilute blood cardioplegia to protect the heart during surgical correction of a VSD. A total of 1200 to 2000 mL of cardioplegia solution is delivered, depending on the size of the heart and

Table 29–1.

Principles of Repair of Postinfarction Ventricular Septal Defects

1. Expeditious establishment of total cardiopulmonary bypass with moderate hypothermia and meticulous attention to myocardial protection
2. Transinfarct approach to ventricular septal defect with the site of ventriculotomy determined by the location of the transmural infarction
3. Thorough trimming of the left ventricular margins of the infarct back to viable muscle to prevent delayed rupture of the closure
4. Conservative trimming of the right ventricular muscle as required for complete visualization of the margins of the defect
5. Inspection of the left ventricular papillary muscles and concomitant replacement of the mitral valve only if there is frank papillary muscular rupture
6. Closure of the septal defect without tension, which in most instances will require the use of prosthetic material
7. Closure of the infarctectomy without tension with generous use of prosthetic material as indicated, and epicardial placement of the patch to the free wall to avoid strain on the friable endocardial tissue
8. Buttressing of the suture lines with pledgets or strips of Teflon felt or similar material to prevent sutures from cutting through friable muscle

Source: Reproduced with permission from Heitmiller et al.[70]

the degree of hypertrophy.[87] Although we have not employed warm cardioplegic induction,[88] we do administer warm reperfusion cardioplegia just before removing the aortic cross-clamp.[89] Patients with multivessel coronary disease and critical coronary stenoses are revascularized before opening the heart in order to optimize myocardial protection. In most of these patients, the saphenous vein rather than the left internal mammary artery is utilized.

Apical septal rupture

The technique of apical amputation was described by Daggett and colleagues in 1970.[16] An incision is made through the infarcted apex of the left ventricle. Excision of the necrotic myocardium back to healthy muscle results in amputation of the apical portion of the left ventricle, right ventricle, and septum (Fig. 29-1A and B). The remaining apical portions of the left and right ventricle free walls are then approximated to the apical septum. This is accomplished by means of a row of interrupted mattress sutures of 1-0 Tevdek that are passed sequentially through a buttressing strip of Teflon felt, the left ventricular wall, a second strip of felt, the interventricular septum, a third strip of felt, the right ventricular wall, and a fourth strip of felt (Fig. 29-2A and B). After all sutures have been tied, the closure is reinforced with an additional over-and-over suture, as in ventricular aneurysm repair, to ensure hemostasis of the ventriculotomy closure.

Anterior septal rupture

The approach to these defects is by a left ventricular transinfarct incision with infarctectomy (Fig. 29-3). Small defects

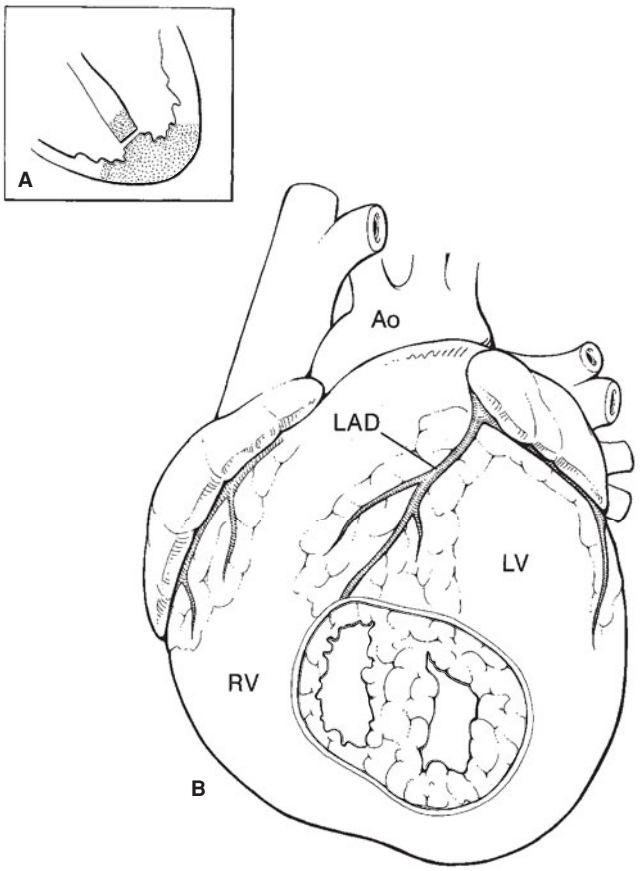


Figure 29-1. (A) Apical postinfarction ventricular septal defect. (B) View of the apical septal rupture, which is exposed by amputating the apex of the left and right ventricles. Ao = aorta; LAD = left anterior descending coronary artery; LV = left ventricle; RV = right ventricle; stippled region = infarcted myocardium.

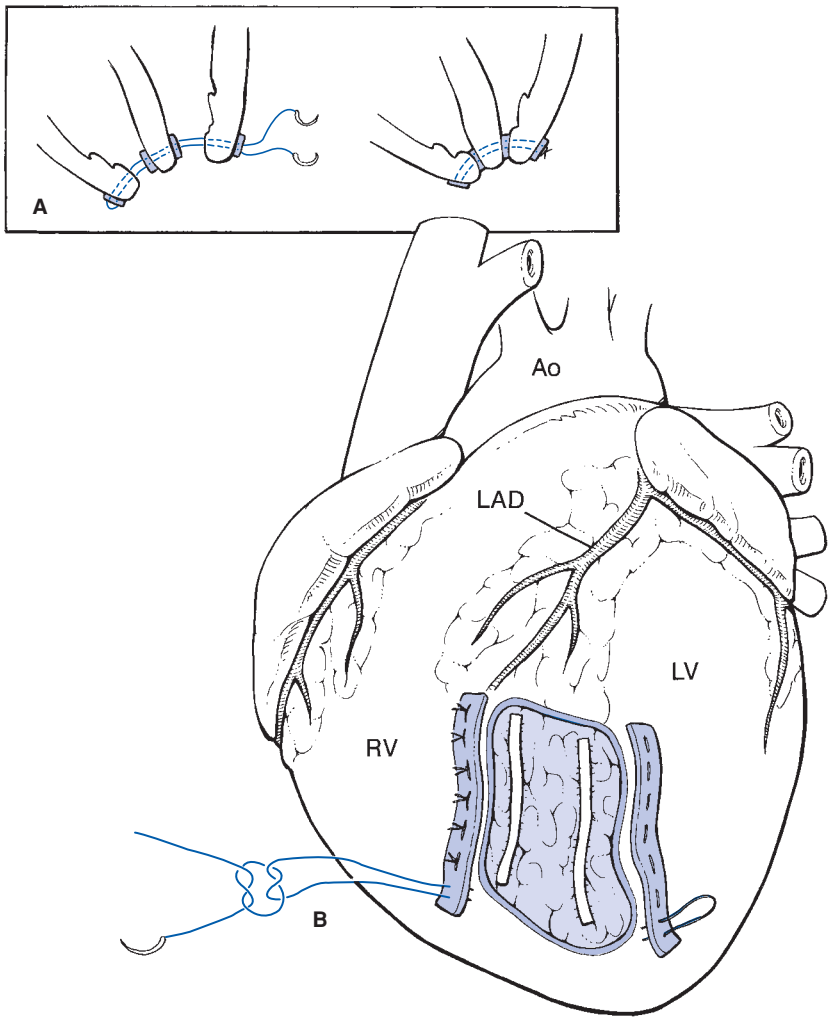


Figure 29-2. (A) The necrotic infarct and the apical septum have been débrided back to healthy muscle. Repair is made by approximating the left ventricle, apical septum, and right ventricle using interrupted mattress sutures of 1-0 Tevdek with buttressing strips of Teflon felt. Felt strips are used within the interior of the left and right ventricles as well as on the epicardial surface of each ventricle. (B) All sutures are placed before any are tied. A second running over-and-over suture (not shown) is used, as in left ventricular aneurysm repair, to ensure a secure hemostatic ventriculotomy closure. Ao = aorta; LAD = left anterior descending coronary artery; LV = left ventricle; RV = right ventricle. (*Adapted with permission from Daggett et al.*[16])

beneath anterior infarcts can be closed by the technique of plication as suggested by Shumacker.[90] This involves approximation of the free anterior edge of the septum to the right ventricular free wall using mattress sutures of 1-0 Tevdek over strips of felt (Fig. 29-4A). The transinfarct incision is then closed with a second row of mattress sutures buttressed with strips of Teflon felt (Fig. 29-4B, C, and D). An over-and-over running suture completes the ventriculotomy closure.

Most anterior defects require closure with a prosthetic patch (DeBakey Elastic Dacron fabric, USCI Division of C.R. Bard, Inc., Billerica, Mass) in order to avoid tension that could lead to disruption of the repair (Fig. 29-5). After débridement of necrotic septum and left ventricular muscle, a series of pledgeted interrupted mattress sutures are placed around the perimeter of the defect (Fig. 29-5A). Along the posterior aspect of the defect, sutures are passed through the septum from right to left. Along the anterior edge of the defect, sutures are passed from the epicardial surface of the right ventricle to the endocardial surface. All sutures are placed before the patch is inserted, and then passed through the edge of a synthetic patch, which is seated on the left side of the septum (Fig. 29-5B). Each suture is then passed through an additional pledget and all are tied. We use additional pledgets on the left ventricular side overlying the patch (Fig. 29-5C) to cushion each suture as it is tied down to prevent cutting through the friable muscle. The edges of the ventriculotomy are then approximated by a two-layer closure consisting of interrupted mattress sutures passed through buttressing strips of Teflon felt (or glutaraldehyde-preserved bovine pericardium) and a final over-and-over running suture.

Posterior/inferior septal rupture

Closure of inferoposterior septal defects, which result from transmural infarction in the distribution of the posterior descending artery, has posed the greatest technical challenge.[20,21] Early attempts at primary closure of these defects by simple plication techniques similar to those used in the repair of anterior defects were frequently unsuccessful because of the sutures tearing out of soft, friable myocardium that had been closed under tension. This resulted in either reopening of the defect or catastrophic disruption of the infarctectomy closure. It was, in large part, the analysis of such early results that led to the evolution of the operative principles enumerated in Table 29-1.

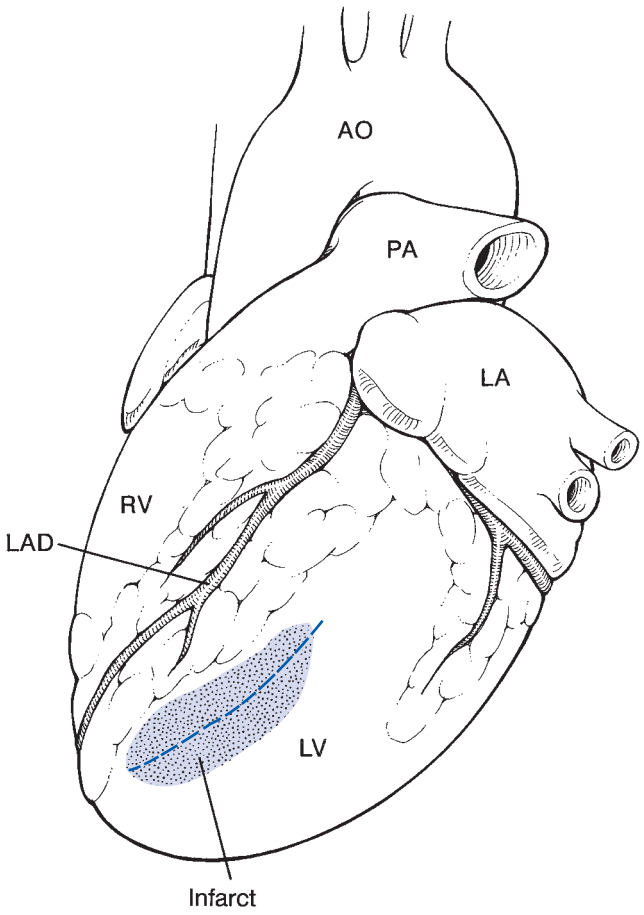


Figure 29-3. Transinfarct left ventricular incision to expose an anterior septal rupture. An incision (dashed line) is made parallel to the anterior descending branch of the left coronary artery (LAD) through the center of the infarct (stippled area) in the anterior left ventricle (LV). Ao = aorta; LA = left atrium; PA = pulmonary artery; RV = right ventricle.

Use of the following techniques has been associated with an improved operative survival. After the establishment of bypass with bicaval cannulation, the left side of the heart is vented via the right superior pulmonary vein. The heart is retracted out of the pericardial well as for bypass to the posterior descending coronary artery. The margins of the defect may involve the inferior aspects of both ventricles, or of the left ventricle only (Fig. 29-6A). A transinfarct incision is made in the left ventricle, and the left ventricular portion of the infarct is excised (Fig. 29-6B), exposing the septal defect. The left ventricular papillary muscles are inspected. Only if there is frank papillary muscle rupture is mitral valve replacement performed. When it is indicated, we prefer to perform mitral valve replacement through a separate conventional left atrial incision, to avoid trauma to the friable ventricular muscle. After all infarcted left ventricular muscle has been excised, a less aggressive débridement of the right ventricle is accomplished, with the goal of resecting only as much muscle as is necessary to afford complete visualization of the defect(s). Using this technique, delayed rupture of the right ventricle has not been a problem. If the posterior septum has cracked or split from the adjacent ventricular free wall without loss of a great deal of septal tissue, then the septal rim of the posterior defect may be approximated to the edge of the diaphragmatic right ventricular free wall using mattress sutures buttressed with strips of Teflon felt or bovine pericardium (Fig. 29-6C and D).

Larger posterior defects require patch closure (Fig. 29-7). Pledgeted mattress sutures are placed from the right side of the septum and from the epicardial side of the right ventricular free wall (Fig. 29-7B). All sutures are passed through the perimeter of the patch and then through additional pledgets, and are then tied (Fig. 29-7C). Thus, as in closure of large anterior defects, the patch is secured on the left ventricular side of the septum. Direct closure of the remaining infarctectomy is rarely possible because of tension required to pull together the edges of the gaping defect. A prosthetic patch is generally required. Originally, we cut an oval patch from a Cooley low-porosity woven Dacron tube graft (Meadox Medicals, Inc., Oakland, NJ). Currently, we cut this patch from a Hemashield woven double velour Dacron collagen-impregnated graft (Meadox Medicals, Inc., Oakland, NJ). Pledgeted mattress sutures are passed out through the margin of the infarctectomy (endocardium to epicardium) and then through the patch (Fig. 29-7D), which is seated on the epicardial surface of the heart. After each suture is passed through an additional pledget, all sutures are tied (Fig. 29-7E). The cross-sectional view of the completed repair (Fig. 29-8) illustrates the restoration of relatively normal ventricular geometry, which is accomplished by the use of appropriately sized prosthetic patches.

Endocardial patch repair with infarct exclusion

The concept that the preservation of left ventricular geometry plays a crucial role in the preservation of left ventricular function[19,91] has laid the groundwork for evolution in the surgical approach to postinfarction VSDs—the technique of endocardial patch repair of postinfarction VSDs described by David,[82,85] Cooley,[92,93] and then by Ross[94] in the early 1990s. This operative technique, which is an application to ventricular septal rupture repair of Dor's technique of ventricular endoaneurysmorrhaphy,[91] involves intracavitary placement of an endocardial patch to exclude infarcted myocardium while maintaining ventricular geometry. Thus, instead of closing the septal defect, it is simply *excluded* from the high-pressure zone of the left ventricle. Institutions have reported impressive results using infarct exclusion,[46] but results in other hands have been mixed. A detailed description of the technique is provided here. The following descriptions are taken from the work of David and associates (with permission).[40,46,85]

In patients with anterior septal rupture, the interventricular septum is exposed via a left ventriculotomy, which is made through the infarcted anterolateral wall starting at the apex and extending proximally parallel to, but 1 to 2 cm away from, the anterior descending artery (Fig. 29-9A). Stay sutures are passed through the margins of the ventriculotomy to aid in the exposure of the infarcted septum.

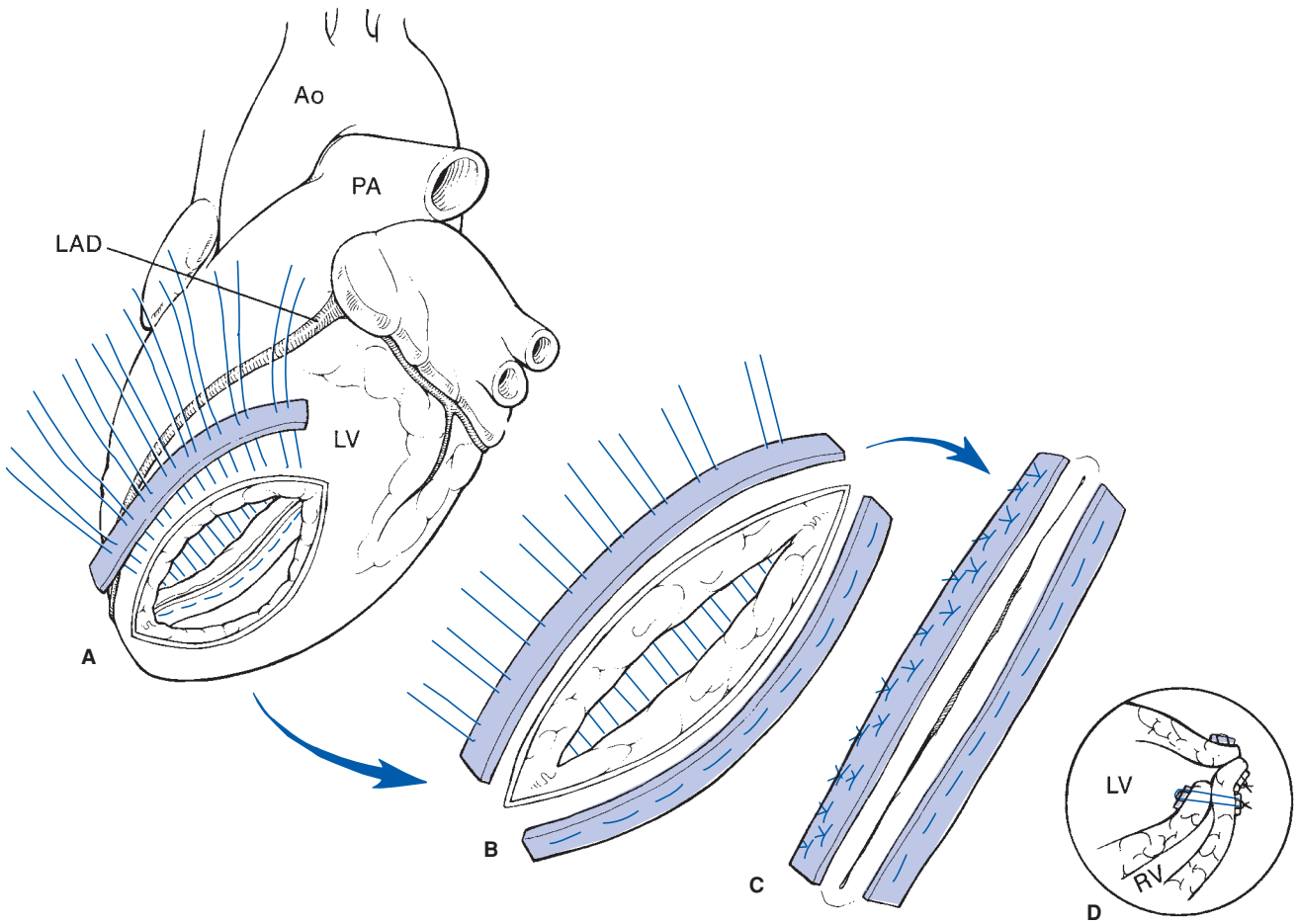


Figure 29-4. (A) Repair of an anterior septal rupture by plicating the free anterior edge of the septum to the right ventricular free wall with interrupted 1-0 Tevdek mattress sutures buttressed with strips of Teflon felt. (B, C, and D) The left ventriculotomy is then closed as a separate suture line, again with interrupted mattress sutures of 1-0 Tevdek buttressed with felt strips. A second running suture (not shown) is used to ensure a secure left ventriculotomy closure. Ao = aorta; LAD = left anterior descending coronary artery; LV = left ventricle; PA = pulmonary artery; RV = right ventricle. (*Adapted with permission from Guyton SW, Daggett WM: Surgical repair of post-infarction ventricular septal rupture, in Cohn LH (ed): Modern Techniques in Surgery: Cardiac/Thoracic Surgery. Mt. Kisco, NY, Futura, 1983; installment 9, p 61-1.*)

The septal defect is located and the margins of the infarcted muscle identified. A glutaraldehyde-fixed bovine pericardial patch is tailored to the shape of the left ventricular infarction as seen from the endocardium but 1 to 2 cm larger. The patch is usually oval and measures approximately 4 × 6 cm in most patients. The pericardial patch is then sutured to healthy endocardium all around the infarct (Fig. 29-9B). Suturing begins in the lowest and most proximal part of the noninfarcted endocardium of the septum with a continuous 3-0 polypropylene suture. Interrupted mattress sutures with felt pledgets may be used to reinforce the repair.[93] The patch is also sutured to the noninfarcted endocardium of the anterolateral ventricular wall. The stitches should be inserted 5 to 7 mm deep in the muscle and 4 to 5 mm apart. The stitches in the patch should be at least 5 to 7 mm from its free margin so as to allow the patch to cover the area between the entrance and exit of the suture in the myocardium.[40] This technique minimizes the risk of tearing muscle as the suture is pulled taut. If the infarct involves the base of the anterior papillary muscle, the suture is brought outside of the heart and buttressed on a strip of bovine pericardium or Teflon felt applied to the epicardial surface of the left ventricle. Once the patch is completely secured to the endocardium of the left ventricle, the left ventricular cavity becomes largely excluded from the infarcted myocardium. The ventriculotomy is closed in two layers over two strips of bovine pericardium or Teflon felt using 2-0 or 3-0 polypropylene sutures as illustrated in Fig. 29-9C. No infarctectomy is performed unless the necrotic muscle along the ventriculotomy is sloughing at the time of its closure, and even then it is minimized, since infarcted muscle will not be exposed to left ventricular pressures when the heart begins to work (Fig. 29-9D). Alternatively, sutures can be passed through the ventricular

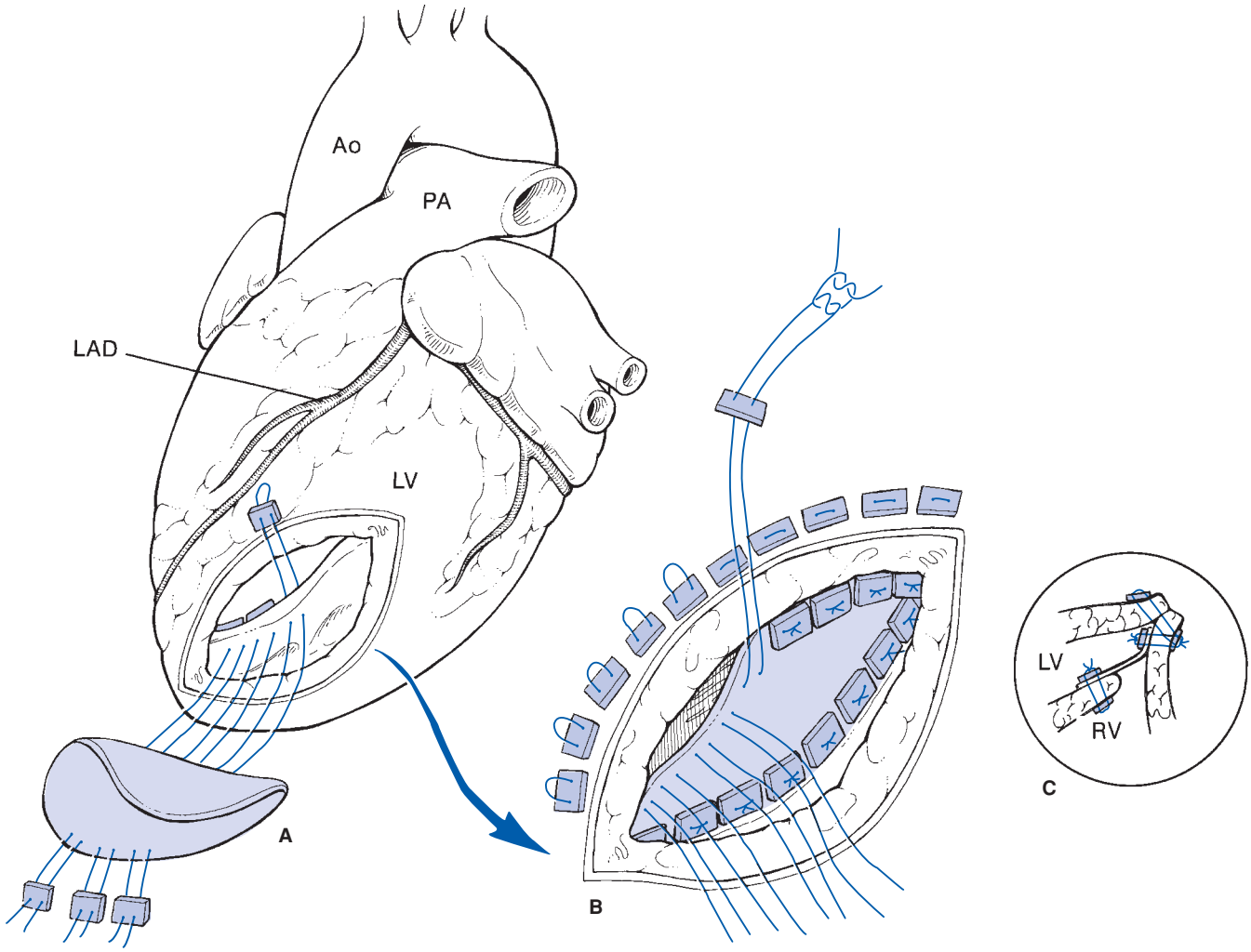


Figure 29-5. (A) Larger anterior septal defects require a patch (DeBakey Dacron fabric, USCI Division of C.R. Bard, Inc., Billerica, Mass), which is sewn to the left side of the ventricular septum with interrupted mattress sutures, each of which is buttressed with a pledget of Teflon felt on the right ventricular side of the septum and anteriorly on the epicardial surface of the right ventricular free wall. All sutures are placed before the patch is inserted. (B and C) We use additional pledgets on the left ventricular side overlying the patch to cushion each suture as it is tied down to prevent cutting through the friable muscle. Ao = aorta; LAD = left anterior descending coronary artery; LV = left ventricle; PA = pulmonary artery; RV = right ventricle. (*Adapted with permission from Guyton SW, Daggett WM: Surgical repair of post-infarction ventricular septal rupture, in Cohn LH (ed): Modern Techniques in Surgery: Cardiac/Thoracic Surgery. Mt. Kisco, NY, Futura, 1983; installment 9, p 61-1.*)

free wall and through a tailored external patch of Teflon or pericardium (Fig. 29-10).[71,89]

In patients with posterior septal defects, an incision is made in the inferior wall of the left ventricle 1 or 2 mm from the posterior descending artery (Fig. 29-11A). This incision is started at the midportion of the inferior wall and extended proximally toward the mitral annulus and distally toward the apex of the ventricle. Care is taken to avoid damage to the posterolateral papillary muscle. Stay sutures are passed through the fat pad of the apex of the ventricle and margins of the ventriculotomy to facilitate exposure of the ventricular cavity. In most cases, the rupture is found in the proximal half of the posterior septum and the posteromedial papillary muscle is involved by the infarction.[46] A bovine pericardial patch is tailored in a triangular shape of approximately 4 × 7 cm in most patients. The base of the triangular-shaped patch is sutured to the fibrous annulus of the mitral valve with a continuous 3-0 polypropylene suture starting at a point corresponding to the level of the posteromedial papillary muscle and moving medially toward the septum until the noninfarcted endocardium is reached (Fig. 29-11B). At that level, the suture is interrupted and any excess patch material trimmed. The medial margin of the triangular-shaped patch is sewn to healthy septal endocardium with a continuous 3-0 or 4-0 polypropylene suture taking bites the same size as those described for anterior defects. In this area of the septum, reinforcing pledgeted sutures may be required.[93] The lateral side of the patch is sutured to the posterior wall of the

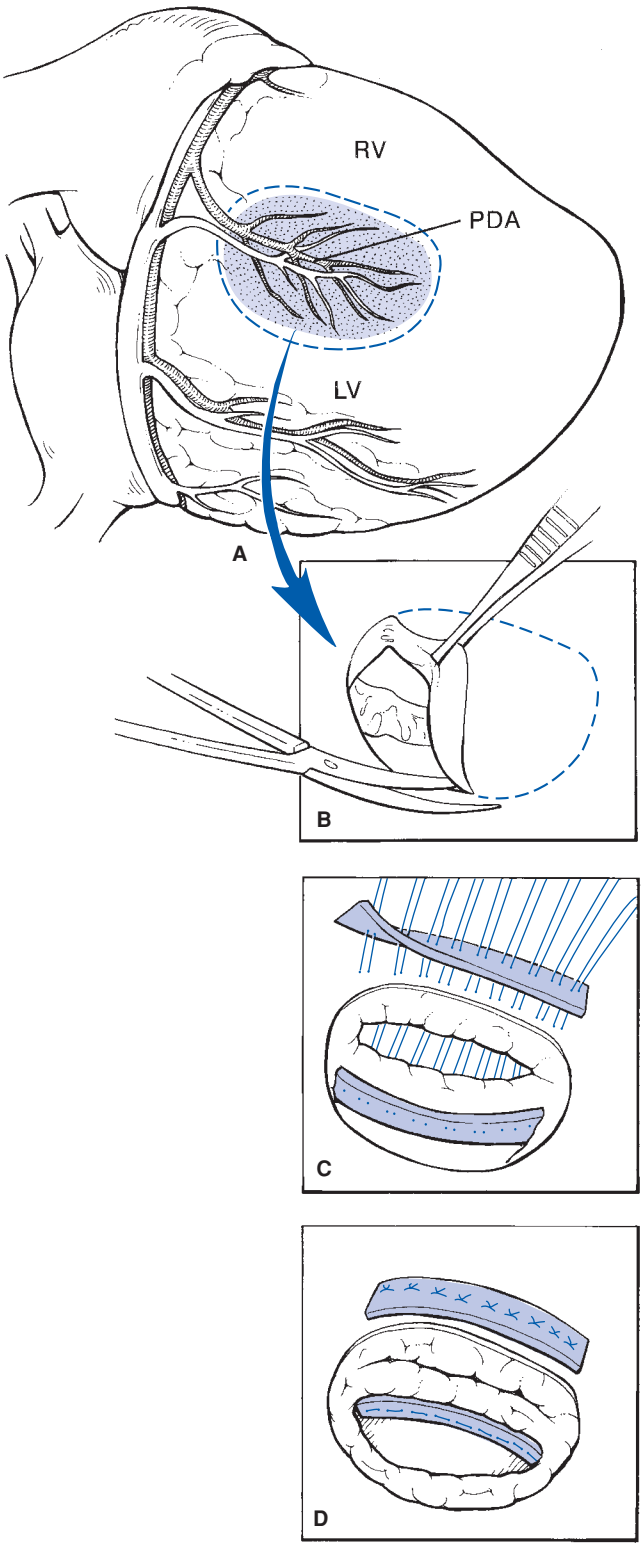


Figure 29-6. (A) View of an inferior infarct (stippled area) associated with posterior septal rupture. The apex of the heart is to the right. Exposure at operation is achieved by dislocating the heart up and out of the pericardial sac, and then retracting it cephalad, as in the performance of distal vein bypass and anastomosis to the posterior descending artery. (B) The inferoposterior infarct is excised to expose the posterior septal defect. Complete excision of the left ventricular portion of the infarct is important to prevent delayed rupture of the ventriculotomy repair. The free edge of the right ventricle is progressively shaved back to expose the margins of the defect clearly. (C and D) Repair of the posterior septal rupture is accomplished by approximating the edge of the posterior septum to the free wall of the diaphragmatic right ventricle with felt-buttressed mattress sutures. The repair is possible when the septum has cracked or split off from the posterior ventricular wall without necrosis of a great deal of septal muscle. The surgeon can perform repair of posterior septal rupture to best advantage by standing at the left side of the supine patient. The left ventriculotomy is then closed as a separate suture line, again with interrupted mattress sutures of 1-0 Tevdek buttressed with felt strips. A second running suture is used to ensure a secure left ventriculotomy closure (not shown). LV, posterior left ventricle; PDA, posterior descending artery; RV, diaphragmatic surface of the right ventricle. (*Adapted with permission from Daggett.*[21])

left ventricle along a line corresponding to the medial margin of the base of the posteromedial papillary muscle. Because the posterior wall of the left ventricle is infarcted, it is usually necessary to use full-thickness bites and anchor the sutures on a strip of pericardium or Teflon felt applied on the epicardial surface of the posterior wall of the left ventricle right at the level of the posteromedial papillary muscle insertion, as shown in Fig. 29-11B. Once the patch is completely sutured to the mitral valve annulus, the endocardium of the interventricular septum, and the full thickness of the posterior wall

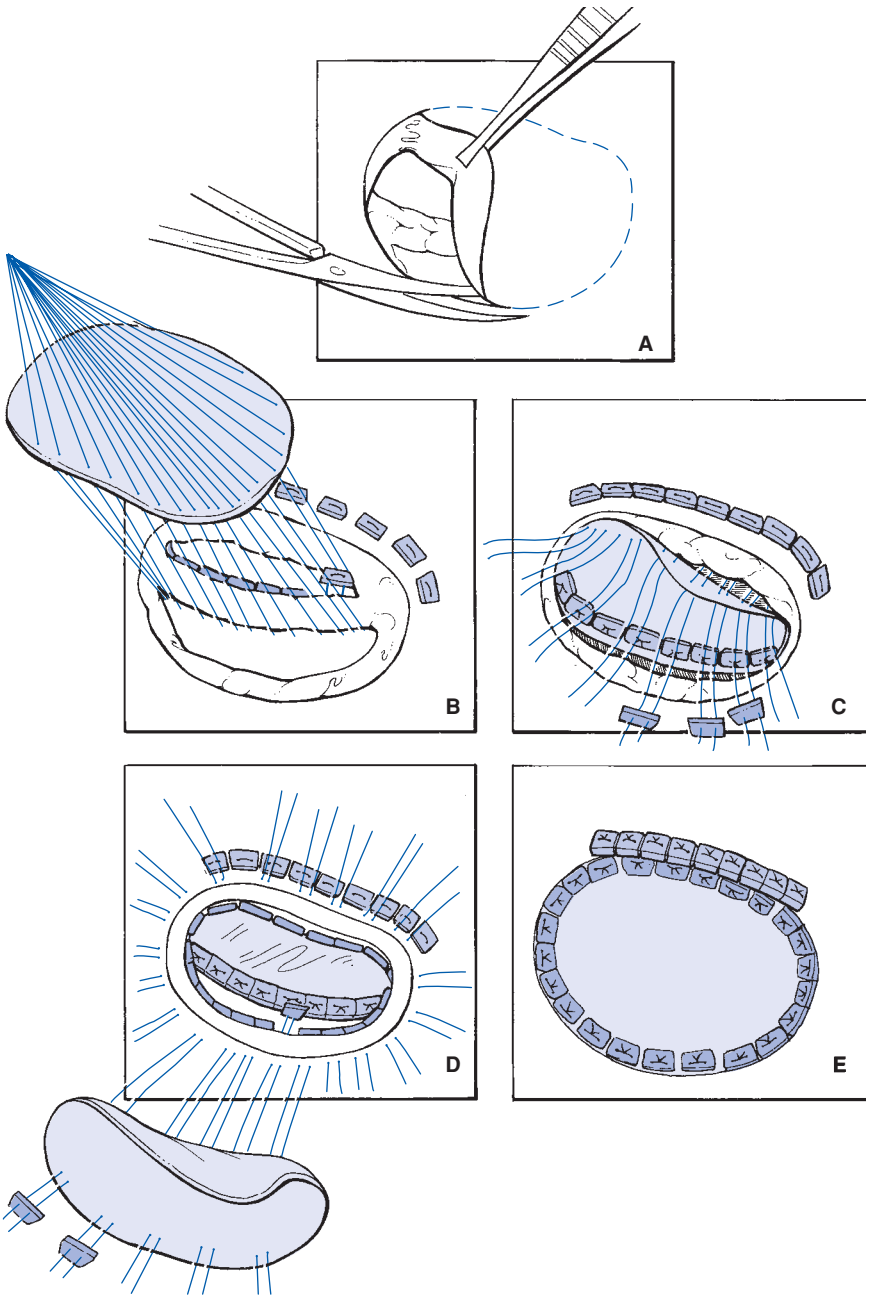


Figure 29-7. (A) Repair of posterior septal rupture when necrosis of a substantial portion of the posterior septum requires the use of patches. (B) Interrupted mattress sutures of 2-0 Tevdek are placed circumferentially around the defect. These sutures are buttressed with felt pledgets on the right ventricular side of the septum and on the epicardial surface of the diaphragmatic right ventricle. (C) All sutures are placed and then the patch (DeBakey elastic Dacron fabric) is slid into place on the left ventricular side of the septum. The patch sutures are tied down with an additional felt pledget placed on top of the patch (left ventricular side) as each suture is tied, to cushion the tie and prevent cutting through the friable muscle. These maneuvers are viewed by the authors as essential to the success of early repair of the posterior septal rupture. (D) Remaining to be repaired is the posterior left ventricular free wall defect created by infarctectomy. Mattress sutures of 2-0 Tevdek are placed circumferentially around the margins of the posterior left ventricular free wall defect. Each suture is buttressed with a Teflon felt pledget on the endocardial side of the left ventricle. With all sutures in place, a circular patch, fashioned from a Hemashield woven double velour Dacron collagen-impregnated graft (Meadox Medicals Inc., Oakland, NJ), is slid down onto the epicardial surface of the left ventricle. An additional pledget of Teflon felt is placed under each suture (on top of the patch) as it is tied to cushion the tie and prevent cutting through the friable underlying muscle. This onlay technique of patch placement prevents the cracking of friable left ventricular muscle that occurred with the eversion technique of patch insertion. (E) Completed repair. (*Adapted with permission from Daggett.*[21])

(Fig. 29-11C), the ventriculotomy is closed in two layers of full-thickness sutures buttressed on strips of pericardium or Teflon felt (Fig. 29-11D). The infarcted right ventricular wall is left undisturbed. If the posteromedial papillary muscle is ruptured, mitral valve replacement is necessary.[85]

There are several theoretical advantages in the technique of infarct exclusion: (1) It does not require resection of myocardium; excessive resection results in depression of ventricular function and insufficient resection predisposes to recurrence of septal rupture; (2) it maintains ventricular geometry, which enhances ventricular function;[43] and (3) it avoids tension on friable muscle, which may diminish postoperative bleeding.[46]

Other techniques

Most other operative techniques that have resulted in successful management of postinfarction of ventricular septal rupture have adhered to the same general principles described above. For example, daSilva and associates[95] report a technique whereby a nontransfixing running suture has been used to secure a large prosthetic patch to the left side of the ventricular septum, with little or no resection of septum muscle. Tashiro and colleagues[96] described an extended endocardial repair in which a *saccular* patch of glutaraldehyde-fixed equine pericardium was used to exclude an anterior septal rupture. Usui and coworkers[97] reported the successful repair of a posterior septal rupture using two sheets of equine pericardium to sand-

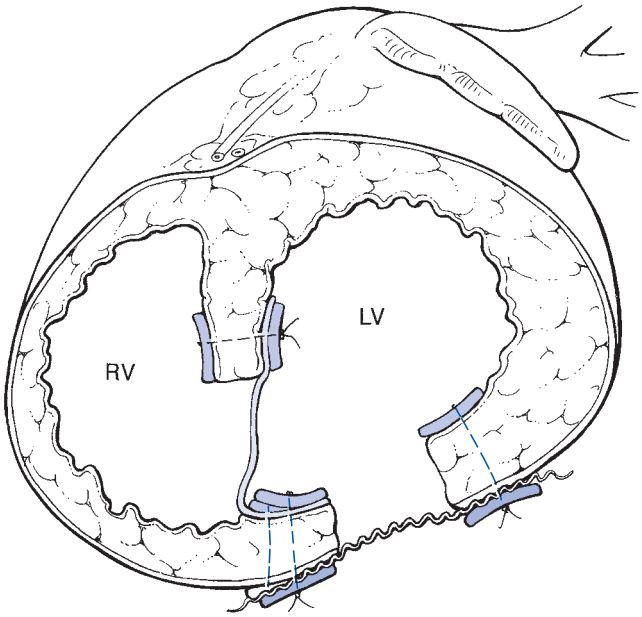


Figure 29-8. Cross-sectional view of the completed repair of posterior septal rupture with prosthetic patch placement of the posterior left ventricular free wall defect created by infarctectomy. LV, left ventricular cavity; RV, right ventricular cavity. (*Adapted with permission from Daggett.*[21])

wich the infarcted myocardium, including the septal defect and ventriculotomy. Others have modified the exclusion technique by use of tissue sealants to aid in the septal closure.[98]

Percutaneous closure

Successful transcatheter closure of postinfarction ventricular septal rupture has been reported using several types of catheter-deployed devices. Early experience was with the CardioSEAL device, a nitinol double-umbrella prosthesis.[99] The device consists of two attached and opposing umbrellas formed by hinged steel arms covered in a Dacron meshwork that theoretically promotes endothelialization. The arms are manually everted to allow the device to be passed through a narrow percutaneous deployment system. When extruded from the guiding catheter, the arms spring backward, resembling a clamshell. The device approaches the septum via the systemic veins and through the atrial septum (or alternatively via the arterial system through the aortic valve). As reported by Landzberg and Lock,[99] the experience at Boston Children's Hospital and Brigham and Women's Hospital indicates that while the device can be routinely deployed in the setting of an acute infarction, the continued necrosis of septal tissue led to decompensation and death in four of seven patients. In contrast, they reported success in six of six patients treated for residual or recurrent septal defects discovered after primary operative repair.

Other catheter devices have also been attempted, including the Amplatzer septal occluder and the Rashkind double umbrella.[100]

The recently developed Amplatzer VSD device allows closure of muscular and membranous VSDs, and it can be used for larger postinfarction defects, with the septal Amplatzer device favored for smaller lesions.[101] In a series of seven patients treated with the Amplatzer, the size of the device ranged from 12 to 24 mm with only one death.[102]

The best use of such devices in an overall treatment strategy is unclear. As a primary treatment, data suggest that the devices have a high early failure rate, but their potential role in improving the risk of an unstable surgical patient is not yet well characterized. Currently, catheter approaches appear to be most effective in treatment of recurrent or residual defects, and we preferentially employ them for these conditions.[103] Device development is an ongoing process, and the future undoubtedly will see use of new devices, especially in the high-risk patient with multisystem failure.

Of interest, two centers have reported using a standard Swan-Ganz balloon catheter from the groin to abolish the shunt in unstable patients with postinfarction septal rupture.[104,105] Hemodynamic improvement was immediate in both patients, who underwent subsequent surgical repair of the defect.

Role of Ventricular Assist Devices

In patients who present for operation with evidence of potentially reversible multiorgan dysfunction, or in patients who have intractable failure following repair, there may be a role for temporary mechanical heart support. There have been anecdotal cases of unstable patients being successfully managed by mechanical support followed by definitive operation.[106]

The theoretical advantages that make mechanical support attractive as an initial therapy in very sick patients with postinfarction VSD include: (1) the potential to reverse end-organ dysfunction; (2) maturation of the infarct leading to firmer tissue, making the closure less prone to technical failure; and (3) recovery of the stunned and energy-depleted myocardium. However, there are potential hazards with mechanical support that are specific to the patient with postinfarction VSD. High right-to-left shunting across the ventricular septum has been reported to cause hypoxic brain injury in a postinfarction VSD patient placed on a HeartMate left ventricular support device.[107] This anecdotal observation suggests that either partial left heart support or preferably biventricular support should be considered when using mechanical assistance in these patients. In a report using the Hemopump axial flow device, two of two patients supported experienced lethal pump failure. Examination of the device at autopsy disclosed necrotic material clogging the catheter system.[108]

Simultaneous Myocardial Revascularization

There has been controversy in the literature concerning the advantages and disadvantages of concurrent coronary artery grafting in patients undergoing emergent repair of postinfarction ventricular septal rupture.[26,31,65,73,109] Some have argued that revascularization provides no survival benefit and subjects patients to preoperative left heart catheterization, a time consuming and potentially dangerous diagnostic

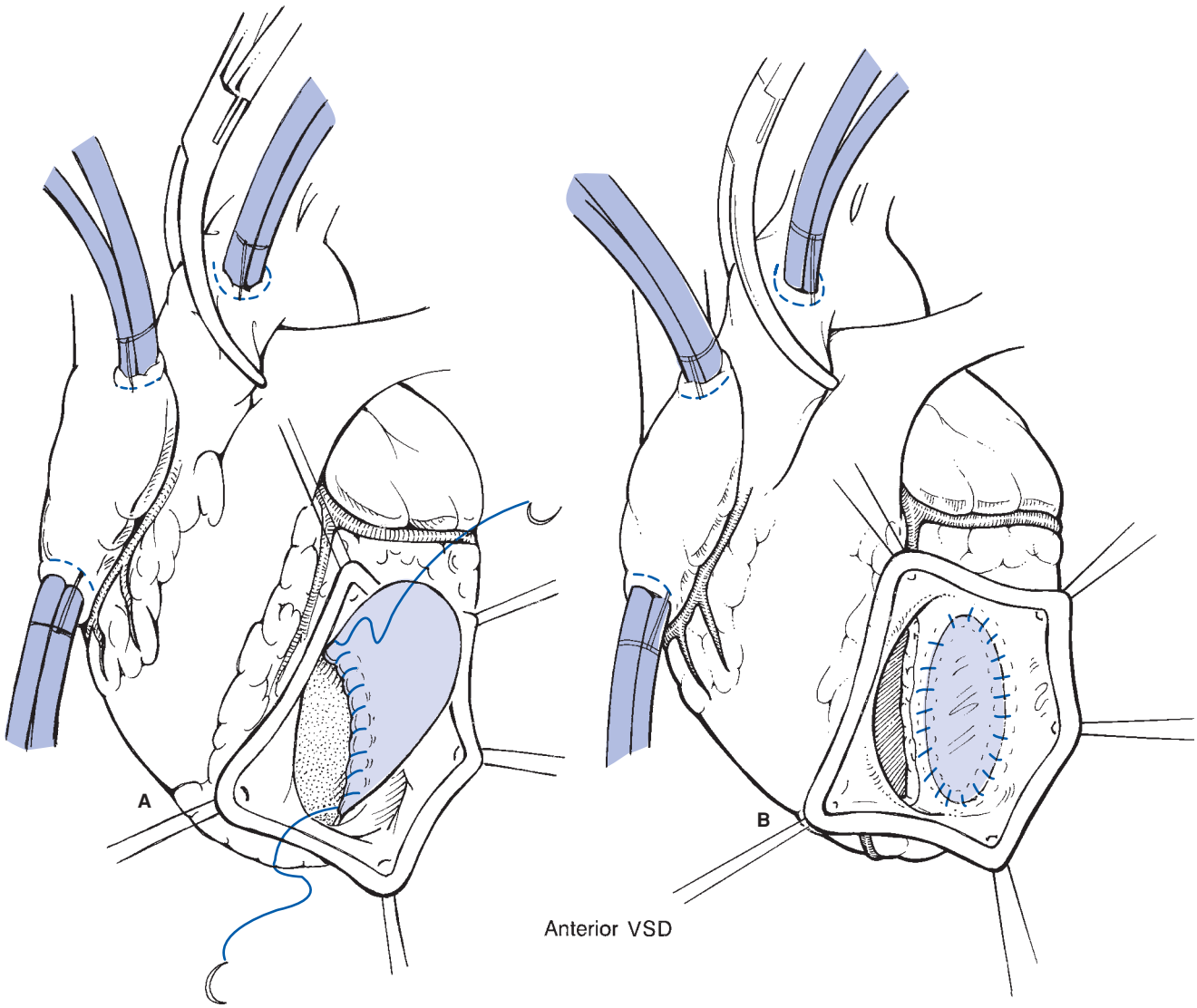


Figure 29-9. Repair of an anterior postinfarction ventricular septal rupture using the technique of infarct exclusion. (A) The standard ventriculotomy is made in the infarcted area of left ventricular free wall. An interior patch of Dacron (Meadox Medicals Inc., Oakland, NJ), polytetrafluoroethylene, or glutaraldehyde-fixed pericardium is fashioned to replace and/or cover the diseased areas (ventricular septal defect [VSD], septal infarction, or free wall infarction). (B) The internal patch is secured to normal endocardium with a continuous monofilament suture, which may be reinforced with pledgeted mattress sutures. There is little, if any, resection of myocardium and no attempt is made to close the septal defect.

procedure.[65] Loisance and associates[109] base their policy of not revascularizing patients with postinfarction septal ruptures on the fact that none of their 20 long-term survivors (five of whom were bypassed) had incapacitating angina or recurrent myocardial infarction.

Some groups use left heart catheterization and coronary bypassing selectively.[25,31] Davies and colleagues[31] found that of 60 long-term survivors (median 70 months; range 1 to 174 months), only five patients developed exertional angina during follow-up and none required revascularization. Their current policy is to avoid left heart catheterization of patients in whom an acquired septal defect is suspected to be a consequence of their first anterior infarction, provided that the patient has no history of angina or electrocardiographic evidence of previous infarction in another territory.[31] This approach is also based on the findings that multivessel disease is much less prevalent in those with an apical septal rupture as a result of anterior infarction.[23]

Weaning from Cardiopulmonary Bypass

The two most common problems encountered in separating from bypass following repair of a postinfarction VSD are low cardiac output and bleeding. Although the treatment of low cardiac output following cardiac surgery is beyond the scope of this chapter, a few agents and principles are worth

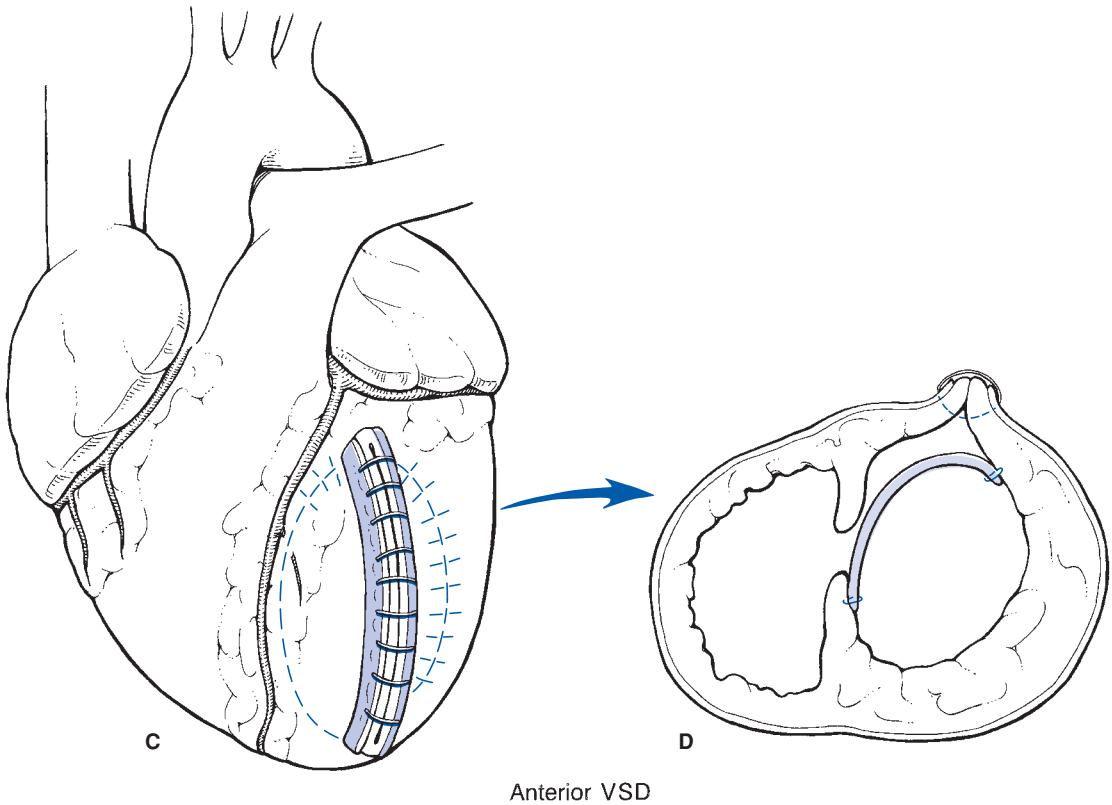


Figure 29-9. (*continued*) Repair of an anterior postinfarction ventricular septal rupture using the technique of infarct exclusion. (C) The ventriculotomy, which is outside the pressure zone of the left ventricle, may be repaired with a continuous suture. (D) On transverse section, one can see that the endocardial patch is secured at three levels: above and below the septal rupture and beyond the ventriculotomy. (*Adapted with permission from David et al.*[46])

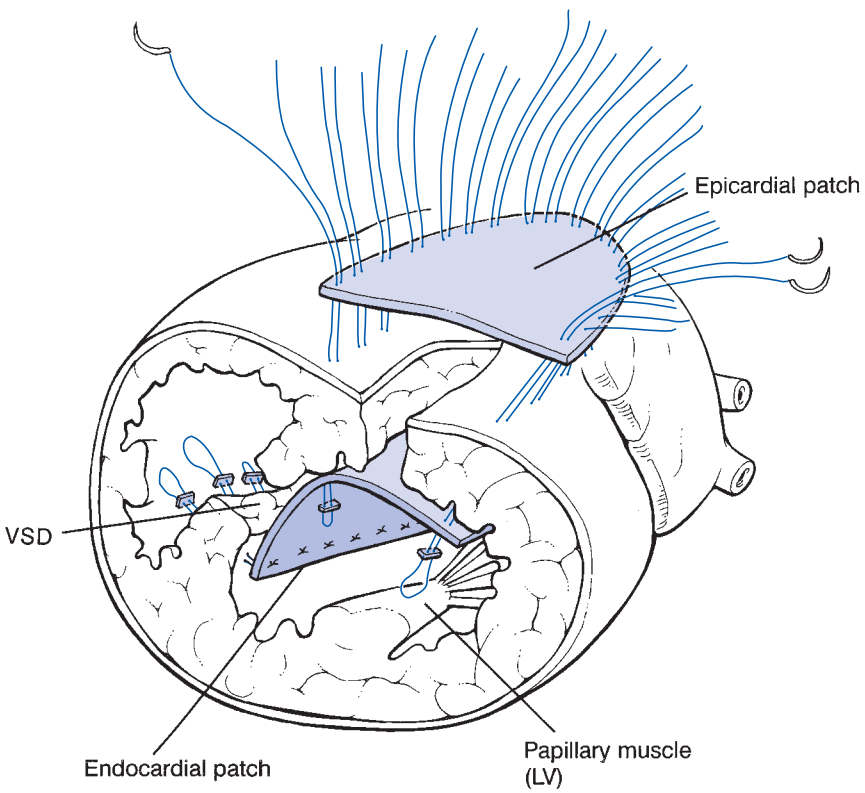


Figure 29-10. Repair of an anterior postinfarction ventricular septal rupture using the technique of infarct exclusion with external patching of the ventricular free wall with tailored Teflon or pericardium. LV = left ventricle; VSD = ventricular septal defect. (*Adapted with permission from Cooley.*[93])

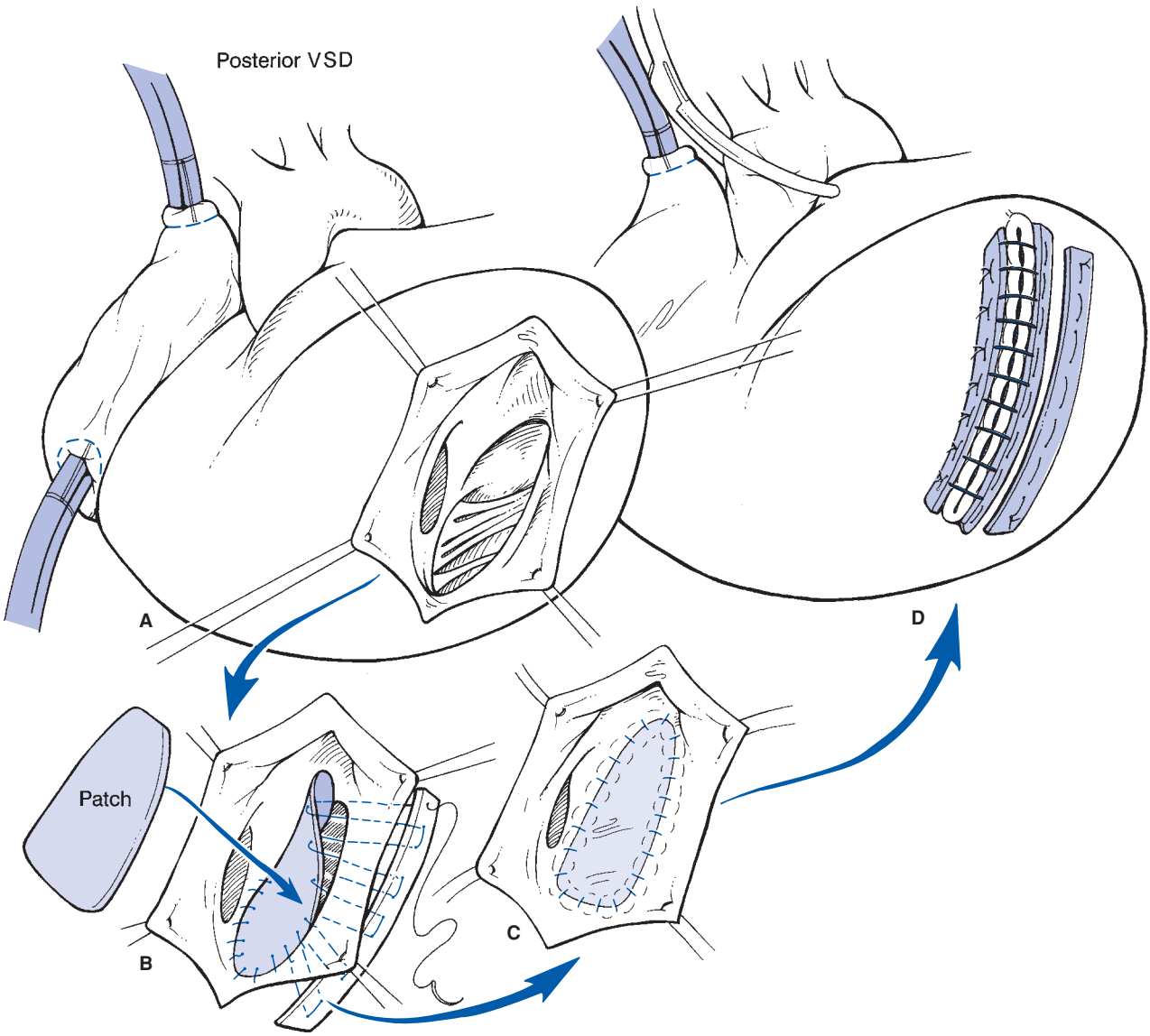


Figure 29-11. Endocardial repair of a posterior postinfarction ventricular septal rupture using the technique of infarct exclusion. (A) An incision is made in the inferior wall of the left ventricle 1 or 2 mm from the posterior descending artery starting at the midportion of the inferior wall and extended proximally toward the mitral annulus and distally toward the apex of the ventricle. Care is taken to avoid damage to the posterolateral papillary muscle. (B) A bovine pericardial patch is tailored in a triangular shape. The base of the triangular-shaped patch is sutured to the fibrous annulus of the mitral valve with a continuous 3-0 polypropylene suture starting at a point corresponding to the level of the posteromedial papillary muscle and moving medially toward the septum until the noninfarcted endocardium is reached. (C) The medial margin of the triangular-shaped patch is sewn to healthy septal endocardium with a continuous 3-0 or 4-0 polypropylene suture. The lateral side of the patch is sutured to the posterior wall of the left ventricle along a line corresponding to the medial margin of the base of the posteromedial papillary muscle. At this point, it is usually necessary to use full-thickness bites and anchor the sutures on a strip of pericardium or Teflon felt applied on the epicardial surface of the posterior wall of the left ventricle. (D) Once the patch is completely sutured to the mitral valve annulus, the endocardium of the interventricular septum, and the full thickness of the posterior wall, the ventriculotomy is closed in two layers of full-thickness sutures buttressed on strips of pericardium or Teflon felt. The infarcted right ventricular wall is left undisturbed. (*Adapted with permission from David et al.*[46])

mentioning. First, most of these patients will have had an IABP inserted before surgery. If not, one should be inserted in the operating room, especially if the low-output state is secondary to LV dysfunction. Also, an IABP may benefit patients with right ventricular failure by improving right coronary artery blood flow due to diastolic augmentation. We have found intravenous milrinone, a phosphodiesterase inhibitor, to be very effective in reversing low-output states secondary to LV dysfunction. Milrinone possesses a balance of inotropic and vasodilatory properties that together produce an increase in cardiac output and reduction in right and left filling pressures and systemic vascular resistance. It is less arrhythmogenic than dobutamine, causes less hypotension than amrinone, and is not associated with thrombocytopenia.[110]

Posterior defects are commonly associated with mitral regurgitation and right heart dysfunction secondary to extensive right ventricular infarction.[38] Management of right heart failure is aimed at reducing right ventricular afterload while maintaining systemic pressure.[104] Initial steps to manage right ventricular dysfunction include volume loading, inotropic support, and correction of acidosis, hypoxemia, and hypercarbia. If patients remain unresponsive to these measures, we have successfully treated right ventricular failure with a prostaglandin E_1 infusion (0.5 to 2.0 μg/min) into the right heart, counterbalanced with a norepinephrine infusion titrated into the left atrium.[111] Inhaled nitric oxide (20 to 80 ppm), which selectively dilates the pulmonary circuit, has also proven efficacious in the treatment of right heart failure.[112]

If a patient cannot be weaned from bypass using conventional therapy, we consider using a ventricular assist device. Indications for a left ventricular assist device are a cardiac index less than 1.8 L/min/m^2, a left atrial pressure above 18 to 25 mm Hg, a right atrial pressure below 15 mm Hg, and an aortic pressure below 90 mm Hg peak systolic. Indications for a right ventricular assist device are a cardiac index less than 1.8 L/min/m^2, an aortic pressure below 90 mm Hg peak systolic, and a left atrial pressure less than 15 mm Hg despite volume loading to a right atrial pressure of 25 mm Hg with a competent tricuspid valve. Important points to remember when instituting ventricular assistance are:

1. Right ventricular failure may not become evident until left ventricular assistance is instituted.
2. Once refractory ventricular failure has been identified, delay in initiating support is associated with increased morbidity and mortality.
3. Closure of a patent foramen ovale is mandatory prior to left ventricular support.
4. Postoperative hemorrhage should be treated aggressively and completely controlled.
5. Residual septal defects may result in right-to-left shunting and severe hypoxia when only left heart support is used.[113]

To prevent postpump coagulopathy, we begin antifibrinolytic therapy with either aprotinin or ε-aminocaproic acid (Amicar) before commencing cardiopulmonary bypass. Since controversy surrounds the issue of increased renal dysfunction and perioperative thrombotic events in patients receiving aprotinin,[114] we prefer to use Amicar in patients who (1) require aortocoronary bypasses, (2) are diabetic, or (3) have known renal dysfunction. Amicar is administered by loading patients with 10 g prior to commencing bypass and then adding another 10 g to the pump prime. During the procedure Amicar is continuously infused at 1 g/h for the duration of surgery. Postpump suture line bleeding may be reduced by application of a fibrin sealant to the ventricular septum around the septal defect *prior* to formal repair.[115] Biological glue may be effective in controlling bleeding suture lines following repair.[116] As a last resort, Baldwin and Cooley[117] have suggested insertion of a left ventricular assist device solely as an adjunct to the repair of friable or damaged myocardium to reduce left ventricular distention and thus control bleeding.

Highlights of Postoperative Care

Early postoperative diuresis and positive end-expiratory pressure ventilation are used to decrease the alveolar-arterial gradient induced by the increased extravascular pulmonary water associated with cardiopulmonary bypass. Once the patient has warmed, we commonly use an intravenous infusion of furosemide combined with mannitol or, if needed, continuous venovenous hemofiltration is employed postoperatively.

Intractable postoperative ventricular arrhythmias secondary to reperfusion injury are sometimes difficult to control using standard therapy. We have been impressed with the efficacy of intravenous amiodarone in these situations (10 to 20 mg/kg over 24 hours).[118]

Operative Mortality and Risk Factors for Death

Table 29-2 summarizes recently reported experience from several centers. Operative mortality, defined as death prior to discharge *or* within 30 days of operation, ranged from 30 to 50%. In the Massachusetts General Hospital experience of 114 patients, operative mortality was 37% (Fig. 29-12A). The risk for death was found to be very high initially, but dropped rapidly (Fig. 29-12B). We identified independent risk factors for early and late death using multivariate methods (Table 29-3). The most important predictor of operative mortality in our study, and in other reports, was preoperative hemodynamic instability. Patients in this group are usually in cardiogenic shock, are emergency cases, are on inotropic support, and usually have intra-aortic balloon pumps. Several variables are highly correlated with hemodynamic instability, and different multivariate models may use one or more of these indicators of severe hemodynamic failure in their final model.

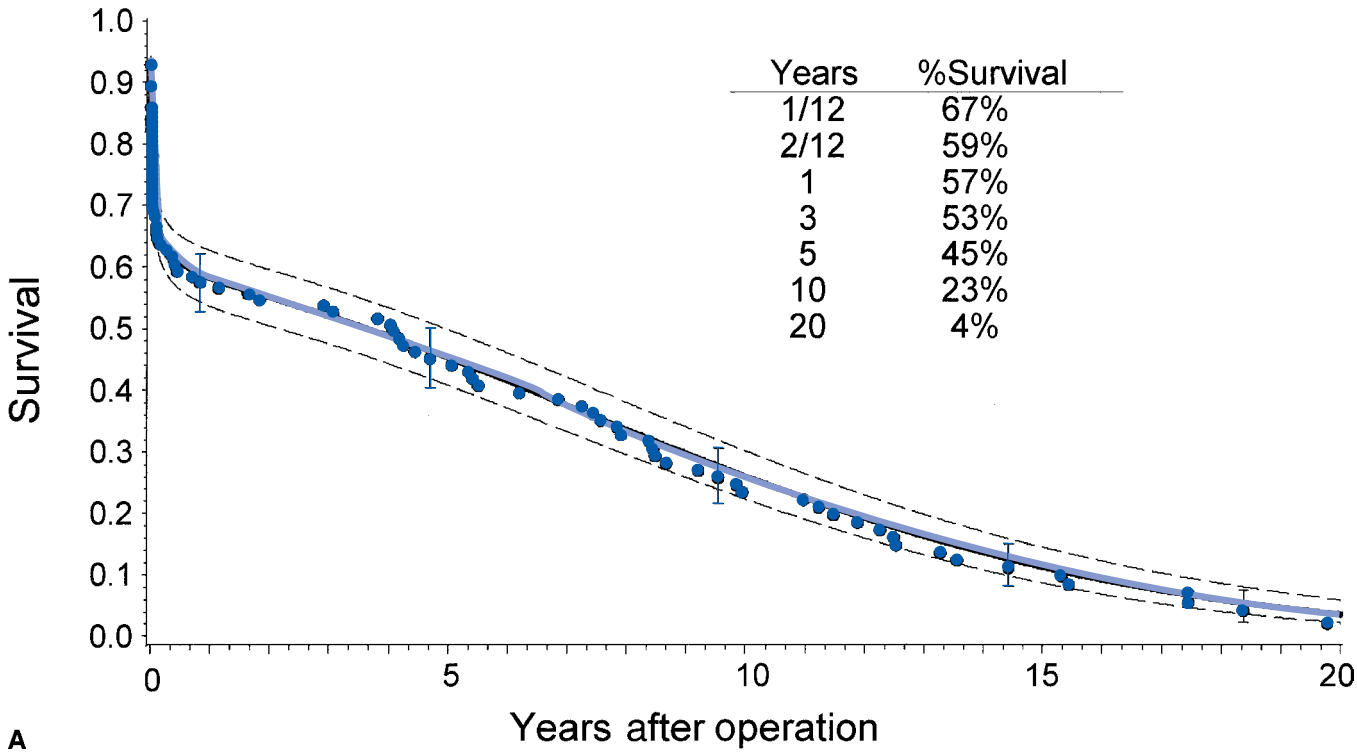
Additional risk factors for early and late death include the presence of left main CAD, previous MI, renal dysfunction, and right heart failure (Fig. 29-13). Other factors have

Table 29–2.

Summary of Recent Clinical Experience with Surgical Repair of Postinfarction Ventricular Septal Defect

Institution	City	Year	No.	Hospital mortality	5-Year survival	Reference
Sweden (multi-institutional)	Sweden	2005	189	41% (30-day)	38%	176
Ospedale di Circolo-Fondazione Macchi	Varese, Italy	2005	50	36%	47%	177
Northwest England (multi-institutional)	England	2003	65	23% (30-day)	—	178
Hospital Haut-Lévêque	Bordeaux	2002	85	42%	33%	179
Massachusetts General Hospital	Boston	2002	114	37%	45%	180
Papworth Hospital	Cambridge	2002	25	48%	—	181
University Hospital	Zurich	2000	54	26%	52%*	182
Sakurabashi Watanabe Hospital	Osaka	2000	16	38%	—	183
Glenfield General Hospital	Leicester	2000	117	37% (30-day)	46%	184
Evangelismos General Hospital	Athens	1999	14	50%	—	185
Texas Heart Institute	Houston	1998	126	46%	—	123
The Toronto Hospital	Toronto	1998	52	19%	65%*	186
Southampton General	Southampton	1998	179	27%	49%	192
Cedars-Sinai	Los Angeles	1998	31	32%	—	187
Mid America Heart Institute	Kansas City	1997	76	41%	41%	188
St. Anthonius Hospital	Nieuwegein	1996	109	28% (30-day)	—	189
Green Lane Hospital	Auckland	1995	35	31% (30-day)	60%*	190
Hospital Cardiologique du Haut-Lévèque	Bordeaux	1991	62	38%	44%	36
CHU Henri Mondor	Créteil	1991	66	45%	44%	191

**Value estimated from published graphical or tabular data.*
Note: Series with less than 10 patients were excluded from the table.



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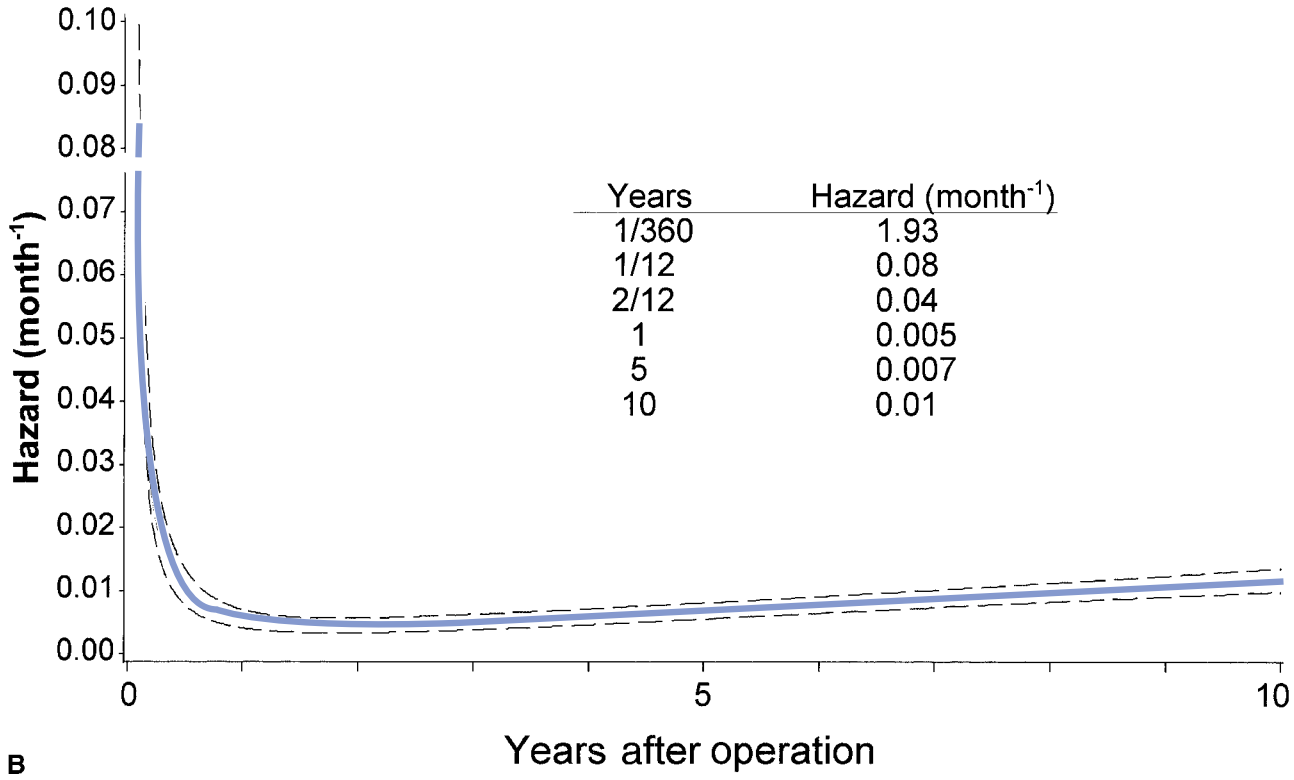

B

Figure 29-12. (A) Time-related survival after repair of postinfarction ventricular septal defect at the Massachusetts General Hospital (n = 114). Note that the horizontal axis extends to 20 years. Circles represent each death, positioned on the horizontal axis at the interval from operation to death, and actuarially (Kaplan-Meier method) along the vertical axis. The vertical bars represent 70% confidence limits (± 1 SD). The solid line represents the parametrically estimated freedom from death, and the dashed lines enclose the 70% confidence limits of that estimate. The table shows the nonparametric estimates at specified intervals. (B) Hazard function for death after repair of postinfarction ventricular septal defect (n = 114). The horizontal axis is expanded for better visualization of early risk. The hazard function has two phases, consisting of an early, rapidly declining phase, which gives way to a slowly rising phase at about 6 months. The estimate is shown with 70% confidence limits.

Table 29–3.

Incremental Risk Factors for Death Following Repair of Postinfarction Ventricular Septal Defect*

	Hazard phase	
Risk factor	**Early**	**Late**
Demographic		
Age (older)	•	•
Clinical history		
Previous myocardial infarction		•
Clinical status		
Blood urea nitrogen (higher)	•	
Creatinine (higher)		•
"Emergency"	•	
Right atrial pressure (higher)	•	•
Catecholamines	•	
Coronary/ventricular septal defect anatomy		
Left main disease		•

**From Massachusetts General Hospital experience; n = 114; 95 events.*

been found to increase the risk of early death. Posterior location of the septal rupture has been associated with an increased operative mortality.[36,38,48,50] This has been attributed to a more technically difficult repair,[19,119] to the increased risk of associated mitral regurgitation, and to associated right ventricular dysfunction that is an independent predictor of early mortality following posterior infarction.[49] A short time interval between infarction and operation selects for sicker patients unable to be managed medically. Older patient age has also been associated with an increased early mortality.[22,78,120,121] In our analysis, we found that the impact of age was more pronounced in the high-risk patient, and should not be used as a reason for denying surgery in an otherwise low-risk elderly candidate (Fig. 29-14).

Our review of the Massachusetts General Hospital experience underscored the large variability of risk to which patients could be segregated using a few clinical variables (Figs. 29-15 and 29-16), most notably indicators of hemodynamic instability (emergency surgery and use of inotropes). The result was that a small group of high-risk patients dramatically affected the overall mortality rate. We believe that this phenomenon makes it very difficult to compare mortality between institutions. A slight difference in practice patterns, such as a tendency of a surgeon or referring cardiologist to deny operation, could substantially affect results. Additionally, any difference in transport dynamics to certain centers could lead to loss of unstable patients, which could create another type of selection bias. In our opinion, these issues are by far the most important source of mortality differences in modern series.

Several centers have reported improved early results with an "exclusion" repair.[46,122,123] Our group has not been able to replicate these results, with a disappointing 60% mortality in 10 patients (higher than the rate achieved historically with traditional techniques).

Regardless of the technique, the most common cause of death following repair of acute postinfarction VSD was low cardiac output syndrome (52%). Technical failures, most commonly recurrent or residual VSD, but including bleeding, were the second most common (23%). Other causes of death include sepsis (17%), recurrent infarction (9%), cerebrovascular complications (4%), and intractable ventricular arrhythmias.

Long-Term Results

Long-term results have been favorable with regard to both mortality risk and functional rehabilitation. Actuarial survival at 5 years for most recent series generally ranges between 40 and 60% (see Table 29-2). Due to the overall high risk of the operation, it is rewarding to note that hospital survivors enjoy excellent longevity, with 1-, 5-, and 10-year survival of 91, 70, and 37%, respectively. They also are quite functional—among 15 of our patients contacted during the most recent follow-up of long-term survivors, 75% were in New York Heart Association functional class I, and 12.5% were class II.[32]

Recurrent Ventricular Septal Defects

Recurrent or residual septal defects have been diagnosed by Doppler color flow mapping early or late postoperatively in 10 to 25% of patients.[23] They may be due to reopening of a closed defect, to the presence of an overlooked defect, or to the development of a new septal rupture during the early postoperative period. These recurrent defects should be closed when they cause symptoms or signs of heart failure or when the calculated shunt fraction (pulmonary-to-systemic flow ratio) is large (Qp:Qs >2.0). When they are small (Qp:Qs <2.0) and either asymptomatic or controlled with minimal diuretic therapy, a conservative approach is reasonable and late spontaneous closure can occur.[23] Intervention in the catheterization laboratory may be useful in closing symptomatic residual or recurrent defects postoperatively.

Chronic Ventricular Septal Defects

In 1987 Rousou and associates reported successful closure of an acquired posterior VSD by means of a right transatrial approach.[124] Filgueira and colleagues have used the transatrial approach for *delayed* repair of chronic acquired posterior septal defects.[125] Approaching a postinfarction

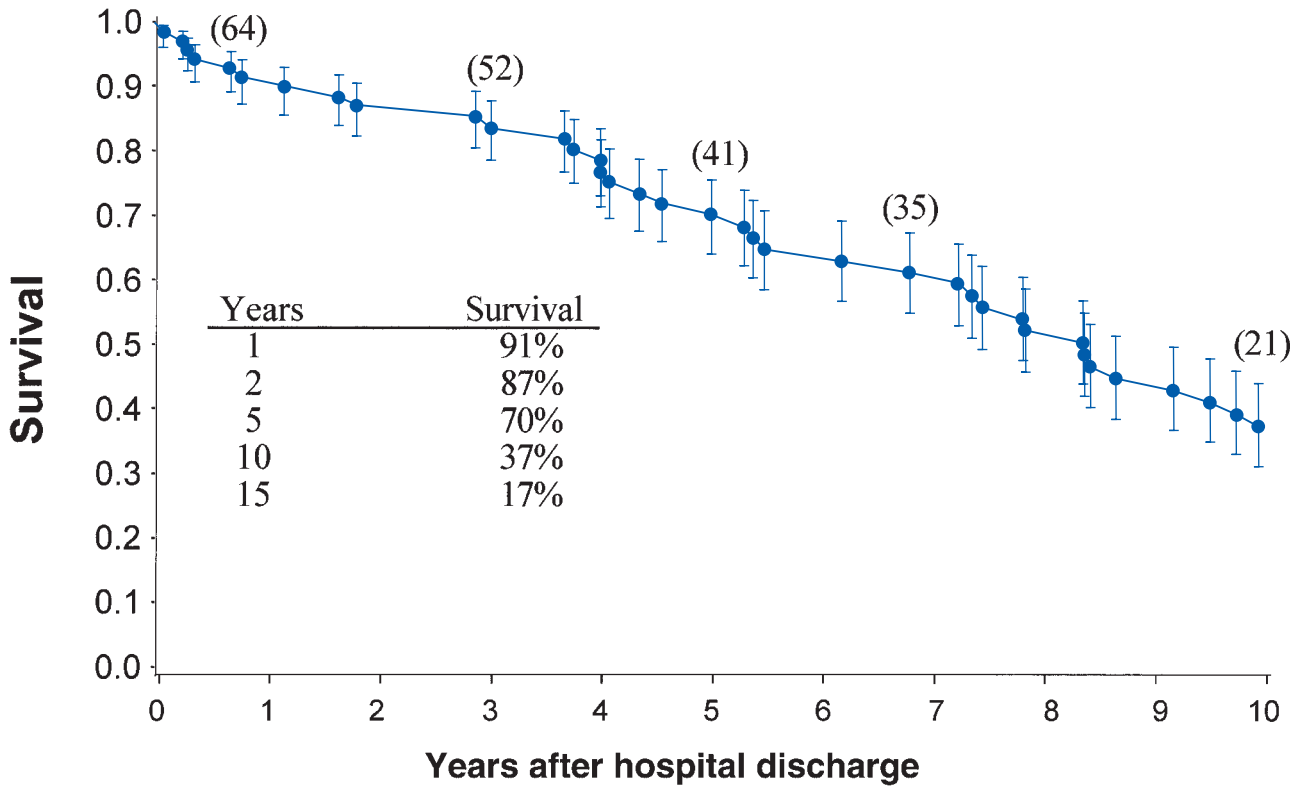

Figure 29-13. Survival in patients who were discharged after repair of postinfarction ventricular septal defect (Massachusetts General Hospital, n = 72). The horizontal axis is expanded and represents the time from hospital discharge to death. The depiction is otherwise similar to that seen in Fig. 29-12A.

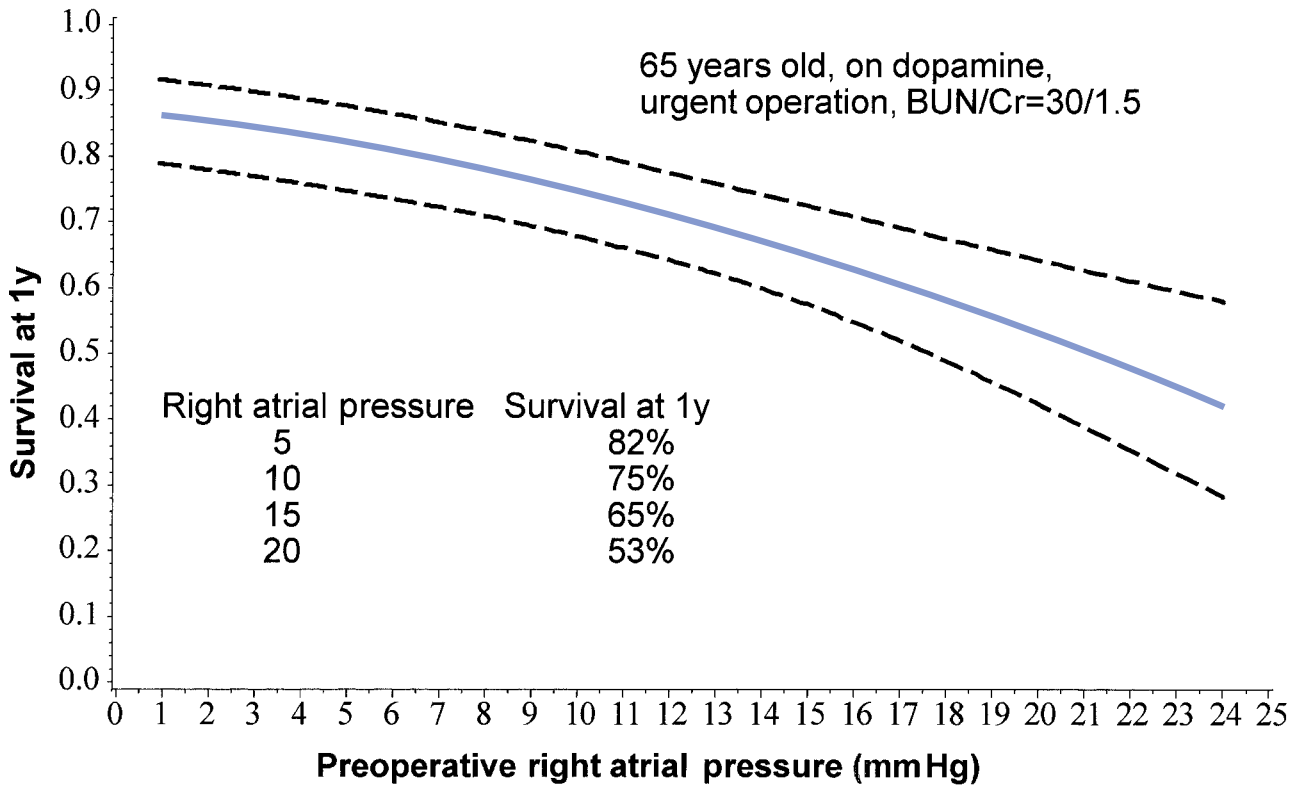

Figure 29-14. Survival at 1 year vs. preoperative right atrial pressure (Massachusetts General Hospital; n = 114). The depiction is a solution of the multivariate equation for a 65-year-old with a blood urea nitrogen of 30 mg/dL, a creatinine of 1.5 mg/dL, not on catecholamines, not an "emergency" case, and without a history of myocardial infarction or left main coronary artery disease.

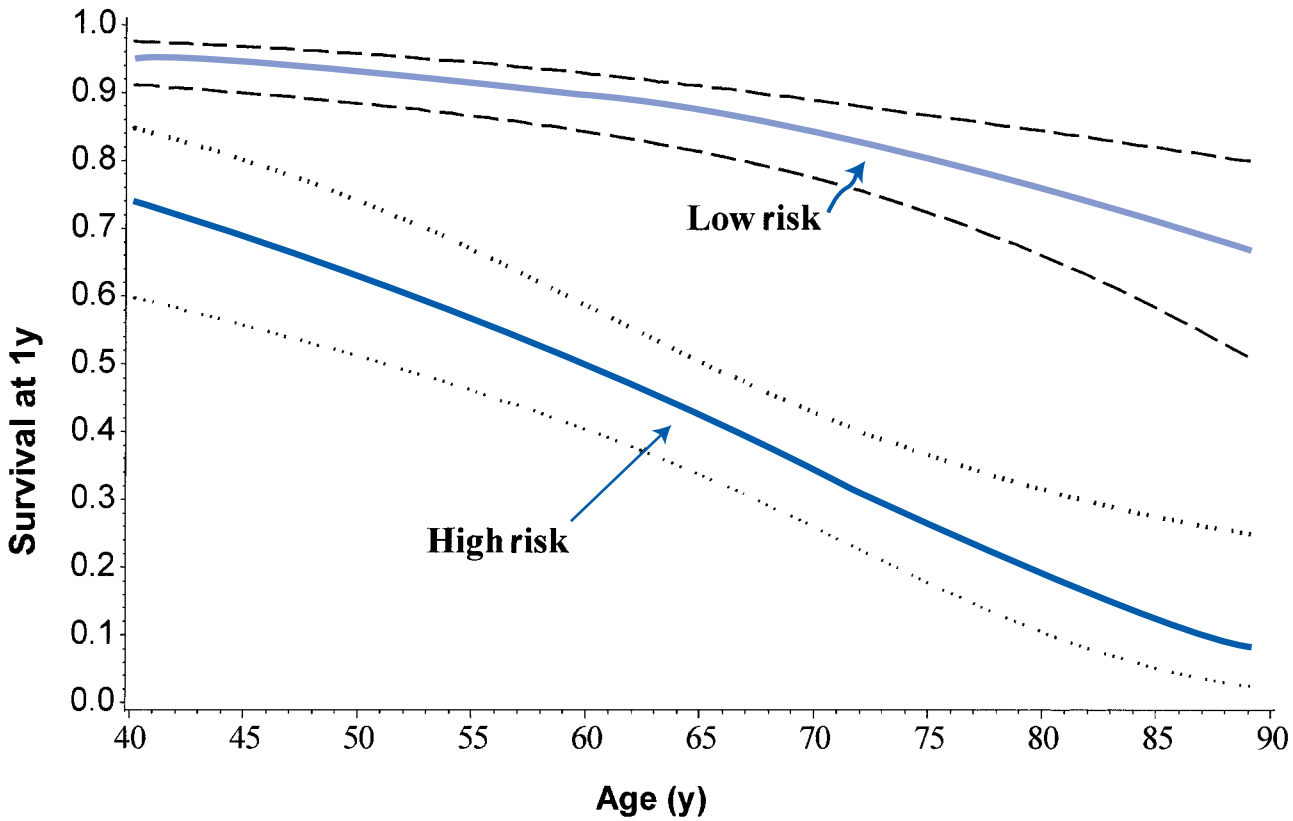

Figure 29-15. Nomograms (specific solutions to the multivariate equation) depicting the effect of age on risk in two different hypothetical patients. In both curves the patient was considered to have no left main disease, a blood urea nitrogen of 30 mg/dL, creatinine of 1.5 mg/dL, and no history of previous myocardial infarction. The curve for "low-risk" was solved for a patient who was not emergent and not on catecholamines. The curve for "high-risk" was for an emergent patient on inotropes. The vertical axis represents the calculated survival at 1 year.

VSD through the tricuspid valve should not be used in acute cases because of the friability of the necrotic septum, poor exposure, and because this technique does not involve infarctectomy, and thus cannot achieve the hemodynamic advantages of elimination of a paradoxically bulging segment of ventricular wall. However, the right heart approach can be used in chronic postinfarction VSD when the septum is well scarred and the patch can be safely sutured to it from the right atrium. We emphasize that while the transatrial approach may be used selectively for the closure of chronic defects, it is unlikely to be an appropriate choice for the closure of acute defects, except perhaps in the rare circumstance when an infarct is localized to the septum with no evidence of necrosis of the free wall of the left ventricle.[40]

POSTINFARCTION VENTRICULAR FREE WALL RUPTURE

History

William Harvey first described rupture of the free wall of the heart after AMI in 1647.[126] In 1765, Morgagni reported 11 cases of myocardial rupture found postmortem.[127] Ironically, Morgagni later died of myocardial rupture.[128] Hatcher and colleagues from Emory University reported the first successful operation for free wall rupture of the right ventricle in 1970.[129] FitzGibbon and associates[130] in 1971 and Montegut[131] in 1972 reported the first successful repairs of left ventricular ruptures associated with ischemic heart disease.

Incidence

Autopsy studies reveal that ventricular free wall rupture occurs about 10 times more frequently than postinfarction ventricular septal rupture, occurring in about 11% of patients following AMI.[24,132] The incidence has been found to be as high as 31% in autopsy studies of anterior MI.[133] Ventricular rupture and cardiogenic shock are now the leading causes of death following AMI, and together account for over two-thirds of early deaths in patients suffering their first acute infarction. Postinfarction ventricular ruptures are more common in elderly women (mean age of 63 years) suffering their first infarction.[134] In the prethrombolytic era, 90% of ruptures occurred within 2 weeks after infarction

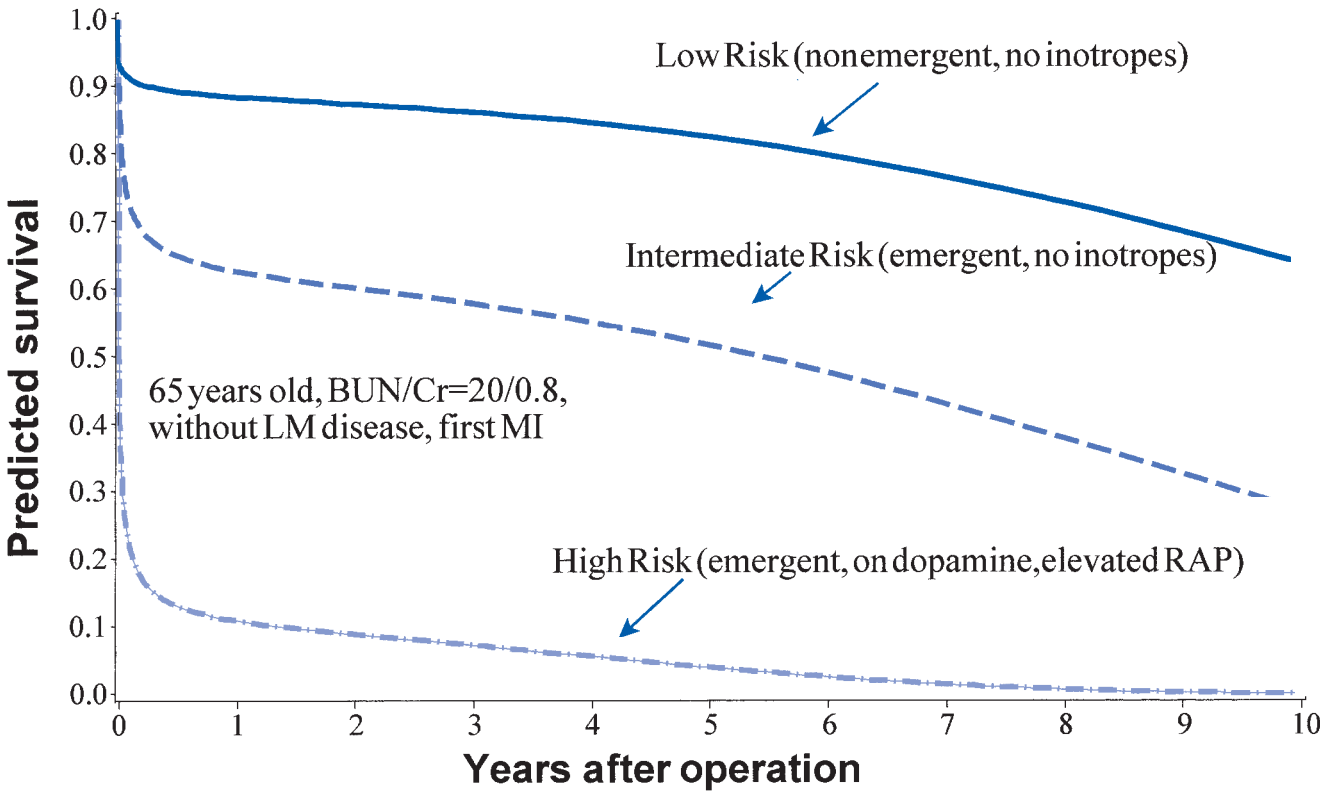

Figure 29-16. Nomograms (specific solutions of the multivariate equation) depicting the predicted survival in three hypothetical 65-year-old patients who present with ventricular septal defect. Each solution is for a patient who has no history of myocardial infarction and without left main coronary artery disease, blood urea nitrogen of 20 mg/dL, and creatinine of 0.8 mg/dL. The "low-risk" patient is nonemergent and not on inotropes with right atrial pressure (RAP) of 8 mm Hg. The "intermediate-risk" patient is emergent and not on inotropes with RAP of 12 mm Hg. The "high-risk" patient is emergent and on inotropes with RAP of 20 mm Hg. Confidence limits have been eliminated to improve clarity.

with the peak incidence at 5 days.[135] In contrast, the time to cardiac rupture (not frequency of rupture) seems to be accelerated by thrombolysis and coronary reperfusion, sometimes occurring within hours from the onset of symptoms.[136] Thus, free ventricular ruptures occur most frequently in hypertensive women over the age of 60 who develop symptoms within 5 days of their first transmural MI.

Opinions differ as to the most common site of left ventricular rupture. The older literature suggests that the anterior wall is the most frequent site.[137] However, more recent series have observed a preponderance of lateral and posterior wall ruptures.[28,132,135] David[138] has suggested that a lateral wall infarction is more likely to rupture than is an anterior or inferior one, but since anterior infarctions are much more frequent than lateral infarctions, overall the most common site of rupture is the anterior wall. Like postinfarction ventricular septal rupture, free wall ruptures may be simple or complex.[42] A simple rupture results from a straight through-and-through tear that is perpendicular to the endothelial and epicardial surfaces, whereas a complex rupture results from a more serpiginous tear, often oblique to the endocardial and epicardial surfaces.[138] Batts and coworkers[135] reported 100 consecutive cases of left ventricular free wall rupture and found that half were simple ruptures and the rest were complex.

Pathogenesis and Pathophysiology

Left ventricular free wall rupture can be divided into three clinicopathologic categories: acute, subacute, and chronic.[139,140] An *acute* or "blow-out" rupture is characterized by sudden recurrent chest pain, electrical mechanical dissociation, profound shock, and death within a few minutes due to massive hemorrhage into the pericardial cavity. This type of rupture is probably not amenable to current management. A *subacute* rupture is characterized by a smaller tear, which may be temporarily sealed by clot or fibrinous pericardial adhesions. These usually present with the signs and symptoms of cardiac tamponade, and eventually cardiogenic shock. Subacute rupture may mimic other complications of AMI such as infarct extension and right ventricular failure, and may be compatible with life for several hours or days or even longer.[138] A *chronic* rupture with

false aneurysm formation occurs when the leakage of blood is slow and when surrounding pressure on the epicardium temporarily controls the hemorrhage. Adhesions form between the epicardium and pericardium, which reinforce and contain the rupture.[30] The most common clinical presentation of patients with false aneurysms of the left ventricle is CHF.[141] A false aneurysm may also be an echocardiographic finding in an otherwise asymptomatic patient recovering from AMI. Angina, syncope, arrhythmias, and thromboembolic complications occur in a small percentage of patients.[141] There are four major differences between a true and false aneurysm of the left ventricle:

1. The wall of a false aneurysm contains no myocardial cells.
2. False aneurysms are more likely to form posteriorly.
3. False aneurysms usually have a narrow neck.
4. False aneurysms have a great propensity for rupture.[142–144]

Rupture of the free wall of the left ventricle may occur in isolation or with rupture of other ventricular structures such as the interventricular septum, papillary muscles, or right ventricle.[141,144]

The pathogenesis of cardiac rupture remains poorly understood. However, cardiac rupture occurs only with transmural MIs and infarction expansion appears to play an important role in its pathogenesis.[39,43,145] Infarct expansion is an acute regional thinning and dilatation of the infarct zone, seen as early as 24 hours following acute transmural MI and not related to additional myocardial necrosis.[146] This regional thinning and dilatation of the infarct zone is a consequence of slippage between muscle bundles, resulting in a reduction in the number of myocytes across the infarcted area.[147] Infarct expansion increases the size of the ventricular cavity, with a consequent increase in wall tension (Laplace effect) that subjects the infarct zone to more tension and predisposes to endocardial tearing.[138] Systemic hypertension aggravates the problem of thinning and dilatation of the infarct wall and increases the probability of rupture.[148] Lack of collateral flow may also promote ventricular rupture.[149]

Since myocardial rupture occurs in regions of complete transmural myocardial necrosis, usually after extensive hemorrhagic transformation of the acute infarct,[145,150,151] and because thrombolytic therapy is associated with the conversion of a bland infarct into a hemorrhagic infarct,[152] there has been an ongoing concern that thrombolysis might increase the likelihood of ventricular rupture.[153] Honan and associates[150] performed a meta-analysis of four large clinical trials (1638 patients) in which streptokinase was used to treat AMIs and concluded that the risk of cardiac rupture was directly related to the timing of thrombolytic therapy. Early treatment (within 7 hours from the onset of symptoms) decreased the risk of cardiac rupture, whereas late treatment (after 17 hours) increased the risk of this complication even though, surprisingly, the overall mortality rate was diminished when streptokinase was given late after acute infarction. In a prospective ancillary study of 5711 patients, Late Assessment of Thrombolytic Efficacy, Becker and colleagues[136] were unable to show an increased risk of cardiac rupture in patients treated with recombinant tissue plasminogen activator 6 to 24 hours after the onset of symptoms. Thus, there is general agreement that early successful thrombolysis decreases the overall risk of cardiac rupture, probably by limiting the extent of necrosis, resulting in a nontransmural instead of transmural infarct, but the impact of late thrombolytic therapy on cardiac rupture remains unclear.

Diagnosis

The clinical picture of a subacute ventricular rupture is primarily that of pericardial tamponade, with pulsus paradoxus, distended neck veins, and cardiogenic shock. Although 5 to 37% of patients with AMI but no rupture may develop a pericardial effusion,[154] echocardiographic signs that increase the sensitivity and specificity for cardiac rupture include effusion thickness greater than 10 mm, echodense masses in the effusion, ventricular wall defects, and signs of tamponade (e.g., right atrial and right ventricular early diastolic collapse and increased respiratory variation in transvalvular blood flow velocities).[155,156] Pericardiocentesis and aspiration of uncoagulated blood has historically been considered the most reliable criterion of subacute ventricular rupture;[157,158] however, false-positive and false-negative diagnoses have been reported.[155] The demonstration of a clear pericardial fluid on pericardiocentesis definitively excludes cardiac rupture.[155] Pericardiocentesis is of therapeutic value in some patients, often providing a short-term circulatory improvement.[159]

In an attempt to define symptomatic, electrocardiographic, and hemodynamic markers that may permit the prospective identification of patients prone to rupture of the heart after AMI, Oliva and colleagues[132] retrospectively studied 70 consecutive patients with rupture and 100 comparison patients with AMI but without rupture. They found a number of markers that were associated with a significant increase in the risk of rupture (Table 29-4). The presence of a lateral infarction, especially with associated inferior or posterior infarction, identified a subset of patients at increased risk for rupture. Persistent, progressive, or recurrent ST-segment elevation, and especially, persistent T-wave changes after 48 to 72 hours, or the gradual reversal of initially inverted T waves, are associated with an increased risk of rupture. Finally, the development of pericarditis, repetitive emesis, or restlessness and agitation, particularly two or three of these symptoms, conveyed predictive value.[133]

Natural History

Acute rupture of the free wall of the left ventricle is invariably fatal, with death usually occurring within minutes of the

Table 29–4.

Sensitivity, Specificity, and Predictive Value of Symptoms and Electrocardiographic Criteria for Cardiac Rupture

	Sensitivity (%)	Specificity (%)	Predictive value (%)
Pericarditis	86	72	68
Repetitive emesis	64	95	90
Restlessness and agitation	55	95	86
Two or more symptoms	84	97	95
ST-segment deviations	61	72	58
T-wave deviations	94	66	66
ST-T–wave deviations	61	68	64

Source: Reproduced with permission from Oliva et al.[132]

onset of recurrent chest pain.[135,138,149] In most of these cases, the sequence of events leading to death is so rapid that there is not enough time for surgical intervention. In contrast, patients with a subacute rupture usually survive hours or days, rarely weeks, following the myocardial tear.[140] Pollack and colleagues[156] found that in 24 cases of postinfarction subacute rupture, survival time (i.e., time from critical event to death) varied between 45 minutes and 6.5 weeks, with a median survival of 8 hours. Núñez and coworkers[160] found that in 29 cases of subacute rupture, 20 (69%) died within minutes of the onset of symptoms, and 9 (31%) lived several hours, allowing time for treatment. Subacute ventricular ruptures are generally considered to be less common than acute free wall ruptures. In recent studies, with high autopsy rates, 21 to 42% of all postinfarction free wall ruptures followed a subacute course.[156,161,162]

Because of its rarity, the natural history of false aneurysm of the left ventricle has not been established.[138] It is believed to have a poor prognosis because of its high probability of rupture;[142,163,164] however, there are patients in whom the diagnosis was made many years after MI.[141,165,166] The increasingly wide application of echocardiography after AMI gives promise of altering clinical outcome for many patients with the various forms of ventricular wall rupture.

Preoperative Management

Usually, the sequence of events leading to death is so rapid in patients with acute rupture of the free wall of the left ventricle that there is not enough time for surgical intervention.[138] These patients usually die within minutes of the onset of recurrent chest pain.[160] However, a high index of suspicion, combined with a novel technique of percutaneous intrapericardial infusion of fibrin glue immediately following pericardiocentesis,[167,168] may afford at least a chance of survival in this surgically untreatable subgroup of patients.

In contrast, patients with subacute left ventricular rupture can be saved with surgery. Once the diagnosis of rupture of the free wall is established, the patient should be immediately transferred to the operating room. No time should be wasted attempting to perform coronary angiography.[136,141,166,175] Inotropic agents and fluids should be started while preparing for surgery. Pericardiocentesis often improves hemodynamics temporarily,[169] and insertion of an intra-aortic balloon pump may be beneficial, even though the principal problem is cardiac tamponade.[158]

The timing of surgery following the diagnosis of false aneurysm of the left ventricle is dependent upon the age of the MI. When a false aneurysm is discovered within the first 2 to 3 months after coronary infarction, surgery is urgently recommended after coronary angiography and ventriculography because of the unpredictability of rupture.[144,172] However, when the diagnosis is made several months or years after MI, the urgency of the operation is not determined so much by the risk of rupture, but rather by symptoms and the severity of the CAD.[138,165]

Operative Techniques

Subacute rupture of the free wall

As soon as the diagnosis of rupture of the free wall of the left ventricle is confirmed by echocardiography, the patient should be transferred to the operating room. In patients with tamponade, severe hypotension may result during the induction of anesthesia. Therefore, we usually complete the sterile preparation and draping of the patient before inducing anesthesia. Some even advocate femoral artery cannulation before the induction of anesthesia.[170] A median sternotomy is performed and upon decompressing the pericardium, the blood pressure commonly rises quickly. This should be anticipated and controlled because hypertension can cause ventricular bleeding to start again, or may even increase the size of the ventricular rent.[138] In most cases, however, the ventricular tear is sealed off by clot, and there is no active bleeding.

Traditionally, postinfarction rupture of the free wall of the left heart has been repaired on cardiopulmonary bypass;[146,157,158,160,170,171] however, some surgeons have suggested that cardiopulmonary bypass is not necessary except perhaps in patients with posterior wall rupture, severe mitral regurgitation, ventricular septal rupture, or graftable CAD.[138,169] Although the ventricular tear can be repaired without aortic cross-clamping, cardiac standstill and left ventricular decompression make the procedure

easier when the rupture is in the posterior wall of the left ventricle.[138]

The term *ventricular double rupture* has been applied when there is rupture of two of the following three structures: the ventricular septum, the ventricular free wall, and papillary muscle.

Four surgical techniques have been used to control ventricular rupture. The first technique involves closing the rent with large horizontal mattress sutures buttressed with two strips of Teflon felt.[129] This method is not recommended because the sutures are placed into necrotic, friable myocardium that can easily tear. The second method combines infarct excision and closure of the defect with interrupted, pledgeted sutures[130,158,170] or a Dacron patch.[172,173] This method usually requires aortic cross-clamping and is probably best reserved for those patients who have an associated VSD.[160] The third technique, described by Núñez and colleagues,[160] involves closing the defect with horizontal mattress sutures buttressed with two strips of Teflon felt, and then covering the closed ventricular tear and surrounding infarcted myocardium with a Teflon patch sutured to healthy epicardium with a continuous polypropylene suture (Fig. 29-17). Good control of active ventricular hemorrhage has been achieved with this method. The fourth method consists of simply gluing a patch of either Teflon[169] or autologous glutaraldehyde-preserved bovine pericardium to the ventricular tear and infarcted area using a biocompatible glue of either fibrin (Tissucol, Immuno AG, Vienna, Austria), butyl-2-cyanoacrylate monomer (Histoacryl Blue, B. Braun, Melsungen AG, Germany), or gelatin-resorcin-formaldehyde (Pharmacie Centrale, C.H.V. Henry Mondor, Créteil, France). This technique does not necessarily require institution of cardiopulmonary bypass and may be the repair of choice when the ventricle is not actively bleeding.[169]

False aneurysm of the left ventricle

Acute false aneurysms are probably best repaired with an endocardial patch using the same methods as those used in repairing true ventricular aneurysms.[138] Chronic anterior false aneurysms can usually be closed primarily if the neck is fibrotic. However, primary closure of the neck of a posterior false aneurysm may exacerbate mitral regurgitation, and it therefore probably should be reconstructed with a patch of Dacron graft or glutaraldehyde-fixed bovine pericardium.[141,144]

Results

Subacute rupture of the free wall

The surgical experience with this entity is largely anecdotal. The single largest experience with surgical repair of postinfarction left ventricular free wall rupture was reported by Padró and colleagues.[169] They treated 13 patients using a Teflon patch glued onto the ventricular tear and surrounding infarcted muscle, and utilized cardiopulmonary bypass in only 1 patient who presented with a posterior defect. All of their patients survived and were alive after a mean follow-up of 26 months. Eleven of them were asymptomatic and two had exertional angina.[169] Núñez and associates[160] operated on seven patients, four of whom survived. Recently the use of unsupported felt secured with cyanoacrylate glue has been described by several authors with encouraging results.[158,173,174]

In ventricular double rupture involving the free wall and the septum, a recent series achieved an operative survival of 60% in five patients.[175] Four of the patients initially had only septal rupture but progressed to include free wall rupture, making this diagnosis a consideration in acute deterioration of medically managed patients with postinfarct VSD.

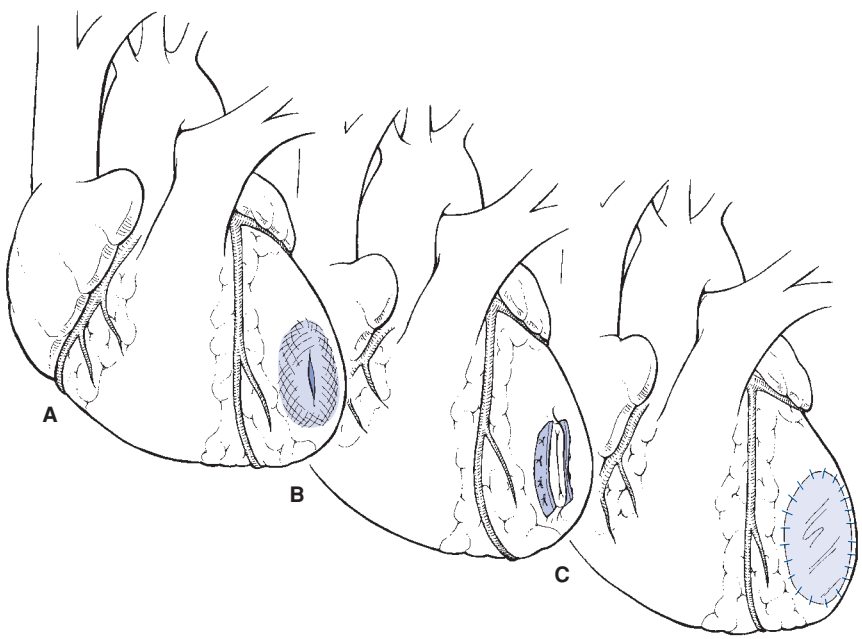

Figure 29-17. Technique to repair rupture of the free wall of the left ventricle. (A) Left ventricular free wall rupture. (B) A limited infarctectomy is closed with horizontal mattress sutures buttressed with two strips of Teflon felt. (C) Then the whole area is covered with a Teflon patch sutured to healthy epicardium with a continuous polypropylene suture. Alternatively, the Teflon patch can be glued to the ventricular tear and the infarcted area using a biocompatible glue. *(Adapted with permission from David.[138])*

Although operative risk cannot be determined from these small numbers, it is likely that without surgery all these patients would have died, and patients who survive surgery tend to do well afterward.[138]

False aneurysm of the left ventricle

Komeda and David[141] treated 12 patients with postinfarction left ventricular false aneurysms; four of them also had mitral valve replacements, one had repair of a fistula between the false aneurysm and the right ventricle, and nine had coronary artery bypass surgery. There were three operative deaths, all in patients who needed mitral valve replacements. Of the eight patients who underwent isolated repair of false aneurysms, all were alive after a mean follow-up of 62 months. Seven patients were asymptomatic and one had angina pectoris.[141] Mackenzie and Lemole[143] reported 14 cases of left ventricular false aneurysm, 12 of which were related to a previous MI. There were three operative deaths. Long-term follow-up was not reported.

Overall, the literature suggests that patients who have isolated repair of false aneurysms of the left ventricle have low operative mortality.[138]

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CHAPTER 30

Ischemic Mitral Regurgitation

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Ischemic mitral regurgitation (IMR) is associated with poor long-term outcome and survival. Although extensive research regarding its mechanism has been conducted, the optimal management of IMR remains elusive. Clinical studies in the past often included mitral regurgitation of nonischemic origin, leading to confusion and incorrect conclusions regarding the true long-term outcome of IMR and its natural history. Recognition of this has improved our understanding of the mechanisms and natural history of IMR.

IMR, often termed *functional mitral regurgitation,* is mitral insufficiency as a result of myocardial infarction or ischemia.[1–6] By definition, the mitral valve leaflets are normal. Whether owing to acute rupture of papillary muscles or chronic changes in left ventricular geometry and remodeling, IMR ultimately is due to ischemic injury to the myocardium. It is important to distinguish IMR from mitral regurgitation resulting from other etiologies. Mitral regurgitation often is associated with coronary artery disease without a direct cause-and-effect relationship. The prevalence of coronary artery disease[7] makes the association of myocardial infarction and nonischemic mitral regurgitation a common clinical entity. IMR also must be distinguished from mitral insufficiency owing to degenerative, rheumatic, congenital, and infectious etiologies. Although likely a related process of left ventricular remodeling, idiopathic dilated cardiomyopathy associated with mitral regurgitation also should be distinguished from IMR.

The wide clinical spectrum of IMR is due to the fact that the disease is a manifestation of postinfarction ventricular remodeling. The size, location, and transmurality of the myocardial infarction (MI) sets in motion left ventricular remodeling that determines the severity, time course, and clinical manifestations of IMR. The presentation may be either acute (with or without papillary muscle rupture and immediately life-threatening) or develop insidiously over time in association with congestive heart failure (CHF).

PREVALENCE

The advancement in catheter-based intervention for coronary artery disease has resulted in improved survival in ischemic heart disease. This improvement in survival most likely will result in an increasing number of patients who subsequently will develop left ventricular dysfunction and IMR. Although many of the previous series[8–13] did not distinguish IMR from other etiologies accurately, the data do give us a reflection of the magnitude of this clinical entity.

Early after an acute myocardial infarction (AMI), between 17% and 55% of patients develop a mitral systolic murmur or echocardiographic evidence of IMR.[2,14–16] Of patients who have cardiac catheterization within 6 hours of the onset of symptoms of AMI, 18% have IMR.[4] In 3.4% of these patients, the degree of mitral insufficiency is severe.[4] Many of the murmurs early after AMI are transient and disappear by the time of discharge.[2,15]

In one study, 19% of 11,748 patients who had elective cardiac catheterization for symptomatic coronary artery disease (CAD) had ventriculographic evidence of mitral regurgitation (MR).[17] In most of these patients, the degree of mitral insufficiency was mild, but in 7.2% of patients the degree of regurgitation was 2+ or greater, and in 3.4% MR was severe with evidence of heart failure.[17] In another study of consecutive cardiac catheterizations, 10.9% of 1739 patients with CAD had MR.[18]

Collectively, these data indicate that IMR is frequent early after AMI but in many patients is mild or disappears completely. The relatively high incidence of IMR (10.9 to 19%) in catheterized patients with symptomatic CAD suggests that chronic IMR persists in many patients after AMI and may develop subsequently in others.[15] Approximately 12.6 million Americans have angina or a history of MI, and untold millions more have asymptomatic coronary atherosclerosis.[7] Using these figures,[7,17,18] the incidence of IMR in

the United States is estimated to be 1.2 to 2.1 million patients, with approximately 425,000 patients having moderate or severe IMR with heart failure.[7,17]

CLASSIFICATION

IMR traditionally has been classified based on the time course of clinical presentation. Acute IMR occurs in the immediate postinfarction period, and patients are often in hemodynamic distress. Fortunately, this population of patients represents a minority of patients with IMR. Chronic IMR represens the clinical presentation for the majority of patients with IMR. The presentation is one of progressive and insidious nature and often is associated with decremental decrease in left ventricular function.

Carpentier's classification for MR provides an insightful way to approach the specific mechanisms of IMR (Fig. 30-1). It is a functional classification and categorizes the improper leaflet coaptation of MR into three types based on leaflet and chordal motion. In type I, the leaflet motion is normal, and MR is a result of mitral annular dilatation. Type II is MR as a result of leaflet prolapse or excessive motion. In type III, there is leaflet restriction, or tethering, and this type is subclassified further into IIIa (i.e., tethering during diastole) and IIIb (i.e., tethering during systole).

IMR can result from type I, type II, or type IIIb dysfunction. Acute postinfarct MR can be a result of type II dysfunction, where there is papillary muscle rupture. However, acute IMR is associated more often with much more subtle changes in the mitral valve apparatus. Chronic IMR can be a result of type I or type IIIb dysfunction. Pure annular dilatation with normal leaflets (type I) results from left ventricular remodeling and its geometric sequelae on the mitral valve apparatus. Type IIIb is the more common dysfunction associated with chronic IMR, and it is the result of papillary muscle displacement and tethering of leaflets. Often, both type I and type IIIb dysfunctions are seen in patients with chronic IMR and cardiomyopathy. The pathophsyiology is a result of left ventricular remodeling as a consequence of ischemia and will be discussed in detail in the next section.

PATHOPHYSIOLOGY

Normal Valve Function

The mitral valve has six anatomic components: leaflets, chordae tendineae, annulus, papillary muscles, left ventricle, and left atrium. The mitral annulus is saddle-shaped (actually a hyperbolic paraboloid with two-directional curvature) with cephalad promontories near the midportions of the anterior and posterior leaflets and caudad depressions at the commissures[19] (Fig. 30-2). This unique shape is present in all mammalian mitral valves and has been shown, using finite-element analysis, to reduce leaflet, annular, and chordal stress.[20] Function of the normal mitral valve is complex and involves precisely timed interactions among the six components. These interactions are described most easily by relating the changes in each of the six components during a cardiac cycle. For this description, the cardiac cycle is divided into four periods: systole, diastole, isovolemic relaxation (IVR), and isovolemic contraction (IVC), as defined below.

End-systole (ES) is defined as the maximum negative left ventricular *dP/dt*,[21] and *end-diastole* (ED) is defined as the peak of the QRS complex. *End isovolemic contraction* (EIVC) is defined as the first time point at which the aortic root *dP/dt* is greater than zero. *End isovolemic relaxation* (EIVR) is defined as the time at which the left ventricular pressure (LVP) is 10% of LVP_{max} and the left ventricular $dP/dt < 0$.[21]

During IVC, *left atrial* filling begins immediately after the mitral valve closes and before the aortic valve opens.[22]

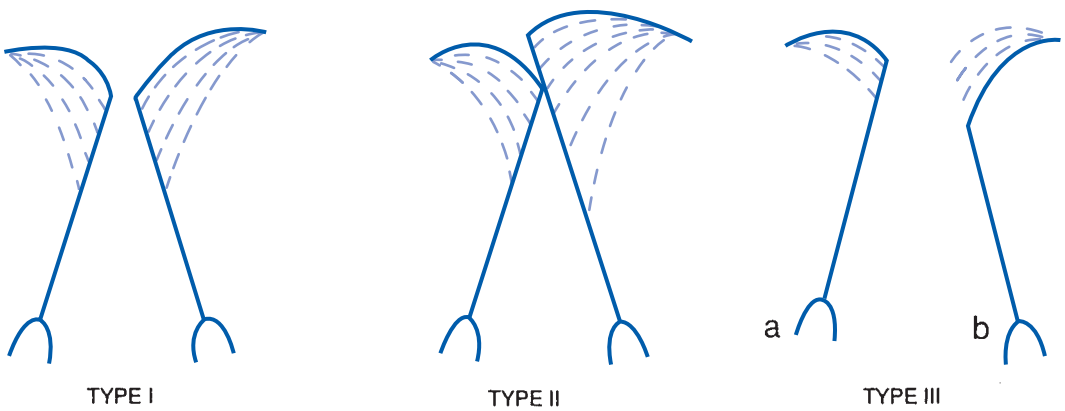

Figure 30-1. Carpentier's functional classification of mitral regurgitation. In type I, the leaflet motion is normal, and mitral regurgitation is a result of mitral annular dilatation. In type II, there is leaflet prolapse or excessive motion. In type III, there is leaflet restriction or tethering, and this type is subclassified further into IIIa (tethering during diastole) and IIIb (tethering during systole). (*Used with permission from Carpentier A: Cardiac valve surgery: The "French correction." J Thorac Cardiovasc Surg 1983; 86:323.*)

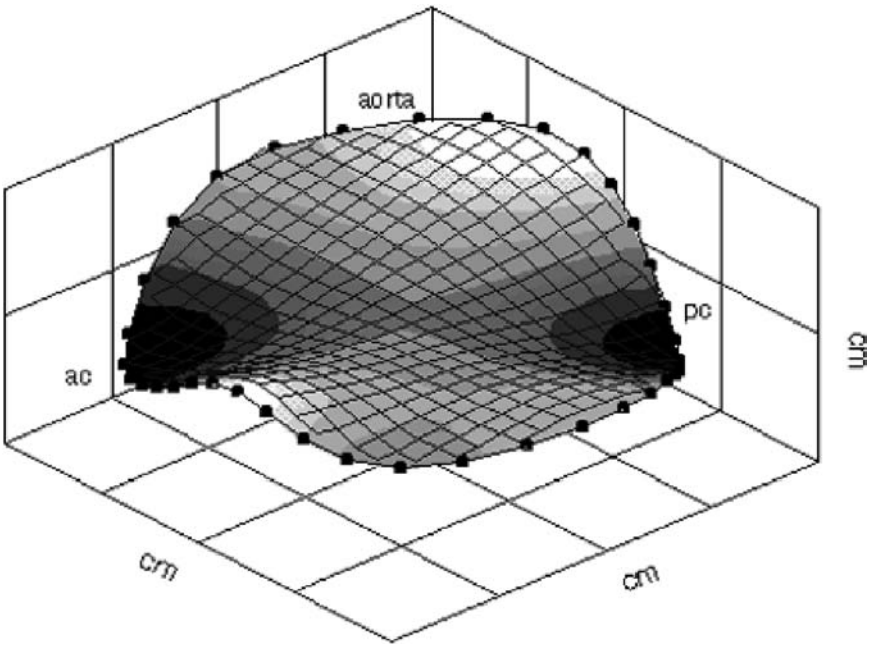

Figure 30-2. Image of a human mitral annulus obtained using three-dimensional transesophageal echocardiography (TEE). The image is reconstructed from two-dimensional images sampled every 10 degrees using a rotational omniprobe gated for heart rate and respiration. The annulus is viewed from posterior annulus (*near*) to aorta (*far*). The pronounced saddle shape of the human mitral annulus is well demonstrated.

Flow through the mitral valve briefly reverses as the leaflets coapt and bulge toward the atrium.[23]

During systole, the left atrium fills rapidly[22] and reaches maximum near ES. The position of the *annulus* ascends (away from the apex) slightly during atrial contraction,[22,24,25] which occurs during late diastole, does not change during IVC, and descends progressively 1 to 1.5 cm toward the apex throughout systole.[22,25,26] The annulus contracts asymmetrically[26,27] during atrial and ventricular systole and in humans reaches a minimal area (mean reduction of 27%) in midsystole.[28] Immediately after atrial contraction, the mitral *leaflets* approach each other and close within 20 to 60 ms after pressure crossover when LVP exceeds left atrial (LA) pressure.[22] Since the total area of leaflet tissue is approximately twice the total area of the annulus,[29,30] the apposition point of the two leaflets at the time of pressure crossover is very near the plane of the annulus.[31,32] At closure, approximately 30% of the anterior cusp and 50% of the longer posterior cusp are in apposition.[31] *Chordae tendineae* attached to the free edges and body of the leaflets[31] restrict the upward movement of the slightly compliant leaflets and produce a tight seal along the line of apposition.[31] Chordal tension peaks in early systole and begins to fall slowly in late systole and rapidly during IVR.[33] *Papillary muscles* begin to shorten during late IVC and throughout systole in synchrony with shortening of the adjacent ventricular wall.[34] The actual distance the papillary muscles shorten is small and ranges between 2 and 4 mm.[35,36] During systole, the directions and timing of *left ventricular* contraction are not necessarily uniform throughout because of the complex anatomic arrangement of muscle bundles[37,38] and the timing produced by the impulse-conduction pattern.[39] Left ventricular shortening is greater in both equatorial axes than in the long axis.[39] Left ventricular wall thickness increases during IVC and decreases rapidly during IVR.[40] Peak wall thickness occurs near ES, but timing of the exact peak varies slightly between ventricular wall segments. During systole, the ventricle twists counterclockwise progressively (as viewed from the apex) along its longitudinal axis to reach a maximum at ES.[41]

During IVR, the *left atrium* begins to empty when LA pressure crosses over and exceeds LVP.[22,23] The atrium empties rapidly in early diastole and diminishes further with atrial contraction in late diastole just before IVC.[42] The left ventricle actually may generate negative pressure in early diastole if LA pressures are low.[43] During IVR, the *mitral annulus* to left ventricular apex distance lengthens as the mitral annulus ascends in early diastole, descends slightly, and ascends again with atrial contraction.[22,27] The area of the mitral orifice increases slightly during IVR and continues to increase during diastole until it reaches a maximum just before the left atrium contracts.[27,28] In humans, the annular area index reaches a maximum of 3.9 ± 0.7 cm^2/m^2.[28] As the annular area increases, its shape changes asymmetrically; most of the area increase is due to lengthening in the posterior and lateral parts of the annulus (away from the fibrous trigone).[27] During IVR, the *mitral leaflets* separate approximately 30 ms before LA pressure exceeds LVP.[22] Peak blood flow through the valve occurs early in diastole, but the mitral leaflets reach their maximal open position *before* peak flow occurs and begin closing while flow is still accelerating.[44]

The *papillary muscles* may shorten very slightly during early IVR[21,34,36,45] but do not begin to lengthen until the beginning of diastole. Papillary muscles reach maximum length shortly after ED during IVC. *Chordal tension* decreases rapidly during IVR and remains near zero until late diastole, when a small increase occurs.[33,44] The *left ventricle* relaxes and dilates after ES and reverses the complex

deformations of left ventricular shape produced by systole. During early diastole and the period of rapid filling, the ventricle dilates primarily along both equatorial axes and much less along the longitudinal base-to-apex axis.[39] Only a little shape change occurs in middiastole and after atrial contraction. Ventricular wall thickness decreases[40] primarily during IVR. Lastly, the ventricle untwists rapidly (rotating clockwise) during early diastole and more gradually during middle and late diastole.[41]

Mechanism of IMR

Acute IMR

Papillary muscle rupture is a rare complication, occurring in 1 to 5% of patients who die after MI.[46] The rupture involves the posteromedial papillary muscle in approximately two-thirds of acute, severe IMR.[15,46–48] This is due to the fact that the vascular supply to the posteromedial papillary muscle depends on one coronary artery (the right coronary artery, or the circumflex artery in a left-dominant system), whereas the anterolateral papillary muscle receives dual supply from the left anterior descending and circumflex arteries.[49] Papillary muscle rupture results in prolapse of the mitral leaflets, often causing severe acute IMR and hemodynamic instability. Acute MR in this setting carries a poor prognosis with high mortality rate.[46,47,50–52]

However, acute IMR often occurs with subtle changes in the mitral valve apparatus in the absence of leaflet prolapse. Annular dilatation traditionally has been regarded as the mechanism of acute IMR. Laboratory work involving an ovine model from the Stanford group has demonstrated the importance of the septolateral (SL) dimension of the mitral annulus in the pathophysiology of IMR.[53–55] The SL dimension, the vertical distance of the mitral annulus from the middle of the anterior annulus to the middle of the posterior annulus, is referred to clinically as the *anteroposterior* (AP) dimension. Timek and colleagues demonstrated that correcting SL distance alone may abolish acute IMR.[54]

However, other experimental studies have demonstrated subvalvular geometric changes as an important contributor to the pathophysiology of acute IMR. With ischemia or infarction, the posterior papillary muscle elongates 2 to 4 mm in the sheep and dog[34,36]; the tip moves 1.5 to 3 mm closer to the annulus.[36,56] In the sheep model of acute IMR, the uninfarcted anterior papillary muscle contracts earlier and more vigorously than before infarction. This moves the tip 4 to 5 mm further away from the annular plane at midsystole than before infarction.[57] The Stanford group has meticulously characterized this discoordination of normal synchronous papillary muscle contraction and its complex effect on leaflet coaptation.[58,59] More recently, Tibayan and colleagues demonstrated that by using mitral suture annuloplasty (Paneth type), altered annular and subvalvular geometry can be corrected, and acute IMR is abolished.[60] Neilsen and colleagues in a pig model of acute IMR demonstrated that imbalanced chordal force distribution is directly related to the development of acute IMR.[61] The authors showed a decrease in tension of the primary chorda from the ischemic posterior left ventricular wall to the anterior leaflet, whereas the tension of the chorda from the nonischemic anterior left ventricular wall to the anterior leaflet increased.

These data suggested that acute IMR is a result of complex interaction of small changes in the mitral valvular complex and not merely simple annular dilatation, as believed previously.[57,62,63] These small changes are difficult to demonstrate by standard imaging technique, making repair challenging in this acute setting. In addition, recent finite-element analysis of the mitral annulus has suggested an association between the normal annular saddle shape of the mitral valve and its competency.[64] Current repair techniques use ring annuloplasty that is essentially flat. Future investigation and more thorough understanding of the mitral apparatus will be needed to improve the results of mitral valve repair.

Chronic IMR

In chronic IMR, mitral valve prolapse has been described[65] in occasional patients, but the vast majority have incomplete mitral valve closure owing to the effect of left ventricular remodeling. Remodeling often manifests as annular dilatation with papillary muscle and chordal restriction of leaflet motion.[65–70,71] Pathologic studies consistently show fibrosis and atrophy of infarcted papillary muscles,[3,15,29,72] and none demonstrate papillary muscle or chordal elongation. Nevertheless, surgeons describe elongated chordae in some patients with MI and MR.[5,73,74] Elongated chordae and mitral valve prolapse without MR probably antedate the infarction in these patients.[75,76] In a patient with pre-existing mitral valve prolapse, ventricular infarction may cause the previously competent valve to leak. This hypothesis explains sporadic observations of mitral valve prolapse in patients with chronic IMR but needs preinfarction echocardiograms for confirmation.

Ovine experiments using sonomicrometry array localization to study postinfarction MR that evolves during the first 8 weeks after MI have added insight relevant to the pathogenesis of chronic IMR. As a result of ischemic left ventricular remodeling, a combination of asymmetric annular dilatation and leaflet tethering by *both* papillary muscles occurs to alter the normal saddle shape of the annulus and produce chronic IMR.[77] Previously thought to be fixed, the anterior portion of the annulus does dilate.[78] The intertrigonal distance has been shown to increase, in addition to the increase in the SL dimension.[79] The annular area dilates by at least 60% at all time points during systolic ejection, but the dilatation involves all the muscular annulus. The posterior or mural portion of the annulus directly adjacent to the infarct moves away from the relatively fixed anterior commissure (at the anterior fibrous trigone) and stretches the anterior portion of the mural annulus and the posterior portion of the aortic-based annulus, which are remote from the infarct. This finding illustrates how a moderately sized (21% of the left ventricular mass) localized infarct remodels and distorts remote, uninfarcted myocardium, including the mitral valve annulus[80] (Fig. 30-3A).

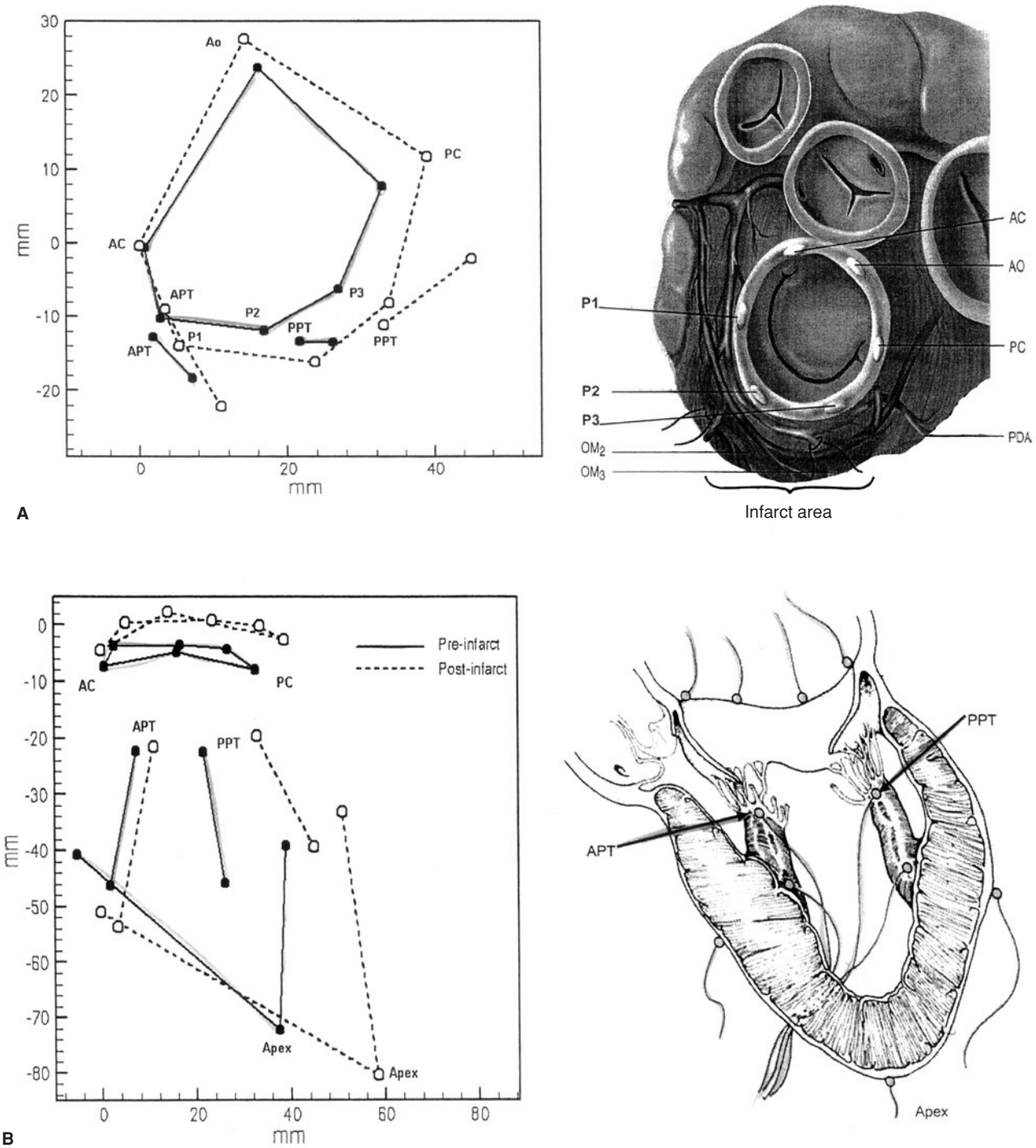

Figure 30-3. (*A*) (*Left*) Two-dimensional axial view of the mitral valve annulus and papillary muscle transducers before (*solid line*) and 8 weeks after (*dashed line*) infarction. (*Right*) An artist's drawing of how the transducers are placed in relation to the mitral annulus and the location of the infarct. Note the stretching of both the posterior part of the aortic portion of the annulus (Ao to PC) and the anterior part of the mural portion of the annulus (Ao to P1 to P2). Also note how the portion of the annulus between P2 and PC along with the posterior papillary muscle tip (PPT) pulls away from the relatively fixed anterior commissure. (*B*) (*Left*) Two-dimensional sagittal view of the sheep mitral annulus and its relationship to the left ventricle and papillary muscles before and 8 weeks after infarction. (*Right*) An artist's drawing is provided for orientation of the sonomicrometry transducers. Note how the PPT and the posterior annulus are retracted away form the anterior commissure. The heart shown in this figure is the same one shown in Fig. 30-2. (*Used with permission from Gorman JH III, Gorman RC, Jackson BM, et al: Annuloplasty ring selection for chronic ischemic mitral regurgitation: Lessons from the ovine model. Ann Thorac Surg 2003; 76:1556.*)

Lateral displacement of the posterior papillary muscle appears to play a major role in the development of chronic IMR.[79] Interestingly, the posterior papillary muscle tip to posterior commissure relationship does not change significantly. Both these points are displaced *together,* away from the relatively fixed anterior commissure as a result of the remodeling process (see Fig. 30-3*B*). This indicates that posterior papillary muscle tethering is more pronounced at its most anterior connection with both leaflets near the center of the coaptation line and not at the commissure. The anterior papillary muscle tip is displaced significantly from both commissures but further from the posterior commissure. This indicates the tethering effect of the anterior papillary muscle is greatest along both leaflets from the anterior commissure to the middle of the coaptation line. Together these findings suggest that in this model the postinfarction ventricular remodeling process tethers the anterior portion of both leaflets.

The concept of leaflet tethering as a contributing factor in the pathogenesis of chronic IMR is not new.[70,81,82] Two recent echocardiographic reports, one studying the same sheep model presented here and one human study, demonstrated findings consistent with the experimental results cited earlier. Otsuji and colleagues applied a very effective three-dimensional echocardiographic technique to quantify leaflet tethering in the same ovine model.[81] These authors also reported midsystolic distortions between both papillary muscle tips and the anterior commissure but did not observe changes between papillary muscle tips and the posterior commissure or annular dilatation. Yiu and colleagues used quantitative two-dimensional echocardiography to corroborate these findings clinically by comparing normal control individuals with a cohort of patients with varying degrees of chronic IMR.[70] They found that ventricular distortions, which most closely correlated with the degree of MR, occurred between the posterior papillary muscle tip and the anterior commissure ($R = 0.55$) and posterior displacement of the anterior papillary muscle tip ($R = 0.65$).

To summarize, the geometric changes that lead to acute IMR are multiple but extremely subtle (<5 mm) and are not reliably imaged by currently available clinical imaging modalities. Chronic IMR involves larger changes (1 to 2 cm) that cause moderate annular dilatation and complex leaflet tethering along the anterior and midleaflet coaptation line. It is a process resulting from complex geometric alteration of the mitral valve apparatus as a result of ischemic left ventricular remodeling.

CLINICAL PRESENTATION AND MANAGEMENT

Acute IMR

Clinical presentation

Clinically, acute IMR usually presents abruptly with chest pain and/or shortness of breath. The presentation is that of an AMI and occasionally may be silent.[46,47,51] These patients often are hemodynamically unstable and in cardiogenic shock. They often are in extremis with symptoms of CHF. These symptoms including pulmonary edema, systemic hypotension, and oliguria, acidosis, and poor periperhal perfusion. On physical examination, most patients will have a loud apical holosystolic murmur that radiates to the left axilla.

Nearly all electrocardiograms (ECGs) are abnormal,[46,47,51] but only slightly more than half are diagnostic of AMI. Some of the nondiagnostic changes include right or left bundle-branch block and nonspecific ST- and T-wave changes in the anteroseptal, lateral, or inferior leads.[46,47,50,51] Most patients are in sinus rhythm.[51,83] In autopsy series, the incidence of subendocardial infarctions is approximately equal to the incidence of transmural infarctions.[46,47] Frequently patients with ruptured papillary muscle have electrocardiographic evidence of an inferior infarction. When the ECG is diagnostic, inferior wall infarctions are much more common than anterior and lateral wall infarctions. Conduction abnormalities are relatively uncommon and are found more often in patients with postinfarction ventricular septal defects.[84]

Chest x-rays nearly always show signs of pulmonary congestion, interstitial pulmonary edema, and pulmonary venous engorgement.[51] Cardiomegaly usually is not present, and there usually are no signs of LA enlargement.[46]

The differential diagnosis includes postinfarction ventricular septal defect, massive AMI without significant MR, and ruptured chordae tendineae without AMI. Right-sided heart catheterization usually shows elevated pulmonary arterial pressures with prominent *v* waves reaching 40 mm Hg or higher.[51,85] Mean pulmonary artery wedge pressures are greater than 20 mm Hg unless cardiac output is very low. Mixed venous oxygen saturations often are well below 50% and reflect low cardiac output, with indices that range from 1.0 to 2.9 L/m^2 per minute.[85] In the presence of a loud systolic murmur, absence of an oxygen stepup in the pulmonary artery is strong evidence against the diagnosis of postinfarction ventricular septal defect. Electrocardiographic evidence of AMI distinguishes acute IMR from acute chordal rupture, but in some instances the two diseases cannot be distinguished until after operation or death.[51]

Transthoracic echocardiography (TTE) assesses the degree of MR, confirms wall motion abnormalities, and may demonstrate flail mitral leaflets. Transesophageal echocardiography (TEE) is the diagnostic imaging tool of choice. This modality definitively documents the degree and characteristics of the MR jet, associated wall motion abnormalities, and the status of the posterior papillary muscle.[86,87] The information provided by TEE is vital in the decision to repair versus replace the mitral valve. Typically, the left atrium is not enlarged, but the left ventricle shows signs of volume overload and segmental wall motion abnormalities. Color-flow Doppler velocity mapping documents the presence of MR after MI[88] and semiquantitates its severity.[89] Ejection fractions vary widely but do not reflect the extent of the left ventricular infarction.

Despite hemodynamic instability, most patients have a diagnostic cardiac catheterization primarily for definition of coronary arterial anatomy; however, the wisdom of prescribing cardiac catheterization for patients in cardiogenic shock is highly questionable in that revascularization of obstructed, remote coronary vessels is not likely to improve a patient's chances for immediate survival.[93] Approximately half of catheterized patients have single-vessel disease, most often of the right coronary artery.[51,85] Most of the remainder have three-vessel disease.[46,47,50,51] Ventriculography shows increased left ventricular volume at both end-diastole and end-systole, severe MR, segmental wall motion abnormalities,[90] and a wide range of ejection fractions, which are generally over 40% and frequently over 60%.[50,85] Left ventricular end-diastolic pressures are elevated with prominent left atrial *v* waves and moderate pulmonary hypertension. Occasional patients have mild or moderate tricuspid regurgitation. Cardiac output usually is low.

Indications for surgery

Prompt surgery is the best chance for survival for most patients with acute, severe postinfarction MR. The goal of medical therapy is to stabilize the patient and to optimize circulatory status in preparation for surgical intervention. A few highly selected patients without papillary muscle rupture early in their presentation have been treated by emergency percutaneous transluminal coronary angioplasty (PTCA) and/or thrombolytic therapy in an attempt to reduce the size of the infarct and thereby reduce MR.[4,65,91,92] PTCA or thrombolysis carried out within 4 hours of the onset of AMI on occasion may produce spectacular reversal of both the infarction and MR.[65,91,92] However, less rapid PTCA may not succeed in pre-empting the infarct and aborting MR.[92] PTCA and thrombolysis in catheterized patients are potentially worth trying if patients reach medical attention soon after the onset of symptoms, are sufficiently stable, and can be followed by echocardiography. However, in many patients, PTCA and thrombolysis do not provide a favorable outcome.[4] In one study, 17% of patients with acute IMR and successful thrombolysis died in the hospital; in those with successful PTCA, 50% died shortly afterward, and 77% were dead in 1 year.[4] Of the survivors, the majority continue to have 3+ or 4+ MR.[4]

For patients who have acute postinfarction angina with 1+ or 2+ MR, urgent myocardial revascularization is indicated to relieve angina and to prevent extension of the infarction. It is important to prevent progression of MR and the development of CHF or cardiogenic shock. This usually is accomplished by thrombolysis, PTCA, or an intracoronary arterial stent. If these measures are unsuccessful, operation is rarely completed in time to reverse the infarction, but early operation may reduce the size of the ultimate infarct.[93–95] The presence of mild to moderate IMR does not increase operative mortality,[96–98] but the presence of CHF is a risk factor.[99] In these patients, the mitral valve generally is not addressed unless intraoperative TEE indicates 3+ or 4+ MR.

Indications for emergency surgery for acute, severe postinfarction MR vary among institutions[4,48,51,52,85,100,101] and probably explain wide discrepancies in reports of hospital mortality.[100,102] In this group of patients, medical therapy does not produce survivors,[50,51] and patients denied operation are not reported.[51] Aged patients are less likely to survive operation,[65,102] and there are only anecdotal reports of successful operation in octogenarians.[103] Other risk factors for hospital death are severe CHF, the number and severity of comorbid diseases such as renal or pulmonary problems, presence of an intra-aortic balloon pump, reduced ejection fraction, and greater number of diseased coronary arteries.[66] Contemporary concerns regarding costs and longevity beyond immediate hospital survival also influence indications for operation and reported mortality.

Operation for acute, severe postinfarction MR consists of mitral valve repair or replacement with or without myocardial revascularization. Nearly all surgeons recommend revascularization of all significantly obstructed coronary vessels away from the site of the infarction.[100] Improved methods of cardioplegia and the open-artery hypothesis support this recommendation even in patients with preoperative cardiogenic shock who have had cardiac catheterization. The wisdom of blind revascularization of remote coronary vessels in patients who have not had preoperative cardiac catheterization and revascularization of the infarct artery more than 4 to 6 hours after onset of pain is less clear.[48] On a statistical basis, only half of patients with acute IMR have multivessel coronary artery disease.[46,51,85] Revascularization of completed infarctions favorably influences subsequent ventricular remodeling.[94–96]

With echocardiographic findings amendable to repair, most surgeons will consider mitral valve repair in the acute setting. Echocardiographic findings favorable to repair include a simple, central regurgitant jet, minimally tethered leaflets, and no papillary muscle pathology such as rupture. However, replacement of the diseased valve should be considered if the effectiveness and durability of the repair are in question. These patients often are critically ill[6] and will not tolerate mitral valve replacement after failed mitral repair. When performing mitral valve replacement, it is important to preserve the chordal attachments to the annulus (Fig. 30-4). The prosthetic valve is sutured to the annulus with running or interrupted sutures. A bioprosthestic valve is a reasonable choice because anticoagulation is not benign and durability is relatively a minor concern in these patients with poor long-term prognosis.[5,6]

Results

Published results of mitral valve replacement for acute IMR are poor.[48,51,52,85,100,102,104] Hospital mortality ranges from 31 to 69% and probably reflects the selection process more than the quality of care. Variables that increase early mortality include patient age, cardiogenic shock, comorbid conditions, the amount of infarcted myocardium, and delay in operation.[50,51,85,102] More recent experience may be better[5,6,105] because of prompt diagnosis, early surgery, complete

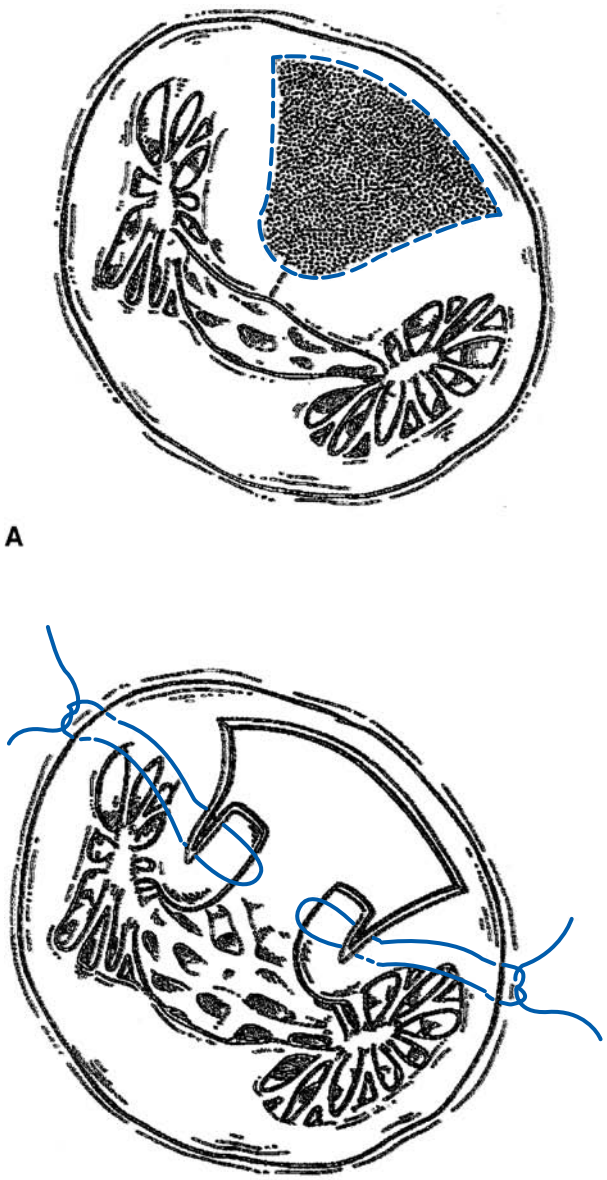

Figure 30-4. Okita's method for retaining chordal attachment to the mitral annulus during replacement of the mitral valve. (A) Diagram showing the mitral valve from the left atrium. The center of the anterior leaflet is excised (*shaded area*), and the leaflet is divided, retaining the chordae from each papillary muscle attached to the residual anterior leaflet tissue. The posterior leaflet may be divided at its midpoint if necessary. (B) Remnants of the anterior leaflets are sutured to the annulus using a single stitch as shown. This tissue is later included in sutures used in sewing the valve to the annulus. (*Modified slightly with permission from Okita Y, Miki S, Kusuhara K, et al: Analysis of left ventricular motion after mitral valve replacement with a technique of preservation of all chordae tendineae. J Thorac Cardiovasc Surg 1992; 104:786.*)

revascularization, and application of chordal preservation techniques that better preserve left ventricular function.[106–110] Several techniques are available for preserving chordae[106,111,112] (see Fig. 30-4). David reported a hospital mortality of 22% in 18 patients using chordal preservation techniques.[105]

Many surgeons do not recommend mitral valve repair for acute IMR,[6,48,51,101,105] but others do.[5,66,111,113] Repair of the valve in acute IMR poses difficult problems. As demonstrated earlier, the anatomic derangements may be very subtle. A reasonable repair option therefore is undersized ring annuloplasty. In cases of papillary muscle rupture, successful reimplantation in conjunction with ring annuloplasty has been reported, but these patients are uncommon and usually much less ill.[5] Intraoperative TEE and color-flow Doppler velocity mapping are essential adjuncts to operation to assess the quality of the repair.[86,87] Long-term (5-year) survival in patients who survive the perioperative period is poor and even in modern reports hovers around 50%.[5,6] Even with the poor prognosis, we believe that mitral valve ring annuloplasty is a reasonable option for pathology amendable to repair.

Chronic IMR

Clinical presentation

Chronic IMR represents the majority of patients with IMR. Between 10.9% and 19.0% of patients with symptomatic CAD who have cardiac catheterization[17,18] and 3.5 to 7.0% of patients who have myocardial revascularization have IMR.[114–117] Most of these patients have 1+ or 2+ MR without heart failure.[17,18,114–116] In patients with chronic IMR, three major variables interrelate to produce the clinical spectrum of patients with varying combinations of symptomatic ischemia and heart failure. As with acute IMR, the three variables are (1) the presence and severity of ischemia, (2) the severity of MR, and (3) the magnitude of left ventricular dysfunction. Patients with obstructive CAD may have no symptoms or have stable, progressive, unstable, or postinfarction angina or its equivalent. Because of disabling symptoms, threat to left ventricular mass, or statistically shortened survival, ischemia is a compelling problem that must be addressed therapeutically. The approach and methods do not differ materially from those for similar patients who do not have IMR. The second variable is the severity of MR. At present, 1+ or 2+ MR in patients without symptoms of heart failure does not compel invasive therapy for MR. More severe MR and/or symptoms of heart failure require evaluation for possible operation irrespective of the therapy needed for ischemia. The third variable is the degree of left ventricular dysfunction, and this is the most difficult to assess in the presence of MR. Symptoms of heart failure may be due to left ventricular dysfunction secondary to ischemia, MR, or both.

The primary purpose of diagnostic studies is to determine the severity of CAD and its anatomy, the severity and mechanism of MR, and the degree of left ventricular dysfunction. In chronic IMR, the ventricular geometry and function reflect remodeling owing to both the MR and the infarction; therefore, these patients may require diagnostic studies and perhaps operative procedures that are different from those for patients with CAD *associated* with MR. It is also important to define comorbidity of other organ

systems by appropriate diagnostic studies dictated by the patient's history, physical examination, and screening laboratory findings.

In patients with IMR, the ECG usually shows evidence of a prior MI.[115,116,118,119] The incidence of arrhythmias varies, but atrial fibrillation, as noted earlier, is quite common. In patients without heart failure and with mild MR, heart size by chest x-ray is normal or slightly enlarged; the left atrium is seldom enlarged. In those with moderate or severe MR and/or severe left ventricular dysfunction, the heart is enlarged, and usually the left atrium is also enlarged.[120]

TTE and TEE are useful in determining the etiology of MR. Two-dimensional echocardiography reliably detects ruptured chordae, annular calcification, and myxomatous degeneration, which are not features of chronic IMR, and differentiates rheumatic valve disease, endocarditis, and congenital deformities. Echocardiography also effectively assesses regional wall motion abnormalities and global left ventricular function. The degree of MR is also well quantified by color-flow Doppler measurements. Characteristics of the MR demonstrated by TEE also will aid in the decision to repair or replacement the mitral valve. An extremely dilated annulus and severe bileaflet tethering and an eccentric or complex regurgitation jet are echocardiographic indications that repair may not be effective or durable.

Cardiac catheterization provides information regarding the coronary arterial anatomy and pathology. Ventriculograms add little to the data provided by TTE or TEE and should be avoided, especially in patients with impaired renal function. Measurements of chamber pressures and estimates of cardiac output contribute to the overall evaluation of left ventricular function. Pulmonary hypertension, when present, typically is moderate and correlates with the degree of left ventricular dysfunction and/or severity of MR.

Indications for surgery

The decision to intervene surgically in IMR can be a challenging process. Chronic IMR represents a set of patients with symptoms of insidious onset and often of chronic duration. Patients may present primarily with symptoms of ischemic CAD and on preoperative workup are found to have significant MR. Although this group of patients may have preserved left ventricular function, compromised ventricular function is not uncommon. The indication to the operating room in this group of patients is CAD not amenable to interventional cardiology. However, intervention on the MR must be considered. Important factors to consider in the decision to intervene on the MR include the following: the impact of coronary artery bypass grafting (CABG) alone on the progression of IMR, the impact of CABG with or without mitral valve repair (MVR) on survival, the additional risk of MVR at the time of CABG, and the choice of valve repair or replacement.

Other patients may present primarily with symptoms of CHF and signs of significant MR. Preoperative catheterization subsequently may reveal significant CAD. These patients tend to have more compromised left ventricular function compared with the first group. The indication for surgery is CHF. In reality, most patients present in a clinical spectrum somewhere along the two clinical scenerios. In this section, however, the indications for surgery of each scenerio will be discussed separately.

IMR AND CAD: In the setting of CABG today, most surgeons agree that concomitant moderate to severe (3 to 4+) MR should be addressed at the time of CABG and that revascularization alone will not ameliorate MR. On the other hand, most surgeons agree that trace to mild (1+) MR should be left alone. The optimal management of mild to moderate (2+) MR remains controversial. Those who advocate the conservative approach of revascularization alone point out that revascularization will improve regional wall motion abnormality and potentially correct IMR.[114,121,122] They also point out that there are data to suggest that survival is not prolonged with MVR[123,124] and thus question subjecting the patient to higher operative risks. Those who advocate an aggressive approach to address the mitral valve point out that studies have suggested that revascularization does not correct IMR[125] and that uncorrected IMR may result in late symptoms and decreased long-term survival.[126] Furthermore, MVR with ring annuloplasty is nearly always technically feasible, obviating the need for replacement. Operative risk with combined CABG/MVR today is much better than the older series previously published, closer to an operative mortality of 3 to 4%.[127–129] Considering the possibility of redo sternotomy with patent grafts for MVR for recurrent IMR, some feel that aggressive management of IMR is justified.

Multiple factors are involved in the decision to address the IMR at the time of CABG. IMR portrays a negative impact on long-term survival. Studies have documented the negative impact of IMR on survival after AMI.[121,130–132] After percutaneous coronary intervention (PCI), IMR was demonstrated to have similar impact on survival. Three-year survival ranged from 46 to 76%, based on the severity of MR, suggesting that the concomitant IMR should be addressed to affect survival.[133] In the setting of CABG, myocardial revascularization alone in patients with chronic IMR has a higher hospital mortality than in patients without IMR.[117] Mild (1+) IMR increases operative mortality to 3.4 to 4.5%,[115–117,134] and moderate (2+) IMR raises operative mortality to 6 to 11%.[115–117,135] Five-year survival is influenced by the severity of left ventricular dysfunction at the time of operation, age, and comorbid disease.[66] Two-year survival for revascularization alone in patients with 1+ and 2+ MR is 88% and 78%, respectively.[126] Five-year survival rates for patients with mild MR range between 70% and 80%.[17,115,118,136] For moderate MR, 5-year survival ranges between 60% and 70%.[137,138]

The impact of CABG alone on the progression of IMR has been examined. Previous data have suggested that CABG alone improves IMR and functional status.[114,121,122] More recent reports have suggested that CABG alone is not the optimal therapy for moderate IMR.[125,139,140] A study published

recently from the Cleveland Clinic Foundation reported that moderate (2+) IMR does not resolve with CABG alone and furthermore is associated with reduced survival.[141] The study suggested that a mitral valve procedure is warranted for such patients presenting for CABG. Between 1980 and 2000, 467 patients with moderate IMR underwent CABG alone. Longitudinal analysis of 267 follow-up echocardiograms from 156 patients demonstrated that early postoperative improvements in IMR did not persist. IMR of moderate or greater severity is present in 60% of patients by postoperative week 6. Interestingly, the risk of postoperative IMR severity was not predicted by cardiac function or extent of CAD. Furthermore, early survival of patients with unrepaired moderate IMR is reduced compared with similar patients without IMR. Campwala and colleagues recently reported their experience with MR progression following isolated CABG surgery.[142] A retrospective review of their registry examined 438 patients with preoperative MR of 2+ or less requiring CABG. New 3 to 4+ MR developed in 10% of patients with no prior MR, 12% with pre-CABG 1+ MR, and 25% with pre-CABG 2+ MR. Preoperative left ventricular dysfunction and large left ventricular size were identified as predictors of MR progression after CABG. Although no correlation was identified between the extent of CAD or the number of grafts performed, incomplete revascularization in the posterior descending artery territory was identified as a significant predictor of MR progression, suggesting a role for incomplete revascularization and left ventricular remodeling in the progression of IMR.

Previous studies have compared the results of CABG alone versus CABG with concomitant MVR in the setting of IMR.[132,143–147] The data suggested that postoperative MR is improved with CABG with concomitant MVR. However, improvement in long-term survival remains controversial. While some studies suggested no improvement in long-term survival with concomitant MVR,[144,146–148] two studies[132,143] comparing CABG versus CABG + MVR in patients with CAD and IMR suggested a significant improvement in survival. Both studies involved patients with 2 to 3+ IMR with depressed left ventricular ejection fraction. A recent study[145] examined 111 patients with moderate to severe IMR and multivessel CAD undergoing either medical therapy, CABG alone, or CABG + MVR. After adjusting for baseline differences, CABG alone and CABG + MVR had a significant risk reduction (>50%) of cardiac death when compared with medical therapy. However, only CABG + MVR independently predicted survival. In addition, history of CHF was an independent predictor of cardiac death. These studies suggested that concomitant MVR with CABG may improve late survival, especially in patients with CHF.

The final factor to consider is the decision to repair or replace the valve. Gillinov's report demonstrated that MVR is effective (at least in the short term) in 97% of patients undergoing elective surgery for 3+ to 4+ chronic IMR.[5] Ring annuloplasty was employed in 98% of these repairs and was the sole surgical maneuver on the valve in over 80%. There was a distinct inclination in this study to undersize the valvuloplasty ring; 79% of the rings were 30 mm or less. Iatrogenic mitral stenosis was not seen even in the patients who received 26-mm annuloplasty devices. However, the benefit of repair versus replacement appears to diminish with high-risk patients. Risk factors included older age, higher New York Heart Association (NYHA) functional class, greater wall motion abnormality, and renal dysfunction.

In summary, patients with CAD and concomitant moderate to severe (3 to 4+) IMR should undergo CABG + MVR. In patients with moderate (2+) IMR, recent studies suggest that an aggressive approach with CABG + MVR is justified, given the lower rate of morbidity and mortality in the current series. Patients with symptoms of CHF appear to benefit most from CABG + MVR. Left ventricular dysfunction and increased left ventricular dimension, along with incomplete revascularization, may predict a higher rate of progression of IMR, suggesting that CABG + MVR should be performed in this particular group of patients. Mild (1+) IMR should be left alone unless (1) preoperative signs and symptoms are suggestive of periods of more severe MR, and (2) intraoperative TEE demonstrates anatomic findings requiring MVR (i.e., significant annular dilatation and leaflet tenting). Most patients with IMR benefit from MVR. In the most complex, high-risk settings, replacement may be preferable, with no demonstrable difference in survival between repair and replacement.

IMR AND CHF: Patients who present primarily with symptoms of CHF and IMR provide surgeons with a fairly straightforward indication for intervention. Preoperative coronary angiogram may demonstrate significant CAD. With the history and/or evidence of prior MI in the presence of left ventricular dysfunction, these patients' clinical scenarios are considered to be consistent with chronic IMR. The indication for the operating room in this group of patients is similar to MR of nonischemic origin. Symptoms of CHF and depressed left ventricular function are indications for surgical repair or replacement, although there are no randomized data to suggest better symptomatic relief and improved survival with surgery. Most surgeons agree that concomitant CABG is indicated in the presence of significant CAD.

In the past, high perioperative morbidity and mortality had made surgeons cautious regarding MVR and MVR + CABG in the setting of left ventricular dysfunction. In the so-called pop-off valve hypothesis, MR associated with left ventricular dysfunction was believed to provide a low-pressure runoff. Surgeons were concerned that correction of the MR might increase ventricular afterload in an already compromised left ventricle. However, this hypothesis has been challenged.[149–152] With so-called reverse remodeling, correction of MR would alleviate excessive ventricular workload and stop the geometric changes of the ventricle associated with heart failure. The Stanford group has reported in an ischemic sheep model of MR that reduction of the annulus by an annuloplasty ring reduces the radius of curvature of the left ventricle at the base, equatorial, and apical levels.[153] This

decrease in the radius of curvature supports the concept that a small ring can restore a more elliptical shape. Reduction of left ventricular dimensions to a more elliptical shape, so-called reverse remodeling, after annuloplasty also has been demonstrated by others in clinical studies.[154–156]

More recent series indeed have demonstrated much lower perioperative morbidity and mortality with mitral valve surgery in the setting of left ventricular dysfunction.[5,6,157,158] Data from most recently published series[124,132,149,150,159–161] demonstrate improvement in left ventricular ejection fraction, MR, and symptoms (NYHA classification) with surgical intervention. However, questions remain regarding improvement in long-term survival and its overall effect on the natural history of IMR. Some have raised questions recently despite previous data about the potential improvement in long-term survival in patients with IMR in the setting of depressed left ventricular ejection fraction.[132,143,145] Two recent studies confirm the dismal prognosis of IMR in end-stage cardiomyopathy.[123,124] In perhaps the largest experience of MVR in patients with severe left ventricular dysfunction, Wu and colleagues[123] examined the impact of mitral valve annuloplasty on mortality risk in patients with MR and left ventricular dysfunction. Reviewing their echocardiographic database ($n = 682$), the authors identified 419 patients who met criteria for surgical intervention: 126 patients underwent MVR, whereas 263 continued conservative medical therapy. The etiology of MR included both ischemic and nonischemic causes. The analysis demonstrated no improvement in long-term survival in the MVR group versus medical therapy. Talkwalkar and colleagues[124] reported a series of 338 patients who underwent MVR. Compared with the control group, depressed left ventricular ejection fraction was more likely to be associated with IMR, concomitant CABG, and NYHA class IV symptoms. Five-year survival was 54%, and when associated with prior CABG, prior MI, or concomitant CABG, it was 0%, 37%, and 63%, respectively.

In agreement with previous reports, these recent studies confirmed the poor prognosis associated with IMR. In Wu's series,[123] 5-year survival in the setting of IMR and left ventricular dysfunction was less than 50%, regardless of surgical versus medical therapy (Fig. 30-5). A randomized study comparing surgical versus medical therapy for IMR is needed to clarify the benefit of mitral valve surgery in this population of patients.

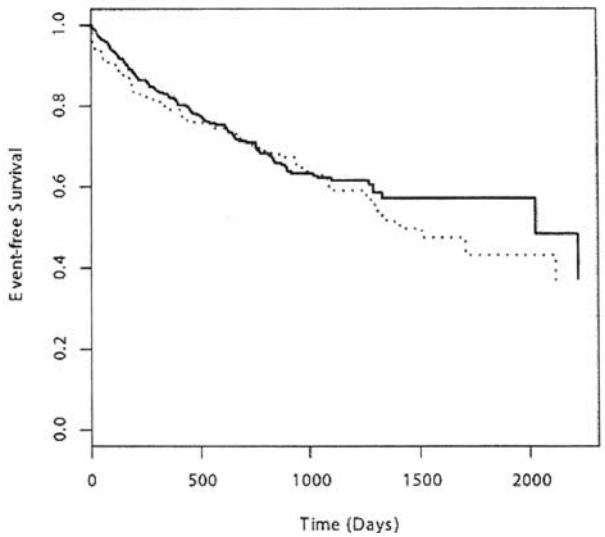

Figure 30-5. Survival in patients with mitral regurgitation and left ventricular dysfunction in the mitral valve annuloplasty group (*dotted line*) and the medical therapy group (*solid line*). (*Used with permission from Wu AH, Aaronson KD, Bolling SF, et al: Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol 2005; 45:381.*)

Results

An undersized annuloplasty ring is effective in the acute correction or reduction of IMR in the majority of patients. However, recurrent MR after annuloplasty is seen in 15 to 30% of patients.[162–164] The Cleveland Clinic reported its series of 585 patients who underwent annuloplasty alone for IMR between 1985 and 2002. A total of 678 postoperative echocardiograms were evaluated in 422 patients. The majority of recurrent IMR occurred within the first 6 months. Overall, 28% of patients 6 months after surgery demonstrated 3 to 4+ MR. The risk factors for recurrent IMR were higher grade of preoperative MR, complex regurgitant jet, and preoperative left ventricular dysfunction.[162]

Evidence of left ventricular reverse remodeling after ring annuloplasty has been demonstrated in small clinical studies with excellent results and freedom from recurrent IMR for up to 2 years.[154–156] Braun and colleagues reported a series of 87 patients with IMR and depressed left ventricular function (mean 32%) who underwent undersized mitral ring annuloplasty and coronary revascularization. MR grade decreased significantly from a mean of 3.1 to 0.6 at 18 months. Both left ventricular end-systolic and end-diastolic dimensions decreased significantly when compared with preoperative echocardiograms. Interestingly, left ventricular end-diastolic dimension was found to be the best predictor of reverse remodeling. Left ventricular end-diastolic dimension exceeding 65 mm was associated with a lower probability of reverse remodeling, suggesting a relationship between recurrent IMR and ventricular geometric dimension. Further studies would be useful to identify preoperative echocardiographic parameters predictive of durable MVR.

Operative results for mitral valve surgery with or without concomitant CABG have improved, with recent series reporting operative mortality of 3 to 4%.[5,6,127–129,157,158] However, 5-year survival remains between 30% and 40%.[17,73,115,116,118] More recently, Gillinov and colleagues reported 5-year survival in the propensity-matched best risk group of 58% for valve repair and 36% for replacement. This group had significantly fewer NYHA class IV patients and less severe MR preoperatively. In the propensity-matched poorer-risk groups (i.e., more severe CHF, MR, and emergency surgery), and for the group as a whole, there was no

difference between repair and replacement, and 5-year survival was uniformly less than 50%.[5]

There has been no randomized study demonstrating a survival benefit with mitral valve repair/replacement in IMR. In a retrospective analysis of cardiomyopathy including both ischemic and nonischemic etiology, Wu and colleagues reported 5-year survival of less than 50% regardless of surgical versus medical therapy in patients with MR and left ventricular dysfunction.[123] Other series also have demonstrated no survival benefit with mitral valve surgery in patients with IMR.[146–148] The similarity of results between surgical and medical therapy points out a need for better understanding of the pathophysiology of IMR and left ventricular remodeling. Furthermore, a randomized study examining the clinical outcome and survival benefit of mitral valve surgery for IMR is needed.

OPERATIVE TECHNIQUE

Operation for acute, severe postinfarction MR often is urgent or an emergency; a high percentage of patients have an intra-aortic balloon pump inserted before induction of anesthesia.[48,85] Monitors include the ECG, arterial blood pressure, a Swan-Ganz catheter with mixed venous oxygen electrode, nasopharyngeal and rectal (or bladder) temperatures, and a catheter for urine output.

For chronic IMR, operation usually is elective, except in patients with uncontrolled symptoms of coronary ischemia, who may require emergency or urgent operation to prevent infarction. Preoperative preparation and intraoperative monitors do not differ from those for other cardiac operations, with the exception of TEE and color-flow Doppler velocity mapping. After induction of anesthesia, the degree of MR, anatomy of the valve, and dimensions and segmental wall motion of the left ventricle are assessed carefully to determine whether or not the mitral valve needs to be addressed. Since anesthesia generally reduces systemic vascular resistance and afterload, assessment of the valve after administration of phenylephrine may unmask more severe MR. If the amount of MR is 2+, transfusion after aortic cannulation to increase preload to 1.5 to 2.0 times resting pulmonary capillary wedge pressure may unmask more severe MR and prompt a decision to expose and repair the valve.[165] If there is a significant discrepancy between the intraoperative degree of MR and that diagnosed by preoperative TEE, it is probably best to treat according to the preoperative value because this is likely what the patient experiences under normal loading conditions. In patients with marginal left ventricular function, a Swan-Ganz catheter with an oxygen electrode and a femoral arterial catheter for possible intra-aortic balloon insertion are recommended.

The most common exposure to the mitral is via median sternotomy. If revascularization is required, arterial and venous conduits are harvested prior to cannulation and imitation of cardiopulmonary bypass. Bicaval cannulation is preferred for exposure of the mitral valve. Both antegrade cardioplegia and retrograde cardioplegia are recommended to minimize myocardial stunning and postbypass left ventricular dysfunction. After initiation of cardiopulmonary bypass, the aorta is cross-clamped, and cardioplegia is given. The left atrium is opened to decompress the left ventricle. If revascularization is needed, the distal coronary anastomoses are performed first to reduce manipulation of the heart and prevent atrioventricular disruption after mitral valve repair or replacement.

In patients with a history of CABG, right thoracotomy is an option to avoid injury to previous bypass grafts during a redo sternotomy. Patent grafts, especially the left internal mammary artery (LIMA) graft to the left anterior descending artery, may be immediately under the sternal table from previous surgery. Owing to the inability to isolate and control the LIMA graft from a right thoracotomy, fibrillatory arrest is needed. Significant aortic valve insufficiency cannot be present for this technique.

Once exposed, the left atrium is opened after developing the interatrial groove, extending the incision behind the inferior vena cava. In cases of redo sternotomy or acute IMR (in which case the left atrium may be small), exposure to the mitral valve can be difficult, and a transseptal approach via the right atrium may be required. Improved exposure also may be obtained by extending the atrial incision superiorly behind the superior cava–right atrium junction. Using a specialized retractor, the left atrium is lifted, and the mitral valve should be exposed for inspection.

An initial inspection reveals the amount of annular dilatation and may indicate segments of the mural annulus that appear disproportionately elongated. Traction sutures in the annulus at each commissure elevate the valve and facilitate exposure of the leaflets, chordae, and papillary muscles. Careful inspection searching for ruptured, elongated, or sclerosed chordae; fibrotic, atrophied papillary muscle; and redundant or defective leaflet tissue is made. Most often the entire valve appears normal; sometimes the posterior papillary muscle seems slightly more yellowish brown than the rest of the ventricle, and the posterior part of the mural annulus seems slightly elongated.

Echocardiographic evaluation is important in the decision to repair or replace the valve. A central regurgitant jet with a dilated annulus is suggestive of a successful repair with a ring annuloplasty. In contrast, eccentric, complex regurgitant jets with severe bileaflet tethering and papillary muscle pathology such as elongation or rupture suggest that mitral valve replacement may be the best durable option.

For mitral valves amendable to annuloplasty repair, usually 2-0 braided sutures are used. Often, exposure to posterior and medial portions of the mitral annulus is easier to achieve. These sutures should be placed first and used to place tension of the mitral annulus to facilitate exposure of the lateral and anterior portions of the annulus. It is essential that the full curve of the needle is used to ensure optimal placement of the sutures in the mitral annulus. Significant tension can develop when these dilated annuli are downsized, so sutures should be placed close together, and crossover may be warranted.

Sizing of the annuloplasty ring can be performed before or after placement of the annuloplasty sutures depending on the size of the left atrium and adequate exposure. Introduced by Bolling, the concept of reducing annular dilatation with aggressive annuloplasty downsizing aims to optimize leaflet coaptation. When choosing an annuloplasty ring, the intertrigonal distance and the surface area of the anterior leaflet are measured. Aggressive downsizing of the annulus (one or two sizes smaller than predicted by measuring the fibrous intertrigonal annulus) can be achieved with minimal risk of the development of systolic anterior motion because the posterior leaflet in IMR often is tethered and restricted. After the size of the ring is chosen, the annuloplasty sutures are placed in accordance with the geometry of the mitral annulus. Once all sutures are placed, the annuloplasty ring is slipped down onto the mitral valve annulus, and the sutures are tied to secure the ring. At this point, a saline test usually is employed to interrogate the competency of the mitral valve repair. If the repair is acceptable, the left atrium then is closed.

If on inspection the valve is not amendable to annuloplasty repair, mitral valve replacement should be performed. Chordal sparing techniques[106–108,111,112,166] should be used if the valve is replaced. These methods have significantly reduced postoperative ventricular dysfunction observed after valve excision in the past and produce no more left ventricular dysfunction than reparative operations.[112] Aged patients in sinus rhythm and patients with a life expectancy of fewer than 10 years who otherwise do not need anticoagulation are candidates for bioprosthetic valves; mechanical valves are recommended for others. The valve is inserted after excising portion of anterior leaflet[107,112] and transposing[111] remaining leaflet tissue to the commissures (see Fig. 30-4). Pledgeted everting sutures (atrial to ventricular) are used for intra-annular placement if downsizing and/or a low-profile valve (i.e., mechanical valve) is desired. Noneverting (ventricular to atrial) pledgeted sutures may be used if a high-profile bioprosthetic valve or friable annulus is encountered. The mural leaflet is plicated into the valve insertion suture line, and the struts of the prosthetic valve are placed along the commissural plane to prevent interference with the valve mechanism and left ventricular outflow tract obstruction.

The atriotomy is closed using running sutures, and any proximal coronary anastomoses are completed. Prior to removing the aortic clamp, all air is evacuated from the ventricle, and the mitral valve is kept incompetent using a transvalvular catheter with ventricular and atrial holes. Absence of air is checked and assessment of ventricular wall motion is made by TEE. Anticipated pharmacologic support is started, and satisfactory left ventricular contractility is established before loading the heart. After weaning, cardiopulmonary bypass is restarted if the left ventricle begins to dilate and wall motion deteriorates; every effort is made to prevent any distension of the ventricle that might reduce myocardial contractile force.[166] Decisions for using intra-aortic balloon pumping or even temporary left ventricular assistance are better made early than after multiple attempts to wean from cardiopulmonary bypass have failed.

FUTURE DIRECTION

Despite best efforts, results with standard annuloplasty with regard to mortality and recurrent IMR have been disappointing. The 5-year survival for surgical therapies for infarction-induced heart failure has hovered stubbornly around 50%. Recurrent IMR after MVR has been reported to be as high as 30% of patients.[162–164,167,168] Although the standard repair (annuloplasty reduction) is effective in correcting the annular dilatation associated with IMR, many investigators point out that it does not address the geometric subvalvular changes associated with postinfarction left ventricular remodeling and may explain the current poor long-term prognosis of IMR. As opposed to the planar standard annuloplasty ring, three-dimensional rings designed to address left ventricular remodeling and its effect on the mitral annulus have been introduced recently. These disease-specific annuloplasty rings will need further investigation before definitive conclusions can be made.

Recent evidence argues that the development of IMR is a complex, multifactorial process resulting from left ventricular remodeling involving the entire mitral apparatus. Many investigators postulate that adjunctive surgical therapy directed at the remodeled ventricle may prove to be a potential therapeutic strategy in the treatment of IMR. Many have stated that IMR is not a valvular process but a ventricular disease process. In a sheep model, Moaine and colleagues demonstrated that external restraint of the infarct zone attenuated remodeling and reduced chronic IMR.[169] Guy and colleagues demonstrated that prophylactic ring annuloplasty before infarction prevented the development of IMR but did not alter the outcome of ischemia-related remodeling.[170] Furthermore, external infarct restraint with mesh before infarction prevented left ventricular remodeling compared with the annuloplasty group. The data suggested that left ventricular remodeling associated with infarct expansion may serve as an important therapeutic target. The Acorn cardiac restraint device (CorCap) is a mesh device that is implanted around the heart to reduce wall stress and address left ventricular remodeling. Clinical trials with the Acorn device have shown that it is safe and effective in patients with advanced heart failure and remodeled ventricles.[171–173] Further investigation is needed before definitive conclusions can be drawn.

Leaflet tethering suggests that surgical strategies aimed at leaflet and subvalvular structures may provide therapeutic benefits as an adjunct to standard annuloplasty repair. Multiple ideas and concepts have been described in the literature. Designed to address both the annular dilatation and subvavular changes associated with IMR, the Coaspsys device consists of an annular head that corrects annular dilatation and a papillary head that repositions the laterally displaced papillary muscles. Animal and human studies have shown

promising results, with this device reducing IMR.[174–176] Chordal cutting of two critical basal chordae of the anterior leaflet first described by Messas[177,178] has been shown to be effective in treating IMR. By relieving leaflet restriction and eliminating the angulation of the anterior leaflet, chordal cutting improves leaflet coaptation while the intact marginal chordae continue to prevent prolapse. Conflicting data from the Stanford group[179,180] demonstrated that cutting of second-order chords neither prevented nor decreased the severity of IMR in a sheep. Kron and colleagues recently reported a successful subvalvular repair as an adjunct to standard annuloplasty.[181] Direct reposition of the displaced posterior papillary muscle toward the right fibrous trigone appeared to ameliorate IMR. In a sheep model, Langer and colleagues confirmed Kron's findings.[182] Anchoring a suture at the right fibrous trigone and passing it through the posterior papillary muscle tip and the ventricular wall, the investigators demonstrated reduction of IMR by tightening the suture. Other groups have demonstrated that reapproximation of both papillary muscles may be beneficial in reducing leaflet tethering and hence IMR.[183–185] The long-term results of these adjunctive procedures are not available, and further investigation is needed.

Finally, despite the mechanistic complexity of IMR, annuloplasty alone proves to be effective in ameliorating IMR in up to 80% of patients.[186] This suggested that a less invasive method to address IMR may benefit this growing population of patients. A catheter-based or percutaneous approach to the treatment of IMR has been investigated. Rigid coronary sinus–based mitral annuloplasty devices deployed percutaneously have been demonstrated to reduce IMR in an animal model.[187–189] Much more work is needed to explore the potential effectiveness and clinical applicability of this new technology.

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CHAPTER 31

Left Ventricular Aneurysm

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DEFINITION

Left ventricular aneurysm (LVA) has been strictly defined as a distinct area of abnormal left ventricular diastolic contour with systolic dyskinesia or paradoxical bulging[1] (Fig. 31-1). Yet a growing number of authors favor defining LVA more loosely as any large area of left ventricular akinesia or dyskinesia that reduces left ventricular ejection fraction (LVEF).[2–4] This broader definition has been justified by data suggesting that the pathophysiology and treatment may be the same for both ventricular akinesia and ventricular dyskinesia.[3,5] Intraoperatively, an LVA also may be defined as an area that collapses on left ventricular decompression.[2,5,6] True LVAs involve bulging of the full thickness of the left ventricular wall, whereas a false aneurysm of the left ventricle is, in fact, a rupture of the left ventricular wall contained by surrounding pericardium.

HISTORY

Left ventricular aneurysms have long been described at autopsy, but LVA was not recognized to be a consequence of coronary artery disease (CAD) until 1881.[7] The angiographic diagnosis of LVA was first made in 1951.[7] A congenital LVA was first treated surgically by Weitland in 1912 using aneurysm ligation. In 1944, Beck[8] described fasciae latae plication to treat LVAs. Likoff and Bailey[9] successfully resected an LVA through a thoracotomy in 1955 using a special clamp without cardiopulmonary bypass. The modern treatment era began in 1958 when Cooley and colleagues[10] successfully performed a linear repair of an LVA using cardiopulmonary bypass. More geometric ventricular reconstruction techniques were devised subsequently by Stoney and colleagues,[11] Daggett and colleagues,[12] Dor and colleagues,[13] Jatene,[14] and Cooley and colleagues.[15,16]

INCIDENCE

The incidence of LVA in patients suffering myocardial infarction (MI) has varied between 10 and 35% depending on the definition and the methods used. Of patients undergoing cardiac catheterization in the Coronary Artery Surgery Study (CASS), 7.6% had angiographic evidence of LVAs.[17] The absolute incidence of LVAs may be declining due to the increased use of thrombolytics and revascularization after MI.[18,19]

ETIOLOGY

Over 95% of true LVAs reported in the English literature result from CAD and MI. True LVAs also may result from trauma,[20] Chagas' disease,[21] or sarcoidosis.[22] A very small number of congenital LVA also have been reported and have been termed *diverticula* of the left ventricle.[23]

False aneurysms of the left ventricle result most commonly from contained rupture of the ventricle 5 to 10 days after MI and often occur after circumflex coronary arterial occlusion. False aneurysm of the left ventricle also may result from submitral rupture of the ventricular wall, a dramatic event that generally occurs after mitral valve replacement with resection of the mitral valve apparatus.[24] Left ventricular pseudoaneurysm also may result from septic pericarditis[25] or any prior operation on the left ventricle, aortic annulus, or mitral annulus.

PATHOPHYSIOLOGY

The development of a true LVA involves two principal phases: early expansion and late remodeling.

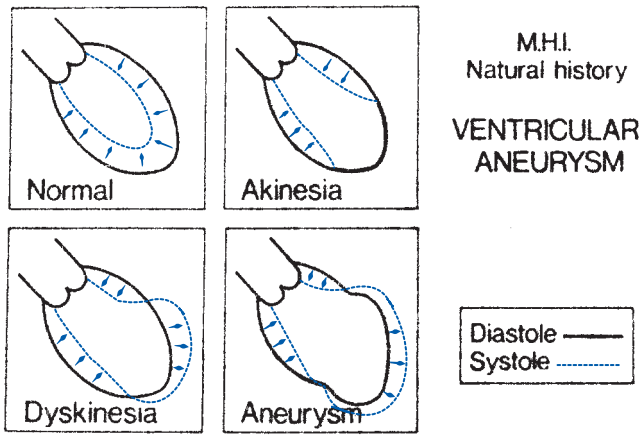

Figure 31-1. Diagrammatic distinction between aneurysm and other states of the left ventricle. (*Reproduced with permission from Grondin et al.*[39])

Early Expansion Phase

The early expansion phase begins with the onset of MI. Ventriculography can demonstrate LVA formation within 48 hours of infarction in 50% of patients who develop ventricular aneurysms. The remaining patients have evidence of aneurysm formation by 2 weeks after infarction.[26]

True aneurysm of the left ventricle generally follows transmural MI owing to acute occlusion of the left anterior descending artery (LAD) or dominant right coronary artery. Lack of angiographic collaterals is strongly associated with aneurysm formation in patients with acute myocardial infarction (AMI) and LAD artery occlusion,[27] and absence of re-formed collateral circulation is probably a prerequisite for the formation of a dyskinetic LVA (Table 31-1). At least 88% of dyskinetic ventricular aneurysms result from anterior infarction, whereas the remainder follow inferior infarction.[7] Posterior infarctions that produce a distinct dyskinetic LVA are relatively unusual.

In experimental transmural infarction without collateral circulation, myocyte death begins 19 minutes after coronary occlusion. Infarctions that result in dyskinetic aneurysm formation are almost always transmural and may show gross thinning of the infarct zone within hours of infarction. Within a few days, the endocardial surface of the developing aneurysm becomes smooth with loss of trabeculae and deposition of fibrin and thrombus on the endocardial surface in at least 50% of patients. While most myocytes within the infarct are necrotic, viable myocytes often remain within the infarct zone. In a minority of patients, extravascular hemorrhage occurs in the infarcted tissue and may further depress systolic and diastolic function of involved myocardium. Inflammatory cells migrate into the infarct zone by 2 to 3 days after infarction and contribute to lysis of necrotic myocytes by 5 to 10 days after infarction. Electron microscopy demonstrates disruption of the native collagen network several days after infarction. Collagen disruption and myocyte necrosis produce a nadir of myocardial tensile strength between 5 and 10 days after infarction, when rupture of the myocardial wall is most common. Left ventricular rupture is relatively rare after the ventricular aneurysmal wall becomes replaced with fibrous tissue.

Table 31–1.

Factors Contributing to Left Ventricular Aneurysm Formation

Preserved contractility of surrounding myocardium
Transmural infarction
Lack of collateral circulation
Lack of reperfusion
Preserved contractility of surrounding myocardium
Elevated wall stress
Hypertension
Ventricular dilatation
Wall thinning

Loss of systolic contraction in the large infarcted zone and preserved contraction of surrounding myocardium cause systolic bulging and thinning of the infarct. By Laplace's law ($T = Pr/2h$), at a constant ventricular pressure P, increased radius of curvature r and decreased wall thickness h in the infarcted zone both contribute to increased muscle fiber tension T and further stretch the infarcted ventricular wall.

Relative to normal myocardium, ischemically injured or infarcted myocardium displays greater *plasticity* or *creep,* defined as deformation or stretch over time under a constant load.[28] Thus, increased systolic and diastolic wall stress in the infarcted zone tends to produce progressive stretch of the infarcted myocardium (termed *infarct expansion*)[29] until healing reduces the plasticity of the infarcted myocardium.

Transmural infarction without significant hibernating myocardium within the infarct region is necessary for subsequent development of a true LVA. Angiographic ventricular aneurysms with evidence of hibernating myocardium (lack of Q waves or presence of uptake on technetium scan) may resolve over several weeks and thus do not represent true LVAs by strict criteria.[30]

Due to increased diastolic stretch or preload and elevated catecholamines, remaining noninfarcted myocardium may demonstrate increased fiber shortening and, ultimately, myocardial hypertrophy in the presence of an LVA.[31] This increased shortening and increased wall stress increase oxy-

gen demand for noninfarcted myocardium and for the left ventricle as a whole.

In addition to increased regional wall stresses, LVA can increase ventricular oxygen demand and decrease net forward cardiac output by producing a ventricular volume load because a portion of the stroke volume goes into the aneurysm instead of out the aortic valve. Net mechanical efficiency of the left ventricle (external stroke work minus myocardial oxygen consumption) is decreased by reducing external stroke work (volume times pressure) and increasing myocardial oxygen consumption.

Left ventricular aneurysms can produce both systolic and diastolic ventricular dysfunction. Diastolic dysfunction results from increased stiffness of the distended and fibrotic aneurysmal wall, which impairs diastolic filling and increases left ventricular end-diastolic (LVED) pressure.

Late Remodeling Phase

The remodeling phase of ventricular aneurysm formation begins 2 to 4 weeks after infarction when highly vascularized granulation tissue appears. This granulation tissue is replaced subsequently by fibrous tissue 6 to 8 weeks after infarction. As myocytes are lost, ventricular wall thickness decreases as the myocardium becomes largely replaced by fibrous tissue. In larger infarcts, the thin scar often is lined with mural thrombus.[32]

After AMI, animal studies show that ventricular load reduction with 8 weeks of nitrate therapy may reduce expected infarct thinning, decrease infarct stretch, and lessen hypertrophy of noninfarcted myocardium.[33] Interestingly, nitrate therapy for only 2 weeks after infarction does not prevent aneurysm formation. This observation emphasizes the importance of late remodeling from 2 to 8 weeks after infarction. Angiotensin-converting enzyme (ACE) inhibitors also reduce infarct expansion and subsequent development of ventricular aneurysm.[34] Because animal studies show that ACE inhibitors nonspecifically suppress ventricular hypertrophy, it is not clear whether suppression of the compensatory hypertrophy of surrounding myocardium ultimately is beneficial or harmful. Intravenous administration of atrial natriuretic factor for 4 weeks has improved ventricular function, dimensions, and fibrosis in rats.[35]

Lack of coronary reperfusion probably is a prerequisite for development of LVA. In humans, reperfusion of the infarct vessel either spontaneously,[30] by thrombolysis,[36] or by angioplasty[37] has been associated with a lower incidence of aneurysm formation. It is speculated that coronary reperfusion as late as 2 weeks after infarction prevents aneurysm formation by improving blood flow and fibroblast migration into the infarcted myocardium. The role of delayed infarct healing in aneurysm development is supported by observations that steroids after MI may increase the likelihood of aneurysm formation.[38]

Arrhythmias such as ventricular tachycardia may occur at any time during the development of ventricular aneurysm, and all these patients have the substrate for reentrant conduction pathways within the heterogeneous ventricular myocardium. These pathways tend to involve border zones surrounding the ventricular aneurysm (see Chap. 54).

NATURAL HISTORY

The excellent prognosis of asymptomatic patients with dyskinetic ventricular aneurysms who were treated medically was demonstrated in a series of 40 patients followed for a mean of 5 years.[39] Of 18 initially asymptomatic patients, 6 developed class II symptoms, whereas 12 remained asymptomatic. Ten-year survival was 90% for these patients but was only 46% at 10 years in patients who presented with symptoms (Fig. 31-2).

Although earlier autopsy series reported relatively poor survival in patients with medically managed left ventricular dyskinetic aneurysms (12% at 5 years), most recent studies report 5-year survivals from 47 to 70%.[17,39–42] Causes of death include arrhythmia in 44%, heart failure in 33%, recurrent MI in 11%, and noncardiac causes in 22%.[39] The natural history of patients with akinetic rather than dyskinetic LVAs is less well documented.

Factors that influence survival with medically managed left ventricular dyskinetic aneurysm include age, heart failure score, extent of CAD, duration of angina, prior infarction, mitral regurgitation, ventricular arrhythmias, aneurysm size, function of residual ventricle, and left ventricular end-diastolic pressure.[39,42] Early development of aneurysm within 48 hours of infarction also diminishes survival.[26]

In general, the risk of thromboembolism is low for patients with aneurysms (0.35% per patient-year),[40] and long-term anticoagulation is not usually recommended.

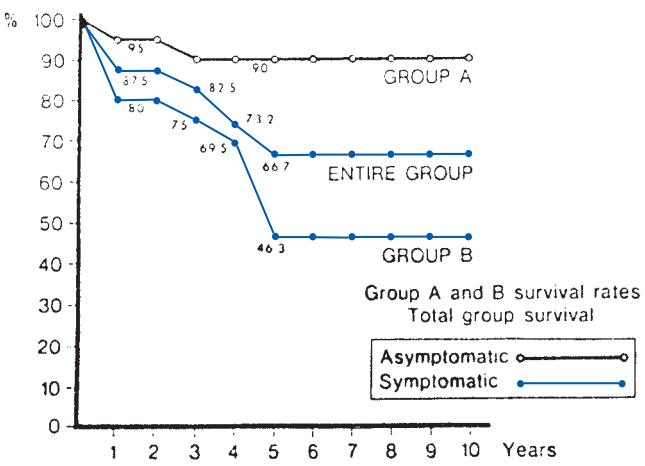

Figure 31-2. Survival in medically treated patients with left ventricular aneurysm based on presence (group B) or absence (group A) of symptoms. (*Reproduced with permission from Grondin et al.*[39])

However, in the 50% of patients with mural thrombus visible by echocardiography after MI, 19% develop thromboembolism over a mean follow-up of 24 months.[43] In these patients, anticoagulation and close echocardiographic follow-up may be indicated. Atrial fibrillation and large aneurysmal size are additional risk factors for thromboembolism.

The natural history of left ventricular pseudoaneurysm is not well documented. Frank rupture of chronic left ventricular pseudoaneurysms is less common than one might expect.[44] Rupture of left ventricular pseudoaneurysms may be most likely in the acute phase or in large-sized pseudoaneurysms.[45] Left ventricular pseudoaneurysms tend to behave similarly to true aneurysms in that they may present a volume load to the left ventricle or may be a source of embolization or endocarditis. Left ventricular pseudoaneurysms after prior cardiac surgery also have been reported to compress adjacent structures such as the pulmonary artery or esophagus.

CLINICAL PRESENTATION

Angina is the most frequent symptom in most series of operated patients with LVA. Given that three-vessel CAD is present in 60% or more of these patients, the frequency of angina is not surprising.[46]

Dyspnea is the second most common symptom of ventricular aneurysm and often develops when 20% or more of the ventricular wall is infarcted. Dyspnea may occur from a combination of decreased systolic function and diastolic dysfunction.

Either atrial or ventricular arrhythmias may produce palpitations, syncope, or sudden death or aggravate angina and dyspnea in up to one-third of patients.[46] Thromboembolism is unusual but may produce symptoms of stroke, MI, or limb or visceral ischemia.

DIAGNOSIS

The electrocardiogram (ECG) frequently demonstrates Q waves in the anterior leads along with persistent anterior ST-segment elevation (Fig. 31-3). The chest radiograph may show left ventricular enlargement and cardiomegaly (Fig. 31-4), but the chest radiograph usually is not specific for LVA.

Left ventriculography is the "gold standard" for diagnosis of LVA. The diagnosis is made by demonstrating a large, discrete area of dyskinesia (or akinesia), generally in the anteroseptal-apical walls. Occasionally, left ventriculography also may demonstrate mural thrombus. Quantitative definition of LVAs has been accomplished using a centerline analysis of left ventricular wall motion on left ventriculography in the 30-degree right anterior oblique view.[4] Hypocontractile segments contracting more than two standard deviations out of normal range are defined as aneurysmal[47] (Fig. 31-5). Outward motion is termed *dyskinetic*, and remaining aneurysmal segments are termed *akinetic*. The fraction of total left ventricular circumference that is aneurysmal thus can be computed as the value %*A*.[4]

Two-dimensional echocardiography is also a sensitive and specific means of diagnosing LVA (Fig. 31-6). Mural

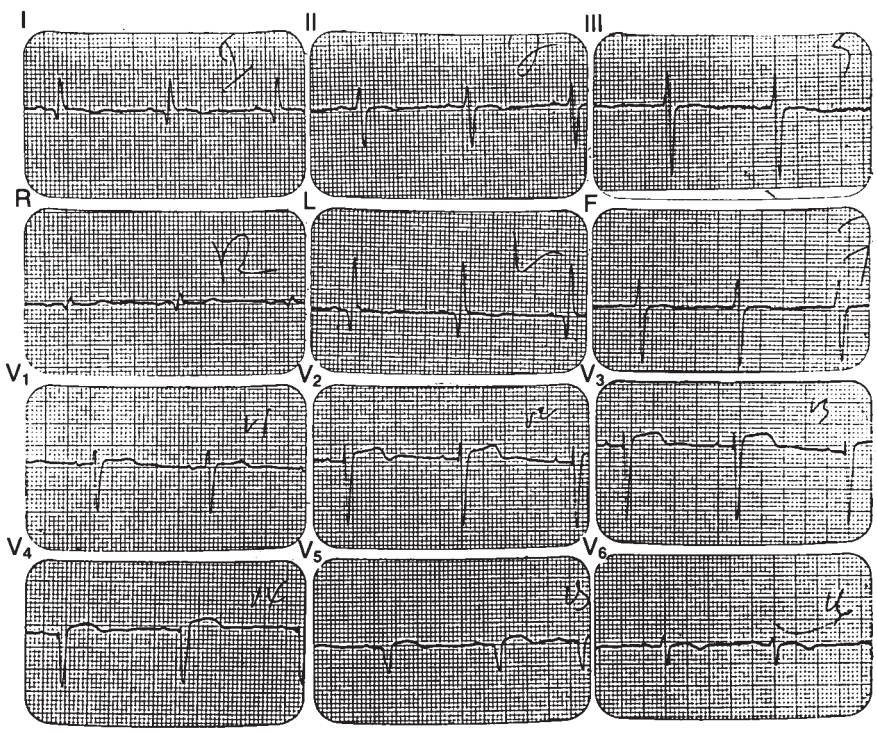

Figure 31-3. Electrocardiogram showing persistent ST-segment elevation with pathologic Q waves in a 60-year-old woman with left ventricular aneurysm. (*Reproduced with Modified from Ba'albaki and Clements.*[46])

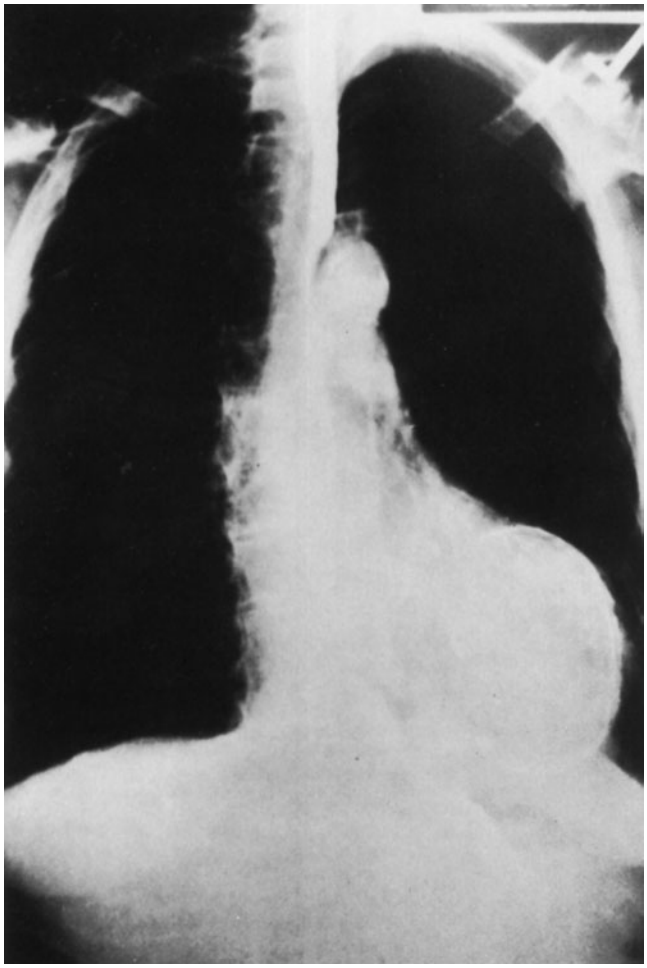

Figure 31-4. Posteroanterior chest radiograph in a patient with a calcified left ventricular aneurysm. (*Reproduced with permission from Ba'albaki and Clements.*[46])

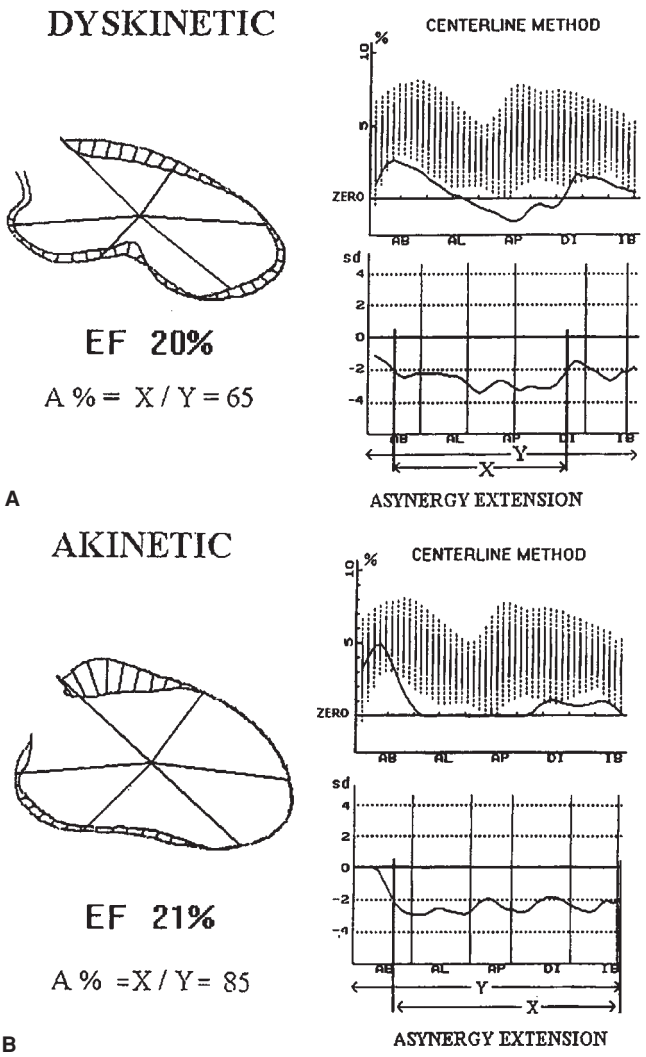

Figure 31-5. Examples of preoperative centerlne analysis in dyskinetic (*A*) and akinetic (*B*) left ventricular aneurysms. Vertical lines indicate the extent of asynergy. (EF = ejection fraction; AB = anterobasal; AL = anterolateral; AP = apical; DI = diaphragmatic; IB = inferobasal.) (*Reproduced with permission from Dor.*[3])

thrombus and mitral valve regurgitation are detected most readily by echocardiography. Echocardiography is also useful for distinguishing false aneurysm from true aneurysm by demonstrating a defect in the true ventricular wall. Tomographic three-dimensional echocardiography and magnetic resonance imaging (MRI) are the most reliable means of assessing left ventricular volume in the presence of LVA.[48] Gated radionuclide angiography reliably detects LVAs, and thallium scanning or positron-emission tomography (PET) can be helpful early after infarction to differentiate true aneurysm from hibernating myocardium with reversible dysfunction. Magnetic resonance imaging (MRI) accurately depicts LVAs and is a reliable means for detecting mural thrombus.[49] Yet, distinguishing true aneurysms from pseudoaneurysms remains difficult, even with MRI.[50]

INDICATIONS FOR OPERATION

Because of the relatively good prognosis for asymptomatic LVA,[39] no indications for repairing chronic, asymptomatic aneurysms are established. Yet, in low-risk patients during operation for associated CAD, investigators report repairing large, minimally symptomatic aneurysms.[7,51]

On the other hand, operation is indicated for symptoms of angina, congestive heart failure (CHF), or selected ventricular arrhythmias (see Chap. 54) (Table 31-2). For these symptomatic patients, operation offers better outcome than medical therapy. To be worthy of operation, a dyskinetic or akinetic LVA should significantly enlarge left ventricular end-systolic volume index (over 80 mL/m^2) and end-diastolic volume (over 120 mL/m^2). These volume criteria, however, are poorly defined and limited by technical difficulty measuring left ventricular volume in aneurysmal left ventricles. Because results are not affected by whether aneurysms are akinetic or dyskinetic, Dor and colleagues feel that dyskinesia is not a prerequisite for aneurysm repair.[3,4]

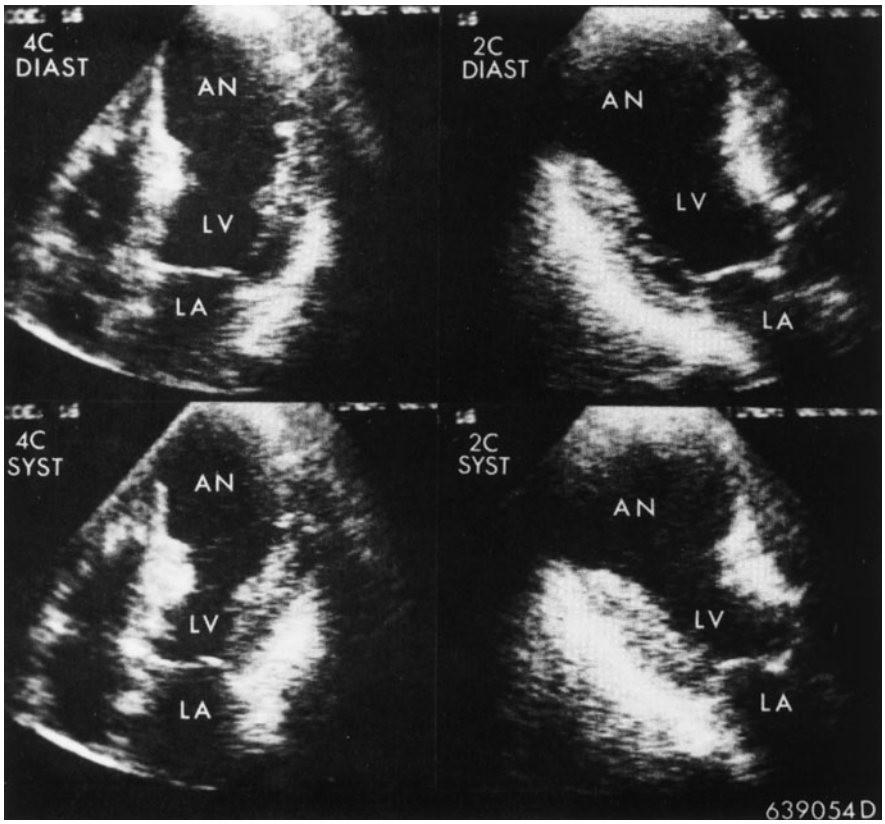

Figure 31-6. Four-chamber (4C) and two-chamber (2C) two-dimensional echocardiograms demonstrating a left ventricular aneurysm (AN) during systole (SYST) and diastole (DIAST). (LV = left ventricle; LA = left atrium.) (*Reproduced with permission from Feigenbaum H: Echocardiography. Philadelphia, Lea & Febiger, 1986; p 484.*)

Operation is also indicated in viable patients with contained cardiac rupture, with or without the development of a false aneurysm. Because left ventricular pseudoaneurysms may have a tendency to rupture when acute or of larger size (either with or without symptoms), operation is indicated.[44,45,52] Similarly, congenital aneurysms have a presumed risk of rupture and should undergo repair independently of symptoms. Rarely, embolism is an indication for operation in medically treated patients at high risk for repeated thromboembolism. The role of operation in asymptomatic patients with very large aneurysms or documented expansion of aneurysms is uncertain.

Table 31–2.

Relative Indications for Ventricular Aneurysm Operation

Documented expansion/large size
Angina
Congestive heart failure
Arrhythmia
Rupture
Pseudoaneurysm
Congenital aneurysm
Embolism
Documented expansion/large size

Relative contraindications to operation for LVA include excessive anesthetic risk, impaired function of residual myocardium outside the aneurysm, resting cardiac index of less than 2.0 liters/m^2 per minute, significant mitral regurgitation, evidence of nontransmural infarction (i.e., hibernating myocardium), and lack of a discrete, thin-walled aneurysm with distinct margins. Global ejection fraction may be less useful than ejection fraction of the basal, contractile portion of the heart in determining operability.[53]

Angioplasty has an uncertain role in the treatment of LVAs but may be indicated in patients with suitable coronary anatomy, one- or two-vessel disease, a contraindication to operation, or asymptomatic status with inducible ischemia.

PREPARATION FOR OPERATION

All patients being considered for operation should undergo right- and left-sided heart catheterization with coronary arteriography and left ventriculography. Patients with at least 2+

mitral regurgitation at cardiac catheterization should have echocardiography to assess the mitral valve and to look for intrinsic mitral valve disease not amenable to annuloplasty.

Preoperative electrophysiologic study is clearly indicated in any patient with preoperative ventricular tachycardia or ventricular fibrillation. The decision to perform an electrophysiologic study in patients without preoperative ventricular arrhythmias is controversial because the incidence of postoperative ventricular arrhythmias is low and not changed by endocardial resection at the time of operation.[7] Electrophysiologic study frequently is not helpful in patients with polymorphic ventricular tachycardia occurring within 6 weeks of MI.[7]

OPERATIVE TECHNIQUES

General Operation

Operation for LVA (i.e., aneurysmectomy, aneurysmorrhaphy, and ventricular restoration) requires cardiopulmonary bypass and a balanced anesthetic technique as generally used for coronary bypass grafting. After induction of anesthesia and endotracheal intubation, an ECG monitor, a Foley catheter, a radial arterial line, and a Swan-Ganz catheter are placed. A median sternotomy is performed, and the patient is given heparin. Saphenous vein or arterial conduits are prepared.

Cardiopulmonary bypass is begun after cannulating the ascending aorta. A single two-stage cannula generally is adequate to cannulate the right atrium, but dual venous cannulation should be considered if the right ventricle is to be opened. Epicardial mapping is performed if necessary. The left ventricle is inspected to identify an appropriate area of thinned ventricular wall. A linear vertical ventriculotomy, generally on the anterior wall 3 to 4 cm from the LAD, is made (Fig. 31-7). The left ventricle is opened (Fig. 31-8), all mural thrombus is removed carefully, and endocardial mapping is performed if necessary. A left ventricular vent now is placed through the right superior pulmonary vein–left atrial junction after mural thrombus is removed. Coronary arteries to be grafted are identified. Endocardial scar, if present, is

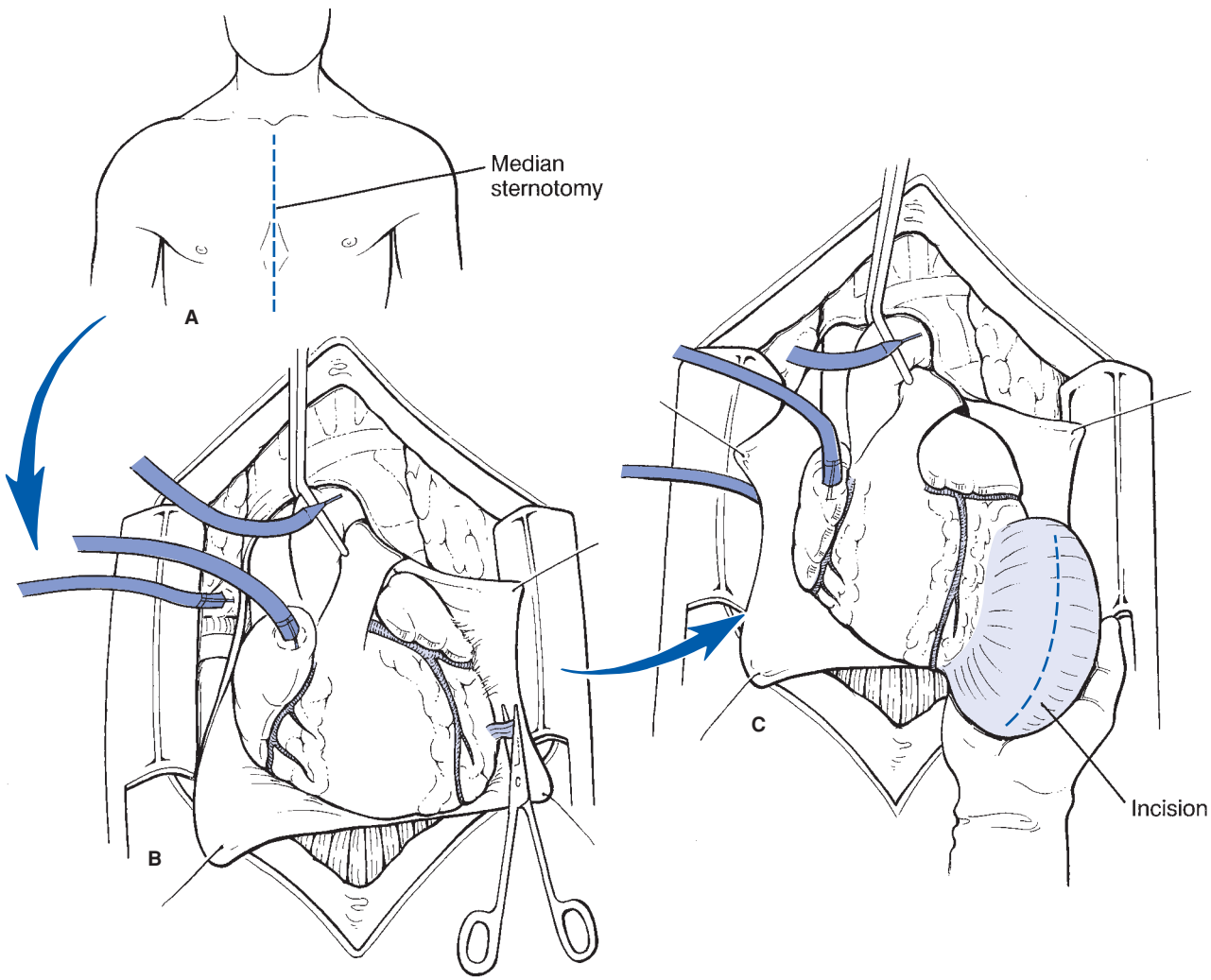

Figure 31-7. Technique of exposure for left ventricular aneurysm repair through a median sternotomy. The ascending aorta and right atrium are cannulated. A left ventricular vent is placed through the right superior pulmonary vein. Pericardial adhesions are divided, and the aneurysm is opened.

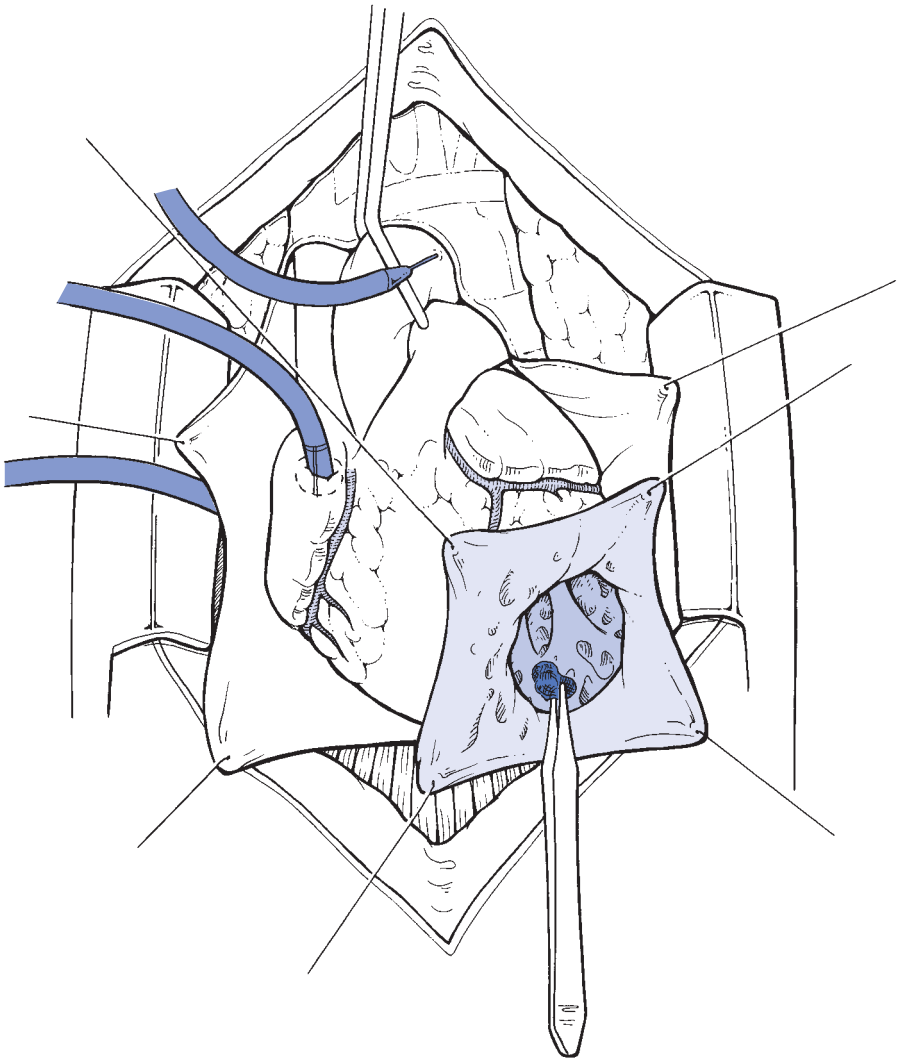

Figure 31-8. With the aneurysm wall opened, thrombus is removed without injury to the papillary muscles.

resected, and afterwards, endocardial mapping is repeated. Body temperature is maintained at 37°C until intraoperative mapping is completed; thereafter, temperature is decreased to 28° to 32°C.

The ascending aorta is clamped, and the heart is arrested with cold anterograde cardioplegia solution. Alternatively, the aorta is not clamped, and the entire procedure is done during hypothermic fibrillation. The LVA is repaired using one of the techniques described below. The distal coronary anastomoses are performed, followed by releasing the aortic clamp.[54] Air is removed by venting the ascending aorta and left ventricle while filling the heart and ventilating the lungs with the patient in the Trendelenburg position. The patient is rewarmed, and proximal coronary anastomoses are performed. Once normothermia is achieved, an electrophysiologic study may be repeated if indicated. Temporary pacing wires are placed on the right atrium and right ventricle, cardiopulmonary bypass is discontinued, and heparin is reversed. The heart is decannulated, and the median sternotomy is closed with mediastinal drains after hemostasis is achieved.

Weaning from cardiopulmonary bypass frequently requires some degree of inotropic support. Typically 5 μg/kg per minute of dopamine, nitroglycerin to prevent coronary spasm, and nitroprusside for afterload reduction are used. An intra-aortic balloon pump (IABP) may be needed in patients with borderline ventricular function. Transesophageal echocardiography is useful for assessing left ventricular function and to detect residual intracardiac air.

Additional inotropic support may not increase cardiac output significantly because of abnormal ventricular compliance and may produce arrhythmias and poorly tolerated tachycardia. Hypokalemia and hypomagnesemia are corrected immediately to minimize arrhythmias. Intraoperative and postoperative ventricular ectopy is treated aggressively with intravenous lidocaine. Intravascular volume shifts are poorly tolerated in these patients because of poor ventricular compliance; therefore, rapid transfusions are avoided by meticulous hemostasis before closing. Because the left ventricle is poorly distensible, stroke volume is relatively fixed, and a resting heart rate of between 90 and 115 beats per

minute is not unusual to maintain a cardiac index of approximately 2.0 L/m^2 per minute.

Growing experience suggests that the ultimate size of the left ventricular cavity at the end of the procedure is critical to patient outcome. Using preoperative and postoperative three-dimensional techniques to image the left ventricle, Cherniavsky and colleagues proposed that the aneurysm resection or patch should produce a postoperative left ventricular end-diastolic volume of about 150 mL.[55]

Plication

Plication without opening the aneurysm is reserved for only the smallest aneurysms that do not contain mural thrombus. A two-layer suture line of 0 monofilament is placed across the aneurysm using a strip of Teflon felt on either side. The suture line is oriented to reconstruct a relatively normal left ventricular contour and does not exclude all aneurysmal tissue.

Linear Closure

After removing all mural thrombus, the aneurysmal wall is trimmed, leaving a 3-cm rim of scar to allow reconstruction of the normal left ventricular contour (Fig. 31-9). Care is taken not to resect too much aneurysmal wall and overly reduce ventricular cavity size. A monofilament 2-0 suture may be used to reduce the neck of the aneurysm to the proper size before closure of the ventricular wall.[14] Anterior aneurysm defects are closed vertically between two external 1.5-cm strips of Teflon felt, two layers of 0 monofilament horizontal mattress sutures, and finally, two layers of running 2-0 monofilament vertical sutures with large-diameter needles (Fig. 31-10).

Circular Patch

Inferior or posterior aneurysms generally require circular patch closure, which also can be applied to anterior aneurysms. After opening the aneurysm (Fig. 31-11) and after débridement of thrombus and aneurysm wall (Fig. 31-12), a Dacron (Hemashield) patch is cut to be 2 cm greater in diameter than the ventricular opening. Interrupted, pledgeted 0 monofilament horizontal mattress sutures are placed through the ventriculotomy rim and then through the patch, leaving the pledgets outside the ventricular cavity (Fig. 31-13). Sutures are tied, and additional interrupted sutures or a second layer of running 2-0 monofilament is placed for hemostasis.

Endoventricular Patch

The endoventricular patch technique is suitable for anterior aneurysms but is less suited for inferior or posterior aneurysms, for which the standard (circular) patch technique is used. After débridement of thrombus, a running 2-0 polypropylene suture may be placed at the aneurysm rim to optimize

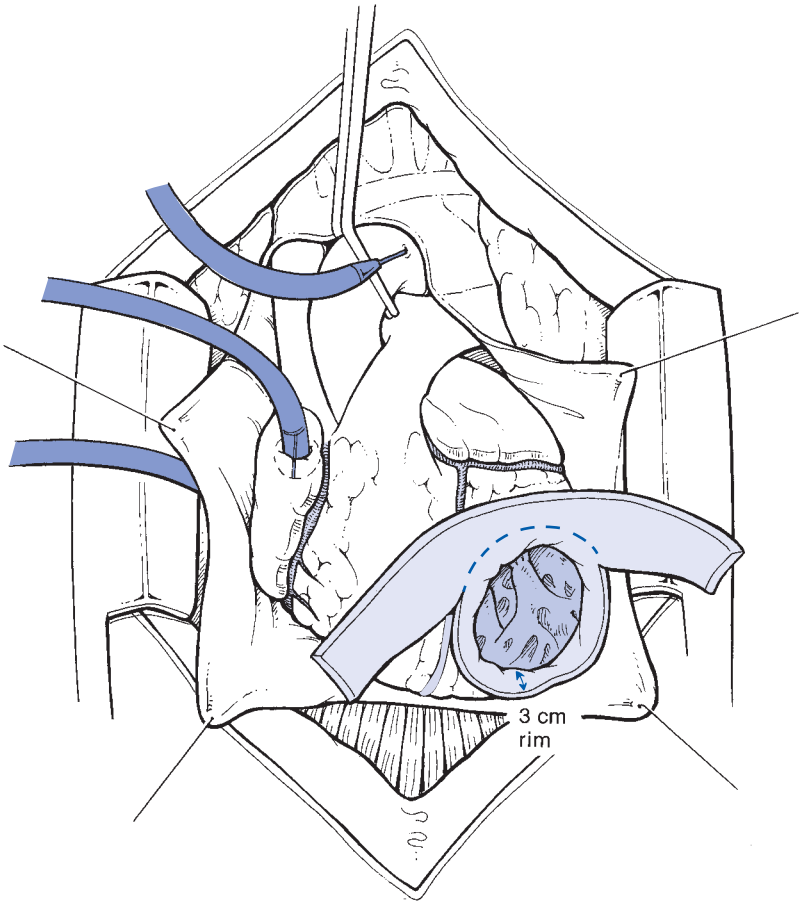

Figure 31-9. Linear repair. The fibrous aneurysm wall is excised, leaving a 3-cm rim of fibrous aneurysm wall attached to healthy muscle.

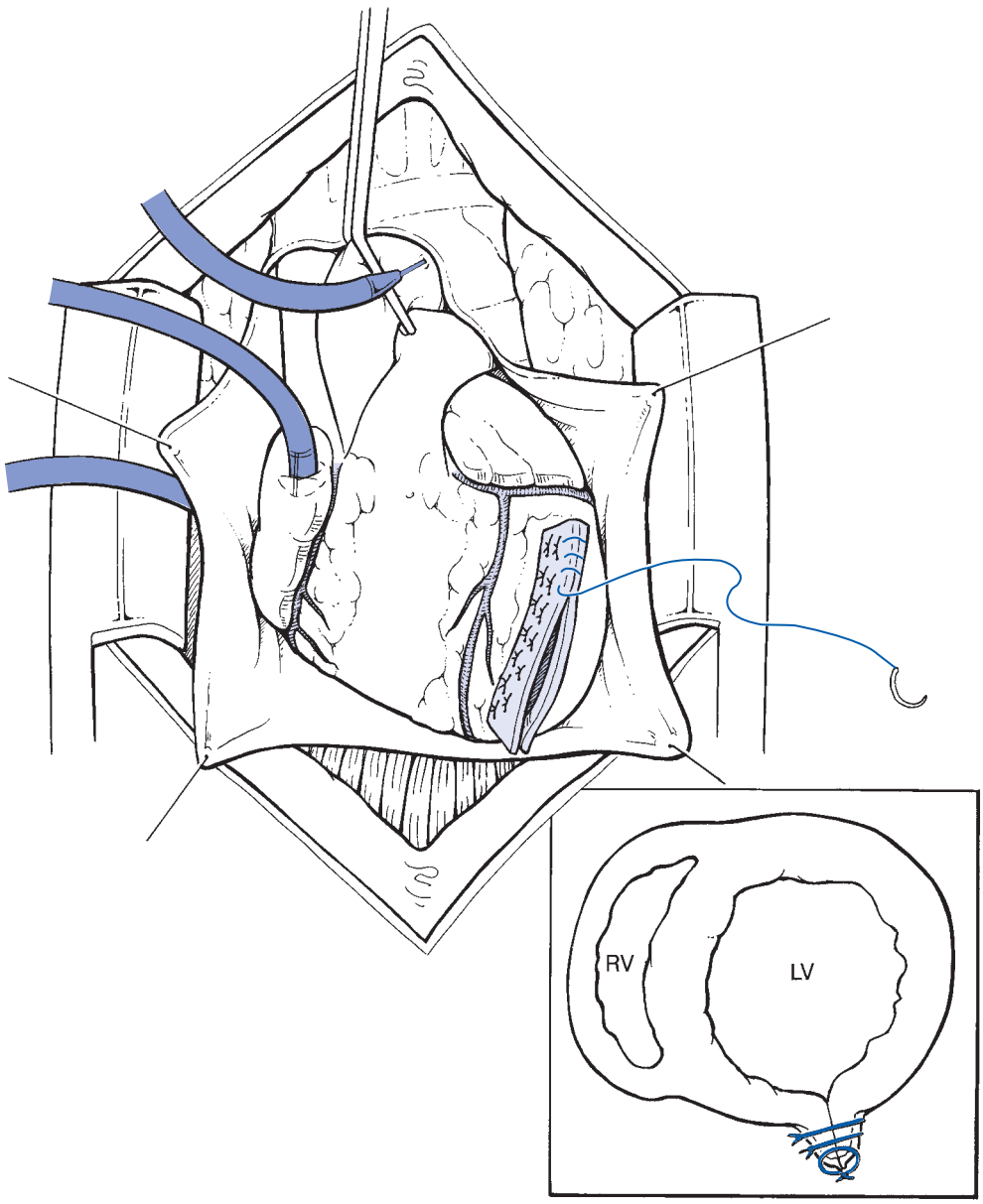

Figure 31-10. Linear repair. The aneurysm walls are closed in a vertical line between two layers of Teflon felt. Two layers of 0 monofilament interrupted horizontal mattress sutures are reinforced with two layers of running 2-0 monofilament sutures.

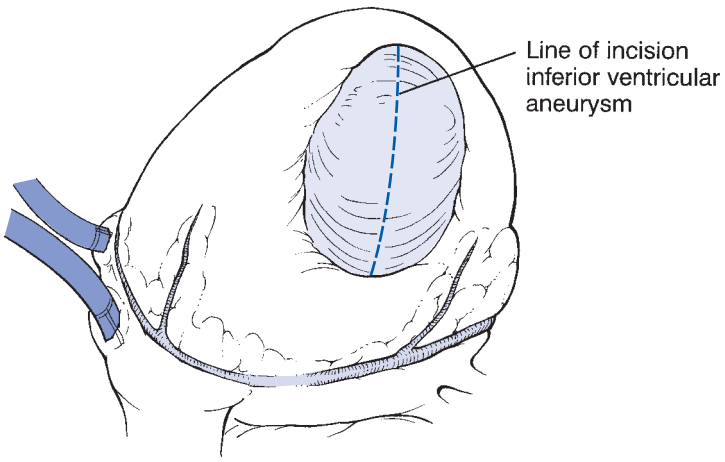

Figure 31-11. Circular patch repair. The aneurysm wall is incised. An inferior aneurysm is shown.

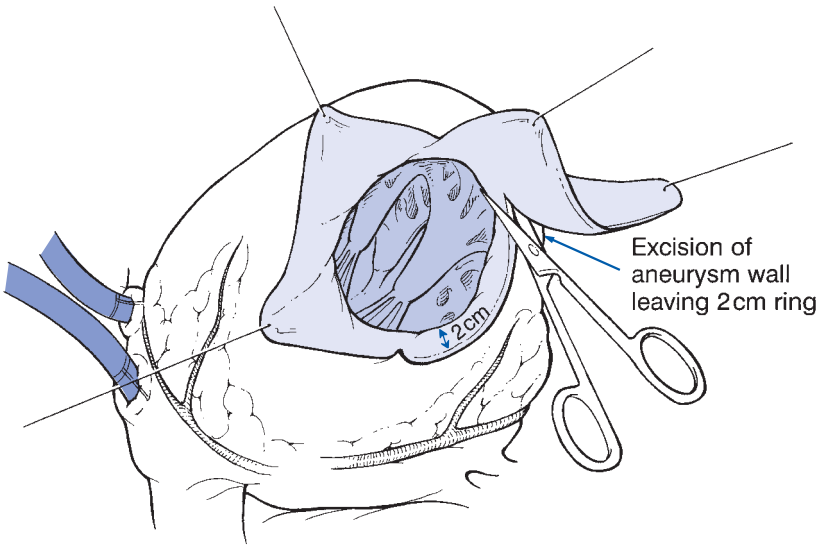

Figure 31-12. Circular patch repair. The aneurysmal wall is excised, leaving a 2-cm rim of fibrous aneurysmal wall attached to healthy muscle.

left ventricular size.[3,14,47,53] If the remaining ventricular defect is small (<3 cm), then the ventricular wall may be closed linearly.[14] More commonly, a patch (e.g., bovine pericardium, Dacron cloth, or polytetrafluoroethylene) is cut to size sufficient to restore normal ventricular size and geometry when secured to the aneurysmal rim (Fig. 31-14). The patch is sutured to normal muscle at the aneurysmal circumference using a running 3-0 polypropylene suture and is secured with single sutures at three or four places around the patch circumference. The patch may extend onto the interventricular septum,[3,47,53] or the aneurysmal septum may be plicated.[14] Interrupted 3-0 sutures are placed as needed to ensure good fit. Care is taken not to distort the papillary muscles. The aneurysmal rim is trimmed to allow primary closure of the native aneurysmal wall over the patch using two layers of running 2-0 monofilament suture without pledgets (Fig. 31-15).

As compared with linear and circular patch techniques, the endoventricular patch technique has technical advantages. An endoventricular patch preserves the LAD for possible grafting and leaves no external prosthetic material to produce heavy pericardial adhesions. The technique facilitates patching the interventricular septum and is suitable for acute infarctions when tissues are friable.[7,16,56]

Other Ventricular Remodeling Techniques

In addition to the techniques just listed, in which left ventricular infarct tissue is excised and/or replaced with patch material, an alternative would be to alter the biologic properties of the infarct scar. Remaining infarct scar (whether aneurysmal or not) then can be seeded with myoblasts or stem cells, which offer the potential to restore cardiac muscle mass and contraction. This technique has been termed *cellular*

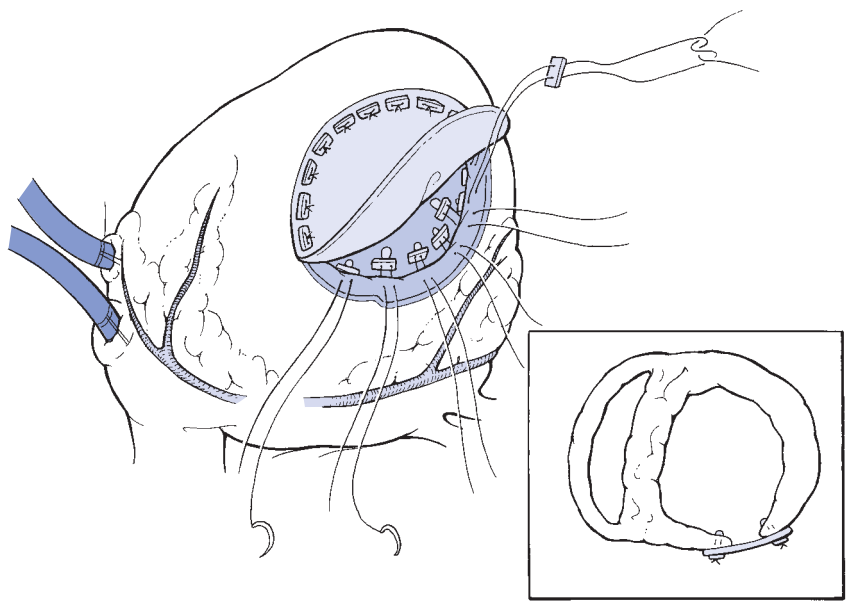

Figure 31-13. Circular patch repair. The aneurysmal defect is closed with a Dacron patch using interrupted 2-0 monofilament horizontal mattress sutures with reinforcing pledgets.

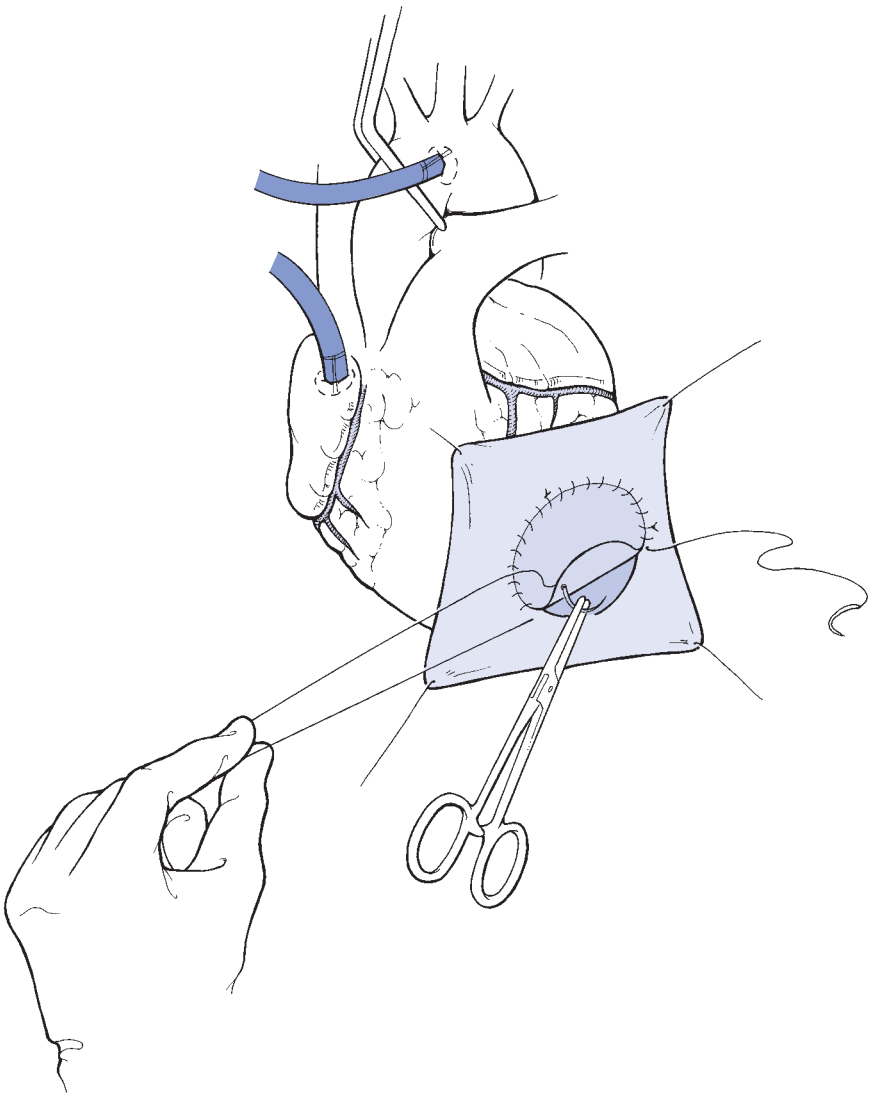

Figure 31-14. Endocardial patch. Without excising the aneurysm wall, the ventricular defect is closed with a Teflon felt patch using 3-0 polypropylene suture secured at three or four points along the suture line. Additional 3-0 pledgeted horizontal mattress sutures may be used to achieve hemostasis.

cardiomyoplasty and has been done only on a limited basis in humans.[57] In animals, cellular cardiomyoplasty has improved global left ventricular performance and geometry using either myoblasts, stem cells that differentiate into myocytes, fibrocytes, or cells seeded onto a graft matrix.[58–62] Only myoblasts or stem cells that differentiate into myocytes have improved regional ventricular contractility. Cellular cardiomyoplasty could be done by direct injection of cells at the time of coronary revascularization or even by transcoronary or intramyocardial injection in the cardiac catheterization laboratory.

Coronary Revascularization

Concurrent coronary revascularization is performed as in standard coronary bypass procedures. Since the endoventricular patch technique does not encroach on the LAD, the left internal mammary artery may be used to graft the LAD coronary artery.

Mitral Regurgitation

The severity of mitral regurgitation should be evaluated before cardiopulmonary bypass by intraoperative transesophageal echocardiography. The need for concurrent mitral valve operation increases as the preoperative ejection fraction decreases[63] (Fig. 31-16). The mitral valve is also inspected from below after opening the aneurysm and beginning repair of the aneurysm. Transventricular mitral valve repair may be done by placing pledgeted polypropylene sutures at both mitral commissures to reduce the circumference of the annulus.[64] This technique produces satisfactory short-term results, but long-term results are not known. Usually the mitral valve is repaired via left atriotomy after completion of the distal coronary artery anastomoses and before releasing the aortic cross-clamp. If mitral regurgitation results from annular dilatation and systolic restriction of leaflet motion (Carpentier type IIIB), Carpentier mitral annuloplasty is done.[65]

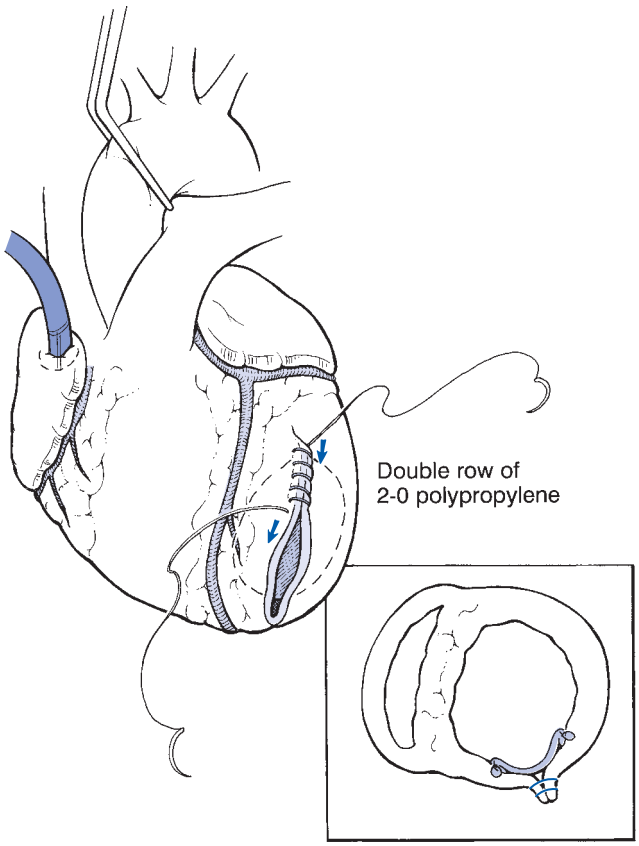

Figure 31-15. Endocardial patch. The aneurysm wall is closed over a Teflon patch after resecting excess aneurysm tissue. A double row of running vertical 2-0 polypropylene sutures is used.

Cardiac Transplantation

In symptomatic patients with sufficient depression of global left ventricular function to preclude aneurysm repair, transplantation is a reasonable alternative. Relative contraindications to cardiac transplantation in patients with LVA include current amiodarone therapy and prior placement of an internal defibrillation device.

Ventricular False Aneurysm

Ventricular false aneurysms are repaired with the same techniques used for true ventricular aneurysms based on the location and size of the aneurysm. The circular patch technique is particularly useful because inferior false aneurysms are common and typically have narrow necks. Usually the wall of the false aneurysm is inadequate to close over the defect.

Ventricular Rupture

Any of the techniques just described may be used to manage a contained ventricular rupture. Because infarcted tissue is particularly friable 5 to 10 days after rupture, closure may be difficult. The endoventricular technique is particularly well suited for this uncommon operation because the patch can be sewn to the margins of healthy endocardium, which may be at some distance from the site of rupture. Patient survival also has been reported by gluing a biologic patch to the ventricular epicardium over the site of the rupture.

EARLY RESULTS

Hospital Mortality

In a compilation of 3439 operations for LVA between 1972 and 1987, hospital mortality was 9.9% and ranged from 2 to 19%.[18] More recent reports indicate that hospital mortality has fallen to 3 to 7% in the last decade using either patch[7,16,63,66,67] or linear closures.[19,51,67] The most common cause of hospital mortality is left ventricular failure, which occurs in 64% of deaths.[51]

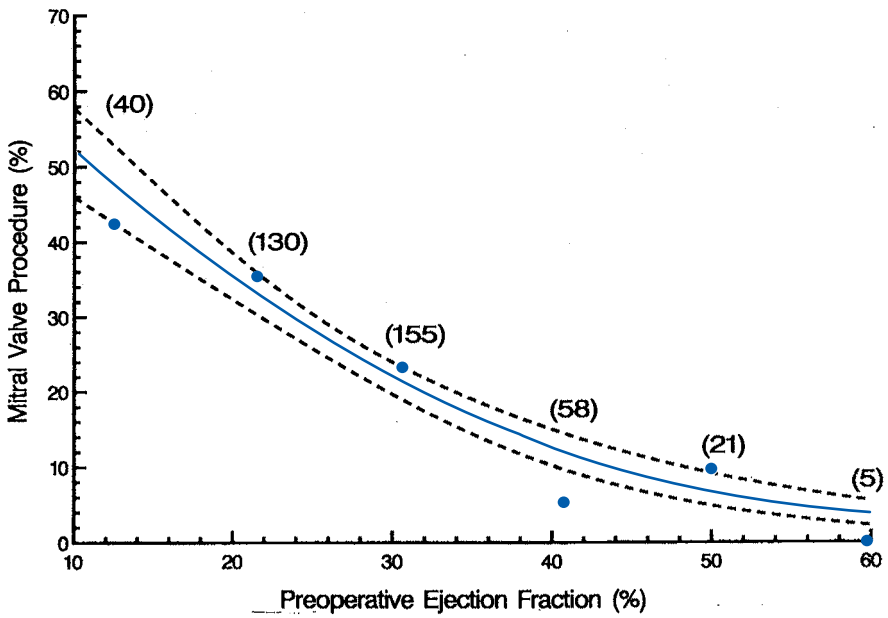

Figure 31-16. Prevalence of performing concomitant mitral valve procedures as a function of preoperative ejection fraction. (*Reproduced with permission from Athanasuleas.*[63])

Table 31–3.

In-Hospital Complications of Ventricular Aneurysm Repair

Low cardiac output 22–39%
Ventricular arrhythmias 9–19%
Respiratory failure 4–11%
Bleeding 4–7%
Dialysis-dependent renal failure 4%
Stroke 3–4%

Risk factors for hospital mortality include increased age,[18,51,63,67] incomplete revascularization,[51] increased heart failure class,[18,67–69] female gender,[18] emergent operation,[18] ejection fraction of less than 20 to 30%,[63,67,68] concurrent mitral valve replacement,[7,18,63] preoperative cardiac index of less than 2.1 L/m^2 per minute,[4] mean pulmonary artery pressure greater than 33 mm Hg,[4] serum creatinine concentration greater than 1.8 mg/dL,[4] and failure to use the internal mammary artery.[69]

In-Hospital Complications

The most common in-hospital complications are shown in Table 31-3 and include low cardiac output, ventricular arrhythmias, and respiratory failure.[18,19,66,67,70] Low cardiac output may be more common in patients undergoing intraoperative mapping due to perioperative cardiac injury.[71]

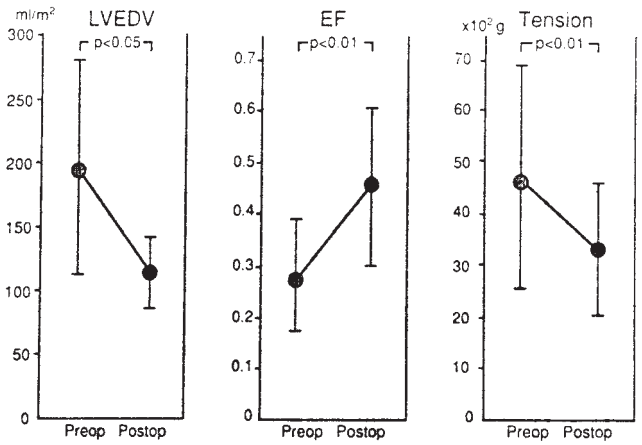

Figure 31-17. Effects of linear aneurysmectomy on left ventricular end-diastolic volume (LVEDV), ejection fraction (EF), and wall tension. (*Reproduced with permission from Kawachi et al.*[74])

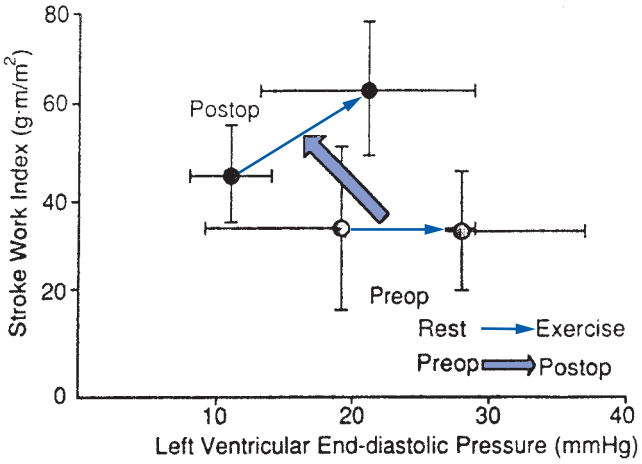

Figure 31-18. Relationship between stroke work index and left ventricular end-diastolic pressure. Data are shown at rest and during exercise before (preop) and after (postop) linear aneurysmectomy. Stroke work index increased only with exercise postoperatively. (*Reproduced with permission from Kawachi et al.*[74])

Left Ventricular Function

The preponderance of data from the last two decades have shown that left ventricular function improves in most patients undergoing operation for LVA. Operation improves

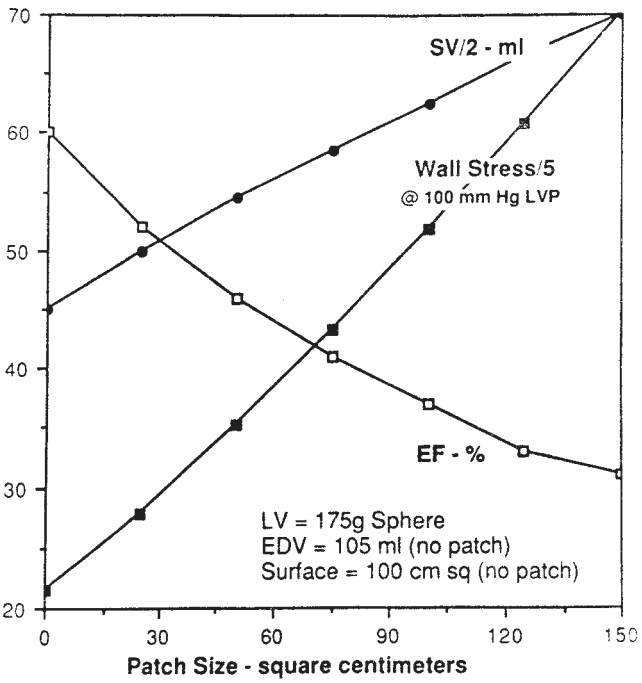

Figure 31-19. Computer prediction of the effects of patch size on stroke volume (SV), ejection fraction (EF), and wall stress (afterload) at a chamber pressure of 100 mm Hg. Predictions are based on data from an animal model of simulated aneurysm repair, neglecting the effects of afterload on stroke volume. Because increasing afterload in reality decreases muscle shortening, patch reconstruction can increase stroke volume only if contractile reserve is sufficient to overcome the afterload from increased ventricular size. (*Reproduced with permission from Nicolosi et al.*[91])

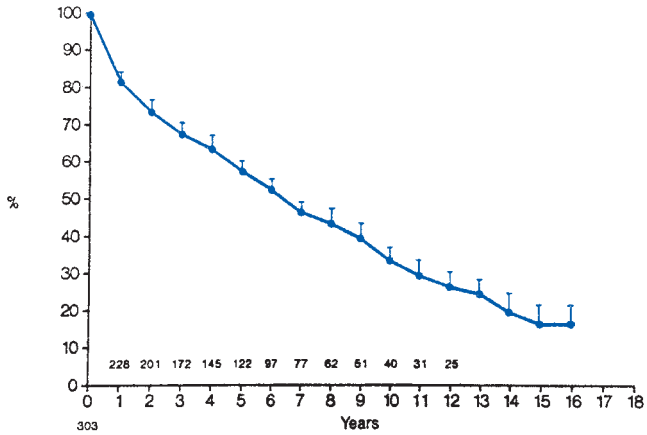

Figure 31-20. Survival in 303 patients undergoing left ventricular aneurysmectomy. (*Reproduced with Modified from Couper et al.*[68])

ejection fraction (EF) whether linear repair[5,8,72–74] or patch repair[13,16,63,75–78] is used (Fig. 31-17). Both techniques decrease end-diastolic and end-systolic volumes[63,73,76,78] and improve exercise response[16,74] (Fig. 31-18). Aneurysmal repair in general also improves diastolic filling, left ventricular diastolic compliance, left ventricular contractility, effective arterial elastance (Ea), and left ventricular efficiency.[31,77–80]

Controversy remains strong regarding whether patch techniques provide results superior to those achieved with linear closures. Stoney and colleagues[11,81] noted lower left ventricular end-diastolic pressure (LVEDP) when more geometric reconstructions were performed. Hutchins and Brawley[82] first noted at autopsy that some patients had severe reduction and distortion of ventricular volume after linear repair. The authors proposed that a more geometric repair might avert these problems. Although no prospective studies compare results from

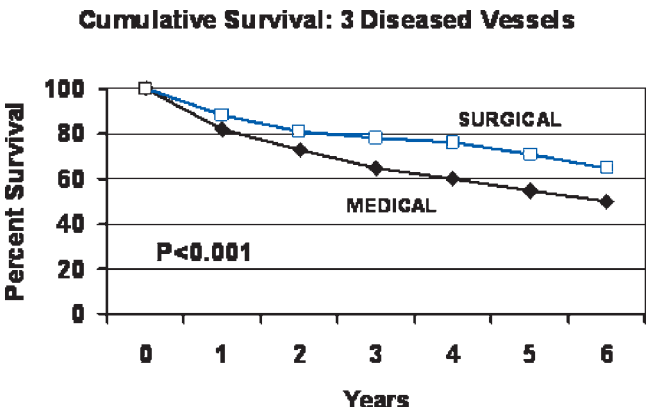

Figure 31-21. Survival in patients with left ventricular aneurysm and three-vessel coronary artery disease treated with medical or surgical therapy. (*Reproduced with permission from Faxon et al.*[42])

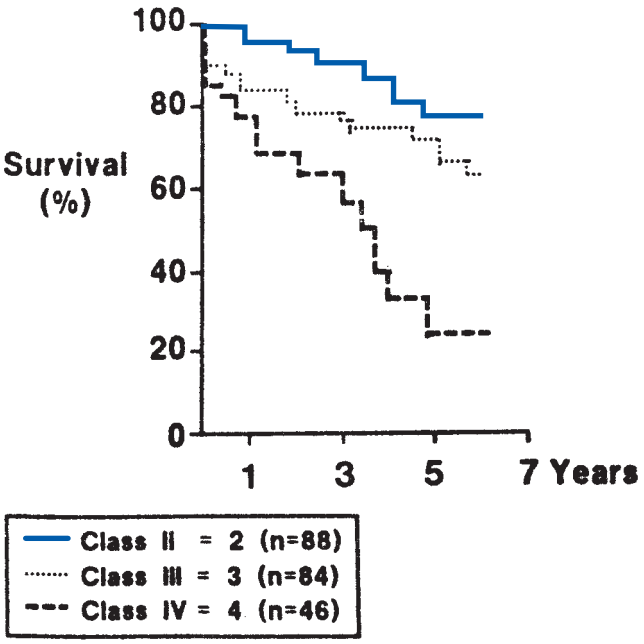

Figure 31-22. Effects of preoperative NYHA functional class on survival after ventricular aneurysm repair and myocardial revascularization. (*Reproduced with Modified from Vauthy et al.*[71])

the two procedures, several very experienced groups attribute improved symptoms, less low cardiac output, and greater improvement in EF to a switch to patch techniques.[7,16,83–86] In other retrospective comparisons, no differences were seen in postoperative symptoms, EF, echocardiographic ventricular dimensions, or late survival between linear and patch repairs.[73,87–90] In an animal model of simulated aneurysm repair, Nicolosi and colleagues[91] found no difference in left ventricular systolic or diastolic function between linear and patch techniques. Two groups reported that switch to patch techniques was associated with increased operative mortality, perhaps owing to excessive volume reduction,[92,93] whereas other groups found improved survival when switching from linear to patch techniques.[94]

The durability of functional benefit from aneurysm repair remains poorly documented. In animals and humans, there is a tendency for the initial improvement in EF, ventricular volume, and filling pressures to diminish over the next 6 weeks to 12 months,[95,96] especially in patients with residual mitral regurgitation.[97]

Although technical differences exist between patch and linear repairs, good functional results are possible with either technique. Suboptimal outcomes result from either technique when left ventricular cavitary volume is overly reduced with resulting decreased stroke volume and impaired diastolic filling.[82,85,96] Excessively small patches reduce stroke volume and impair diastolic filling, but excessively large patches reduce EF and increase wall stress (Fig. 31-19).

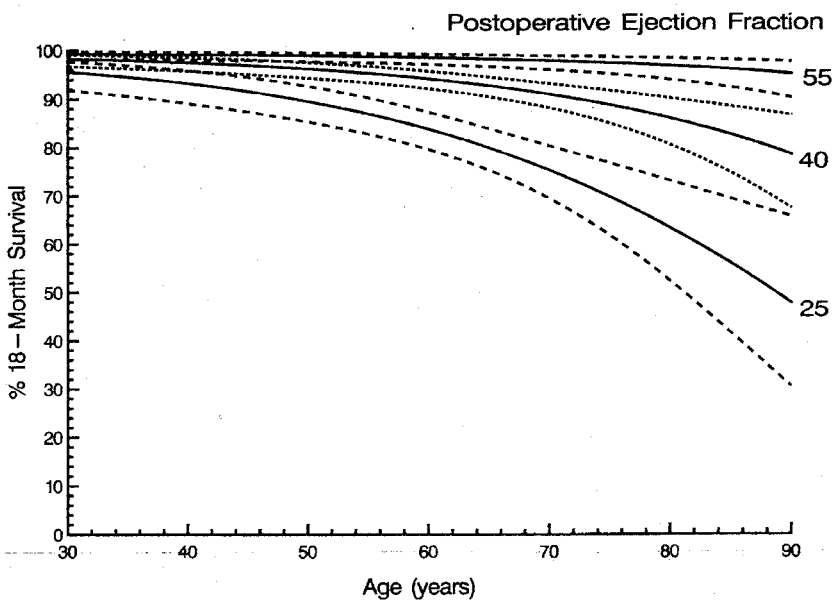

Figure 31-23. Nomogram of 18-month survival after ventricular restoration as a function of patient age and postoperative ejection fraction. (*Reproduced with permission from Athanasuleas.*[63])

LATE RESULTS

Survival

Survival after operation for LVA is variable largely due to differences among patient populations. Five-year survival in recent series varies between 58 and 80%,[5,68] 10-year overall survival is 34%,[68] and 10-year cardiac survival is 57%[51] (Fig. 31-20). Cardiac causes are responsible for 57% of late deaths,[71] and most cardiac deaths result from new MIs. In aneurysm patients randomized to medical or surgical therapy in the CASS (most of the patients had minimal symptoms), survival was not different between medical or surgical therapy, except for patients with three-vessel disease.[42] These patients had better survival with surgery (Fig. 31-21).

Preoperative risk factors for late death include age, heart failure score, EF of less than 35%, cardiomegaly on chest radiograph, LVEDP greater than 20 mm Hg, and mitral regurgitation[42,51,71,87] (Figs. 31-22 and 31-23). The prospective, randomized STICH (Surgical Treaments for Ischemic Heart Failure) trial may provide more definitive data regarding the effect of surgical ventricular restoration on survival, ventricular size and function, quality of life, and exercise capacity.[98]

Symptomatic Improvement

Studies consistently demonstrate improvement in symptoms after operation relative to preoperative symptoms[5,72] (Fig. 31-24). In the study of Elefteriades and colleagues,[72] using a linear repair, mean angina class improved from 3.5 to 1.2 and mean congestive heart failure class improved from 3.0 to 1.7. In the randomized CASS, the subset of patients with LVA achieved a better heart failure class with surgical therapy than with medicine, and rehospitalization for heart failure was less common for the surgical therapy group than for the medicine group.[42] At 18 months, 85% of patients are free of rehospitalization for congestive heart failure, with rehospitalization peaking at 2 to 4 months.[63]

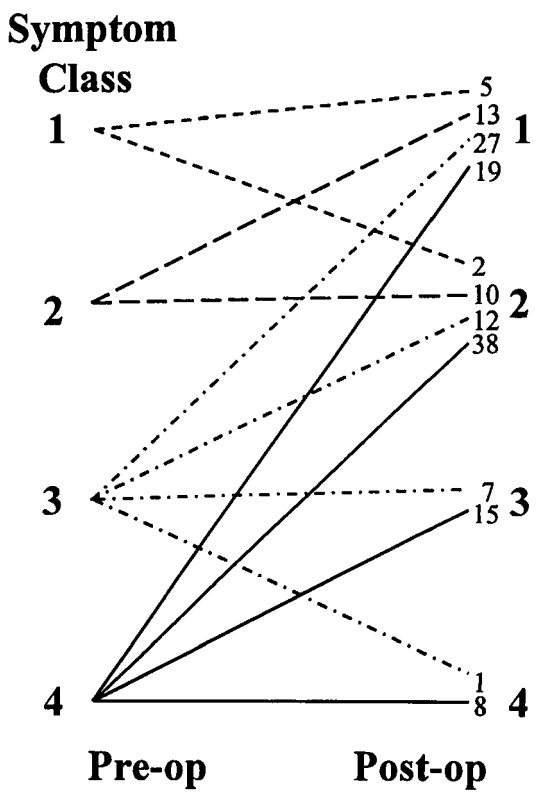

Figure 31-24. Preoperative (Preop) and postoperative (Postop) symptoms of congestive heart failure (NYHA class) in patients undergoing left ventricular aneurysmectomy. (*Reproduced with permission from Mickleborough et al.*[5])

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PART

IVa

Valvular Heart Disease (Aortic)

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CHAPTER 32

Pathophysiology of Aortic Valve Disease

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The aortic valve is a semilunar valve positioned strategically at the end of the left ventricular outflow tract (LVOT). The normal working of this valve is critical to maintaining efficient cardiac function. This chapter looks to explore the anatomic and physiologic properties of the aortic valve.

EMBRYOLOGIC DEVELOPMENT

Embryologic development of the aortic valve is closely associated with development of the LVOT. During the early stages, the main arterial segment (truncus arteriosus) of the primary heart tube is connected to the primitive right ventricle. With subsequent cardiac loop formation, the truncus arteriosus, together with distal segments of the ventricular outlet component, is divided by endocardiac cushion tissue into subaortic and pulmonary outflow tracts. The truncus arteriosus eventually develops into the pulmonary arteries and aorta. As seen in Fig. 32-1, a septum develops within the truncus arteriosus and subsequently fuses with the underlying ventricular septum. At the point of fusion between these two septal components, separation of the ventricular chamber is accomplished by development of the aortic valve.

The right and left cusps of the aortic valve develop from the aortic side of the truncal septum. Opposing this septum, the embryonic posterior aortic valve develops from the truncoconal lining. As development continues, the aortic valve leaflets grow to become nearly uniform in size.

ANATOMY

The aortic valve separates the terminal portion of the LVOT from the aorta. It is a tricuspid valve consisting of three semilunar cusps (left, right, and noncoronary) and the aortic valve annulus (Fig. 32-2). The cusps themselves are attached within the expanded aortic sinuses. The sinus of Valsalva is defined as the space between the edge of the leaflets and the aorta.

Because two of these sinuses give rise to coronary arteries, conventionally they have been named as the *right coronary, left coronary,* and *noncoronary sinuses.* Because of the oblique position of the aortic root, the sinuses themselves are rarely in strictly right and left position. The ostia of coronary arteries usually open from the upper part of the sinus of origin, the ostium of the left coronary artery often being a little higher than the ostium of the right. Areas where attachments of two adjacent cusps to the aorta meet comprise commissures. The commissure between the noncoronary and left coronary leaflets is positioned along the area of aortic valve–mitral valve continuity. Beneath this commissure is the so-called fibrous aortomitral curtain. This is an important anatomic landmark that guides the surgeon toward root enlargement procedures; also, spread of infection/calcification commonly occurs along this curtain. To the right of this commissure, the noncoronary leaflet is attached to the posterior diverticulum of the LVOT. This is the part where the aortic valve is directly related to the right atrial wall. The commissure between the noncoronary and right coronary cusps is positioned directly above the penetrating atrioventricular bundle and membranous septum. The commissure between the right and left coronary cusps is positioned opposite a facing commissure of the pulmonary valve. The adjacent parts of these two aortic cusps are directly related to the right ventricular infundibulum. The lateral part of the left coronary sinus is the only part of the aortic valve that is not related to another cardiac chamber but is in direct relationship with the free pericardial space.

The aortic valve may be described as having a passive valve mechanism that is quite different from the mitral valve. Because of its passive mechanism, the structure of the aortic valve must open and close with minimal pressure differences between the ventricle and aorta. During closing, this same

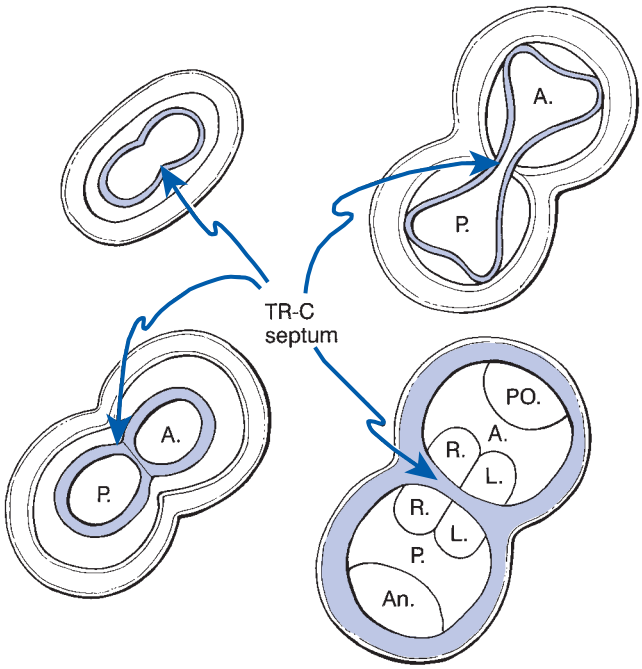

Figure 32-1. Development of the aorta and pulmonary artery is shown, with subsequent development of the aortic valve leaflets. (*Top left*) The truncoconal (TR-C) septum is beginning to divide the truncoconal segment. (*Top right*) This septum continues until division of the aorta and pulmonary artery is completed (*shown at bottom left*). (*Bottom right*) The right and left aortic valve leaflets are derived from the truncoconal septum, whereas the posterior leaflet is derived from the endocardial tissue opposite the truncoconal segment.

mechanism must prevent backflow by perfectly aligning the cusps, which must have enough structural integrity to withstand systemic pressures. The line of closure of the valve is just below the free edge. At the center of the free edge is a nodular thickening called the *nodule of Arantius* from which a thin fibrous projection, Lambl's excrescence, often emanates.

There is no true aortic valve annulus in contrast to the mitral valve. The commonly designated "annulus of the aortic valve" is actually an aortic ring and is the last impediment to flow prior to blood reaching the aorta.

The junction between the ventricular chamber and the aorta is designated as the *ventricular arterial junction.* This must be viewed as either an anatomic or physiologic junction. The physiologic junction is marked by attachments of the semilunar valves that define the separation between the ventricular outflow chamber and proximal aorta. However, there is a discrepancy between this physiologic junction and the anatomic junction owing to, in part, muscular tissue of the ventricle and, in part, fibrous tissue of the septum and mitral valve. As can be seen in Fig. 32-3, the commissures are above the anatomic junction, but the bases of the semilunar attachments of the aortic leaflets are at the true anatomic junction.[1] The fibrous skeleton of the heart forms the posterior wall of the outflow tract, where the leaflets are in fibrous continuity with those of the mitral valve[1] (see Fig. 32-3).

A valve leaflet is composed of collagen, elastin, and glycosaminoglycans. These are the main components for the three principal layers of the leaflet: the fibrosa or arteriosa, the spongiosa, and the ventricularis. As can be seen in Fig. 32-4, the arterial and ventricular sides of the aortic leaflet are associated with the corresponding aortic and ventricular walls. There is no demarcation between the outer layers of the leaflet and the corresponding wall.[2] The outer layers of the leaflet form a continuum with the aortic or ventricular endothelium.

The ventricular side of each aortic valve cusp contains elastin-rich fibers aligned in a radial direction, perpendicular

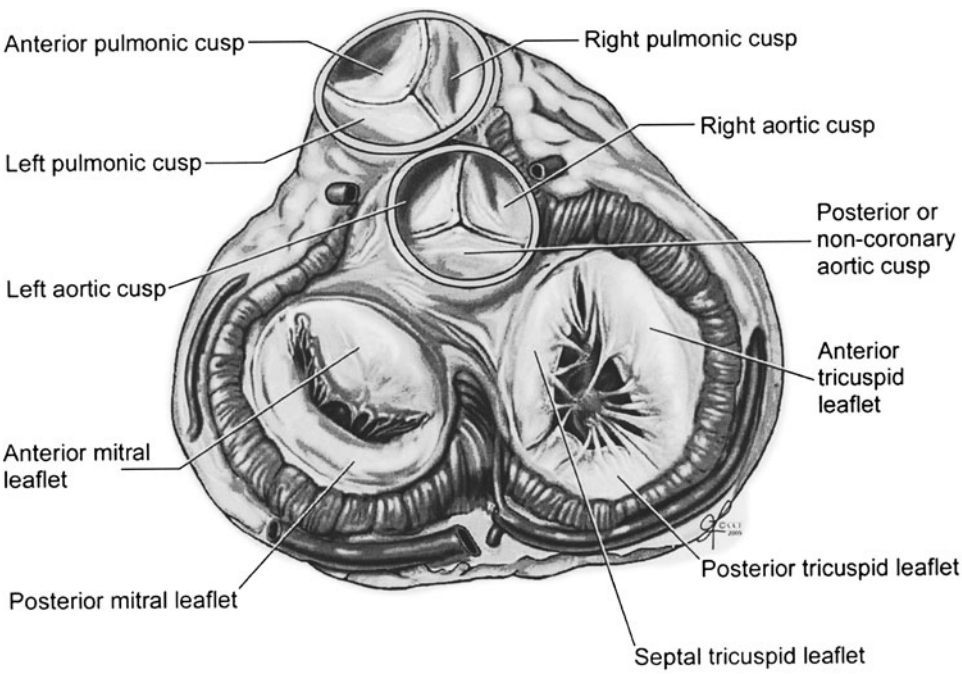

Figure 32-2. Anatomic relationship between the aortic valve and surrounding structures.

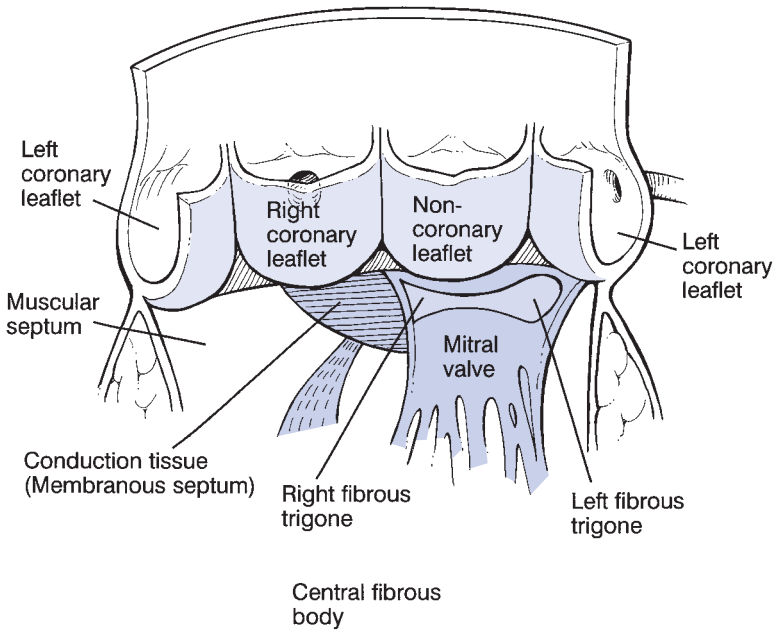

Figure 32-3. A schematic diagram of the relationship of the aortic valve leaflets to the structures underlying the commissures. The noncoronary leaflet straddles the central fibrous body overlying the anterior leaflet of the mitral valve. The conduction tissue traversed the membranous septum between the right coronary and noncoronary leaflets.

to the leaflet free margin. Elastin is mechanically coupled to collagen. The purpose of elastin in the aortic valve leaflet is to maintain a specific collagen fiber configuration and return the fibers to their initial state once the external forces of blood flow subside.[3] In addition, there is a collagen component lying parallel to the free margin in a circumferential direction. The aortic side contains a collagen-rich layer referred to as the *corrugated fibrosa.* These fibers are arranged in a circumferential direction and, in a relaxed state, assume a waveform pattern. The middle layer, referred to as the *spongiosa,* consists mainly of loose connective tissue or mucopolysaccharides. These principal layers of the aortic leaflet provide the necessary biomechanical properties for proper valve function.

On the arteriosa (fibrosa) side of the valve leaflet, endothelial cells are present. Endothelial cells normally align in the direction of stress. In an artery, endothelial cells are aligned in the direction of blood flow because flow stress is the major stress. However, endothelial cells on the aortic valve leaflet are arranged in a circumferential pattern; i.e., they are arranged perpendicular to blood flow. Therefore, shear stress of blood flow across the aortic valve is not the major stress. The major stress across the aortic valve is in the circumferential direction and is perpendicular to blood flow.[4]

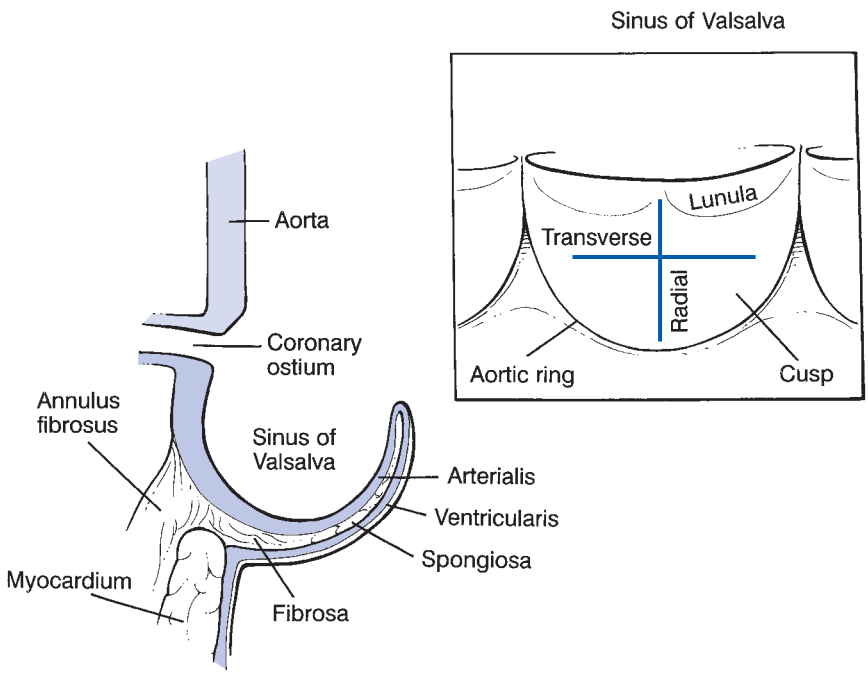

Figure 32-4. Schematic representation of a cross section through the aortic valve leaflet showing the continuity of endocardial and endothelial components with the aortic valve. Inset illustrates the radial and transverse (circumferential) axes of the valve leaflet and the line of attachment to the aortic wall.

MECHANICS OF MOVEMENT

The opening and closing of the aortic valve constitute a passive mechanism responding to the pressure fluctuations of the cardiac cycle and pressure differences between the ventricular chamber and the aorta. Although pressure changes during the cardiac cycle may create some structural changes in the valve mechanism to facilitate opening or closing, the principal component is the pressure difference between the ventricle and the aorta. Under normal circumstances, the valve leaflets offer little impediment to flow because the specific gravity of the leaflets is equal to that of blood.[5] Proper function depends on rapid closure in response to minimal forces moving the valve leaflets.

Opening

During diastole, the pressure difference between the aorta and the ventricle creates stress on the valve leaflets. This stress toward the central portion of the aortic opening constricts the base of the aortic root. In addition, the elastic properties of the aortic root contribute to this decrease in diameter. During late diastole, as blood fills the ventricle, a 12% expansion of the aortic root occurs approximately 20 to 40 ms prior to aortic valve opening.[6,7] Dilatation of the root alone helps in opening the leaflet to about 20%. Actually, the leaflets begin to open even before any positive pressure is applied owing primarily to the effect of aortic root dilatation.[8] As pressure rises in the ventricular outflow tract, tension across the leaflets lessens. As pressure continues to rise, the pressure difference across the valve leaflets is minimal, and no tension is present within the leaflet.[6] At this point, without constriction of the aortic root at the leaflet attachments owing to redistributed stress during diastole, the aortic root expands to allow the valve to open rapidly at the beginning of ejection. Ejection takes place with a brisk upward movement of the straightened leaflets, and the angle at their bases becomes more acute. These mechanisms permit the valve to open quickly and to offer minimal resistance to ejection.[9]

Closure

Closure of the aortic valve is one of the more elegant mechanisms of the valve apparatus.[10] A principal theory involved in closure is the *vortex theory*. The vortex theory recognizes the importance of the sinus of Valsalva in providing a reservoir of blood for small developing vortices. These small vortices allow full expansion of the opened valve leaflets. However, by maintaining the space between the edge of the leaflet and the aortic wall, reversal of flow at the end of systole provides rapid closure. As ejection occurs, deceleration of blood at the stream edge creates small eddy currents of vortices. These small vortices along the aortic wall move gradually toward the base of the ventricular arterial junction at the edge of the leaflet and the top of the sinus of Valsalva. As flow declines at the end systole, the pressure difference across the opened aortic valve leaflets decreases. At the end of ejection and prior to valve closure, the vortices within the sinus of Valsalva balloon the valve leaflets toward the center of the aorta. The angle at the base of each leaflet becomes more obtuse and rounded, in contrast to the sharp angle at maximal valve opening. This point of flexure begins to move up the valve leaflet and eventually terminates at the free margin of the valve cusp.[9] Therefore, the mechanism of valve closure begins during ejection with development of vortices within the sinus of Valsalva priming the leaflets for valve closure. When pressure between the ventricular outflow tract and aorta equalizes, a small reversal of flow occurs owing to the deceleration of ejected blood. This small flow reversal causes the leaflets to close rapidly.

Apposition of the valve leaflets occurs briskly. The second heart sound occurs after complete closure of the aortic valve.[11] The valve leaflets act as an elastic membrane, with stretch and recoil producing the sound; the sound is not produced by physical apposition of the valve leaflets. The second heart sounds depends on the elasticity of the valve leaflets and diastolic blood pressure to cause reverberation of the leaflets.

AORTIC STENOSIS

Prevalence and Etiology

Valvular aortic stenosis (AS) without accompanying mitral valve disease is more common in men than in women and is rarely rheumatic in etiology. Age-related degenerative calcific AS is currently the most common cause of AS in adults and the most frequent reason for aortic valve replacement (AVR) in patients with AS.[12]

The prevalence of aortic valve abnormalities as detected by population-based echocardiographic study increases with age, with 2% of people 65 years of age or older having isolated calcific AS, whereas 29% exhibit age-related aortic valve sclerosis without stenosis.[12]

Acquired aortic stenosis

The most common cause of AS is degenerative calcification of the aortic valve. Although previously considered to be the result of years of mechanical stress on an otherwise normal valve, the evolving concept is that the degenerative process leads to proliferative and inflammatory changes, with lipid accumulation, upregulation of angiotensin-converting enzyme (ACE) activity, and infiltration of macrophages and T lymphocytes ultimately leading to calcification of the aortic valve.[12–17] Progressive calcification, initially along the flexion lines at their bases, leads to immobilization of the cusps. The characteristic pathologic findings are discrete, focal lesions on the aortic side of the leaflets that can extend deep into the aortic annulus. The deposits may involve the sinuses of Valsalva and the ascending aorta. The risk factors for the development of calcific AS are similar to those for atherosclerosis and include elevated serum levels of low-density lipoprotein

(LDL) cholesterol and lipoprotein A [Lp(a)], diabetes, smoking, and hypertension.[18,19] Age-related aortic valve sclerosis is associated with an increased risk of cardiovascular death and myocardial infarction (MI). Beta-HMG CoA reductase inhibitors (statins) have emerged as a potential therapy for treating aortic valve calcification. Experimental animal study has shown that aortic valves from a 2-month experimental hypercholesterolemia study develop atherosclerosis and that treatment with atorvastatin produces improvement in the valve lesion.[20] Growing evidence from retrospective studies demonstrates that therapy with statins is a potential approach to the treatment of aortic valve disease. Up to 50% of annual reduction in measurable disease progression, whether quantified by Doppler echocardiographic jet velocity or valve area or by electron-beam tomographic valve calcium scores, was noticed in patients treated with statins.[21–23] The largest prospective clinical trial (Schottische Aortic Stenosis and Lipid Lowering Trials, SALTIRE), however, failed to demonstrate a slowing of progression of AS in patients treated with high doses of atorvastatin.[24] Furthemore, there is conflicting evidence indicating that statins may stimulate bone cell calcification and ossification of the aortic valve.[25] Currently, there are two ongoing prospective trials in Europe evaluating the cholesterol-lowering medications as a therapeutic strategy to slow the progression of aortic valve stenosis (AVS): Simvastatin and Szetimide in Aortic Stenosis (SEAS)[28] and RAAVE (rosuvastatin).[26] Results of these studies will be helpful in our further understanding of potential therapies for this disease.

Calcific AS is also observed in a number of other conditions, including Paget disease of bone and end-stage renal disease. Ochronosis with alkaptonuria is another rare cause of AS, which also can cause a rare greenish discoloration of the aortic valve.

Bicuspid aortic stenosis

Calcified bicuspid aortic valve represents the most common form of congenital AS. Bicuspid aortic valves are present in approximately 2% of the general population. Gradual calcification of the bicuspid aortic valve results in significant stenosis most often in the fifth and sixth decades of life, earlier in unicommissural than in bicuspid valves and earlier in men than in women.[30] The abnormal architecture of the unicommissural or bicuspid aortic valve induces turbulent flow, which injures the leaflets and leads to fibrosis, increased rigidity, leaflet calcification, and narrowing of the aortic valve orifice.[31] Bicuspid valves often are associated with dilatation of the ascending aorta related to accelerated degeneration of the aortic medium that in some cases may progress to aneurysm formation.[32] Recent work suggests that a DNA transcriptional error, possibly for the gene encoding endothelial nitric oxide synthetase, may be implicated in the genetic abnormality that leads to bicuspid aortic valve.[33] It appears that the microfibrils within the aortic valve and the aortic root are defective in structure in patients with bicuspid aortic valve disease. This leads to a decrease in mechanical support for the valve, thereby contributing to accelerated "wear and tear" and, hence, degenerative changes in the valve matrix.[33]

Rheumatic aortic stenosis

Rheumatic AS represents the least common form of AS in the adult population.[34] Rheumatic AS is rarely an isolated disease and usually occurs in conjunction with mitral valve stenosis.[35] Rheumatic AS is characterized by diffuse fibrous leaflet thickening of the tricuspid valve with fusion to a variable extent of one or two commissures. The early stage of rheumatic AS is characterized by edema, lymphocytic infiltration, and revascularization of the leaflets, whereas the later stages are characterized by thickening, commissural fusion, and scarred leaflet edges.

Overall distribution of causes of AS varies significantly among different age groups. Among patients younger than 70 years of age, congenitally calcified bicuspid valves were responsible for half of surgical cases. In contrast, in patients over 70 years of age, degenerative calcific stenosis is by far the most prevalent cause of stenosis, accounting for 48% of all surgical cases.[36]

Pathophysiology

Myocardial response

AS causes gradual obstruction to left ventricular outflow. Left ventricular output is maintained by the development of left ventricular hypertrophy (LVH), which may result in a large pressure gradient across the stenotic valve for a period of many years without any decrease in cardiac output, dilatation of the left ventricle, or development of symptoms. As the left ventricle becomes less compliant, atrial systole becomes more important for maintaining cardiac output, and onset of atrial fibrillation may result in clinical worsening and ventricular decompensation.

Critical obstruction to the left ventricular outflow is reached with (1) an increase in peak systolic pressure gradient of greater than 50 mm Hg in the presence of normal cardiac output and (2) a decrease in effective aortic orifice area of less than 0.5 cm^2/m^2 of body surface area (usually <0.8 cm^2).

Myocardial hypertrophy in patients with AS is characterized by increased gene expression for collagen I and II and fibronectin that is associated with activation of the renin-angiotensin system.[35] Reduction in renin-angiotensin parallels regression of hypertrophy after AVR.[37] In late stages of severe AS, the left ventricle decompensates with resulting dilated cardiomyopathy (Fig. 32-5). Cardiac output declines, and the pulmonary artery pressure rises, leading to pulmonary hypertension. Experimental studies have indicated a role of apoptotic mechanisms in the progression of LVH to failure in patients with AS.[38] For the 50% of patients who present with symptoms of congestive heart failure (CHF), mean survival is less than 1 year.[39]

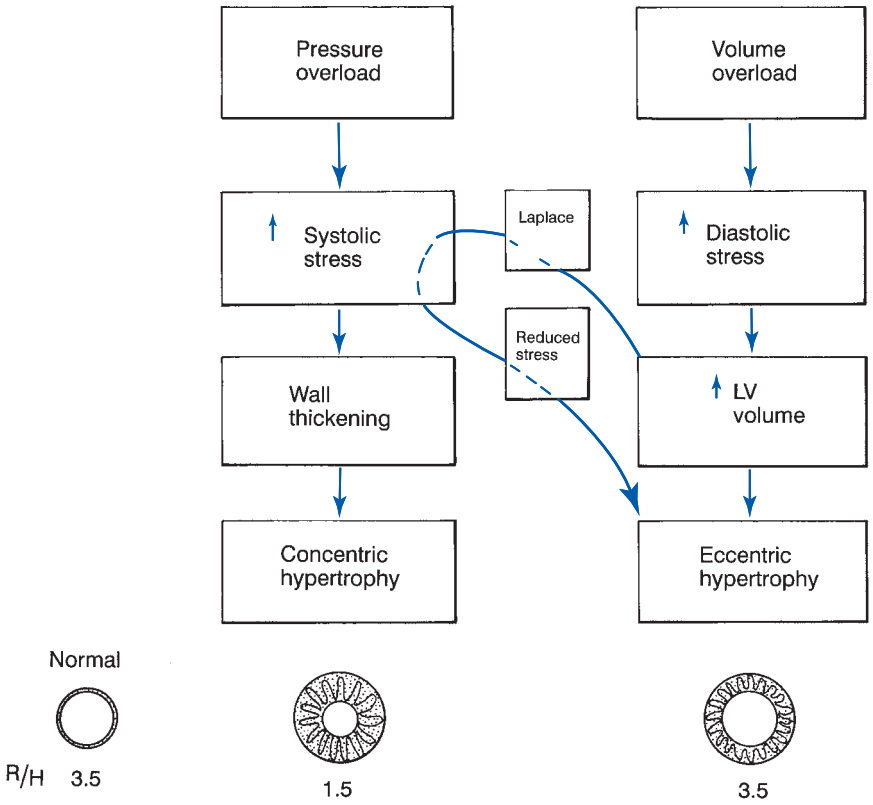

Figure 32-5. Schematic representation of the pathophysiology of pressure and volume overload. With pressure overload, an increase in systolic wall stress provides the stimulus to increase wall thickness and normalizes peak systolic stress. This progresses to concentric hypertrophy, where the ratio of the radius to wall thickness is markedly less than normal. This development is in sharp contrast to volume overload, wherein the increase in diastolic stress provides a stimulus for elongation of myofibrils to increase left ventricular (LV) volume. Because of the increase in LV volume, by Laplace's law, systolic stress increases to induce wall thickening, which reduces stress and produces eccentric hypertrophy. Eccentric hypertrophy increases LV volume and wall thickness; however, the ratio of ventricular radius to wall thickness (R:H) remains normal. (*Modified with permission from Grossman W, McLaurin LP, Stefadouros MA: Left ventricular stiffness associated with chronic pressure and volume overloads in man. Circ Res 1974; 35:793.*)

Coronary circulation

Left ventricular outflow obstruction results in elevation of left ventricular systolic and diastolic pressures, decreased aortic pressure, and increased left ventricular ejection time. Increased left ventricular pressure with left ventricle volume overload results in left ventricular failure. Prolonged left ventricular ejection time (LVET) results in a decrease in diastolic time and thus myocardial perfusion time. Left ventricular hypertrophy, increased systolic pressure, and prolongation of ejection result in increased myocardial oxygen consumption. Reduced coronary artery flow also may lead to inadequate myocardial oxygen supply in patients with AS, even in the absence of coronary artery disease (CAD). Myocardial ischemia in patients with AS can be induced by an increase in myocardial oxygen demand as a result of exercise or isoproterenol administration, as documented by an increase in the lactate levels, even in the absence of CAD. Myocardial oxygen supply-demand disparity is the main mechanism for angina in patients with AS (Fig. 32-6). Rarely, angina results from calcium emboli to the coronary arteries.

Syncope

Syncope most commonly is due to the reduced cerebral perfusion that occurs during exertion secondary to the decrease in arterial pressure consequent to peripheral vasodilation in the presence of a fixed cardiac output. Syncope also may be the result of dysfunction of baroreceptor mechanisms and a vasodepressor response to the increased left ventricular systolic pressure during exercise. Approximately 15% of patients present with syncope; only 50% survive 3 years.

Hemodynamics

The severity of AS is assessed by estimating the mean systolic gradient and aortic valve area (AVA). The Gorlin formula is used to determine the stenotic orifice area derived from the pressure gradient and cardiac output from the fundamental relationships linking the area of an orifice to the flow and pressure drop across the orifice. The AVA is calculated from the Gorlin formula using the following equation:

$$\text{Aortic valve area} = \frac{\text{cardiac output}}{44.3(\text{SEP})(\text{HR})\sqrt{\text{mean gradient}}}$$

The systolic ejection period (SEP) is a time period (in seconds) defined from aortic valve opening to closure. The cardiac output can be measured using the Fick or thermodilution technique. The normal AVA is 2.6 to 3.5 cm^2 in adults. Valve areas of 0.8 cm^2 or less represent severe AS. In low-output states, the Gorlin formula systematically may predict smaller valve areas than are actually present. Several reports also indicate that the AVA area from the Gorlin formula increases with increases in cardiac output.[40]

In patients with AS, the transvalvular pressure gradient is best measured with a catheter in the left ventricle and another in the proximal aorta. Pressure gradients can be estimated by obtaining catheter-derived pressures on both sides

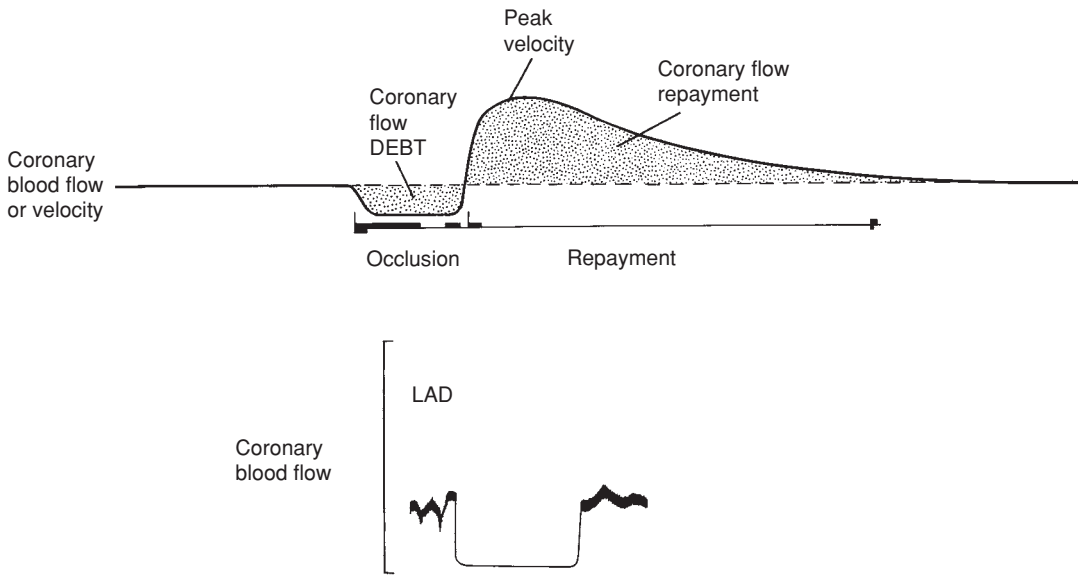

Figure 32-6. (*Top*) Coronary flow dynamics during temporary occlusion in a normal heart. (*Bottom*) Coronary blood flow is interrupted in the left anterior descending coronary artery (LAD) in a patient with aortic stenosis. In the normal heart, during 10 seconds of occlusion, the myocardium incurs a coronary flow deficit that is more than repaid during a hyperemic response after flow resumes. In a patient with aortic stenosis, either an attenuated or no hyperemic response occurs after 10 seconds of occlusion, indicating little or no coronary flow reserve.

of the valve. The mean pressure gradient across the aortic valve is determined by planimetry of the area, and it is this gradient that is applied to calculation of the valve orifice area. The peak-to-peak gradient, measured as the difference between peak left ventricular pressure and peak aortic pressure, is used commonly to quantify the valve gradient.

Using Doppler methods, velocity is converted to gradient using the Bernoullli equation: Gradient $= 4 \times V^2$.

Echocardiographic measurements of AVA represent the current clinical standard for assessment of the severity of AS. Transesophageal echocardiography (TEE) offers an alternative method for assessment of AVA using planimetry of the multiplane systolic TEE short-axis views of the aortic valve.[41]

Decrease of AVA by about 50% to 1.5 cm^2 results in only a small gradient. However, further progression of AS results in a more significant increase in gradient. The average increase in gradient is 7 to 10 mm Hg per year; however, there is large individual variation.[42] The unpredictable rate of progression of AS mandates careful follow-up. Although most patients with AS have surgery when the AVA is less than 0.7 cm^2 or there is a mean systolic gradient of more than 50 mm Hg, patients may become symptomatic sooner and require AVR before these thresholds are reached.

Clinical Presentation

Symptoms

The cardinal manifestations of acquired AS are *angina pectoris, syncope,* and ultimately, *heart failure.* Patients with congenital or rheumatic AS present with symptoms most commonly in the fifth or sixth decade of life, whereas patients with degenerative calcific AS symptoms commence in the seventh through ninth decades. Angina usually occurs in two-thirds of the patients with critical AS and is precipitated by exertion and relieved by rest. Syncope is due to decreased cerebral perfusion during exertion. Syncope at rest may be due to transient arrhythmias, i.e., atrial fibrillation with loss of the atrial "kick" contribution to left ventricular filling with a resulting decrease in cardiac output or to transient atrioventricular block owing to extension of the calcification into the conduction system. Some patients may have severe or even massive gastrointestinal bleeding secondary to angiodysplasia, occurring predominantly in the right colon as well as in the small bowel or stomach. This complication arises from shear-stress-induced platelet aggregation with reduction in high-molecular-weight multimers of von Willebrand factor and increases in proteolytic subunit fragments. These abnormalities correlate with the severity of AS and are correctable by aortic valve repair.[43] Exertional dyspnea and orthopnea usually are late symptoms. Other late manifestations of severe AS include atrial fibrillation and pulmonary hypertension. Infective endocarditis can occur in younger patients with AS; it is less common in elderly patients with a severely calcified valve.

The interval from the onset of symptoms to the time of death is approximately 2 years in patients with heart failure, 3 years in those with syncope, and 5 years in those with angina.[44]

Signs

Signs of AS include systolic ejection crescendo-decrescendo murmur that radiates to the neck and is often accompanied

by a thrill. In some patients, a regurgitant systolic murmur may be present, representing rupture of mitral chordae tendineae. A previous report has indicated that patients with ruptured chordae tendineae have extensive calcification of the mitral annulus and no evidence of rheumatic or myxomatous mitral pathology.[45] These data suggest that mitral annular calcification in conjuction with elevated left ventricular pressures predisposes the patient with AS to rupture of the mitral chordae tendineae.[45] Other signs of AS include delayed second heart sound (S_2) because of prolongation of the systolic ejection time. The S_2 also may be single when the aortic component is absent, and if the aortic component is audible, this may give rise to a paradoxical splitting of S_2.

The classic *pulsus parvus,* or small pulse, is a sign of severe AS or decompensated AS and occurs when stroke volume and systolic and pulse pressures fall. A wide pulse pressure is also characteristic of AS. Prolongation of the ejection phase with slow rise in the arterial pressure also gives rise to the *pulsus tardus. Pulsus parvus et tardus* is diagnosed by palpation. As ejection begins, work is lost at the stenotic valve with a resulting decrease in amplitude and delayed timing of carotid upstroke.

Left ventricular hypertrophy is evident as a sustained apical thrust or heave. This sign is present only when failure occurs because until failure occurs, the hypertrophy is not accompanied by dilatation, and the apical impulse is not displaced. Conversely, absence of an apical thrust (except in muscular patients, those with emphysema, and those with adiposity) suggests a mild or moderate AS. Other physical findings of significant AS include prominence of a jugular venous *a* wave secondary to a decreased right ventricular compliance because of right ventricular hypertrophy, as well as evidence of the prominent left atrial kick.[45]

Electrocardiogram

Most patients with severe AS present with QRS complex or ST-T interval abnormalities reflecting LVH. Patients with a higher gradient are more likely to show a "strain" or "systolic overload" pattern. The conduction abnormalities may result from septal trauma secondary to high intramyocardial tension from hypoxic damage to the conducting fibers or from extension of valvular calcifications into the fibrous septum.

Roentgenogram

The roentgenographic characteristics of compensated AS include concentric hypertrophy of the left ventricle without cardiomegaly, poststenotic dilatation of the aorta, and calcification of the valve cusps. With decompensation, there is cardiomegaly in the posteroanterior projection and pulmonary venous congestion. It is important to recognize that a routine chest x-ray (CXR) may be within normal limits in patients with hemodynamically compensated AS. The rounding of the lower-left heart border may be subtle, the poststenotic aortic dilatation may be equivocal, and the valvular calcification may be invisible on posteroanterior view. Of equal importance, the presence of cardiomegaly in a normotensive patient with isolated AS indicates a decompensated AS.

Echocardiography

Ultrasonic examination of the heart is an invaluable diagnostic tool in confirming the diagnosis of AS and in quantifying disease severity. The recommendations for the diagnostic use of echocardiography were established by an American College of Cardiology/American Heart Association (ACC/AHA) task force in 1998.[46] In echocardiographic evaluation of AS, the purpose of echocardiography is to (1) define the severity and etiology of the primary valvular lesion, (2) define the hemodynamics, (3) define coexisting abnormalities, (4) detect secondary lesions, (5) evaluate cardiac chamber size and function, and (6) re-evaluate the patient after intervention. There are several typical and important echocardiographic findings in patients with AS: The aortic leaflets are thickened and calcified with reduced movement; the reduced valve orifice often can be visualized; in the case of bicuspid aortic valve, the cusps are asymmetric; and the left ventricle shows significant myocardial hypertrophy with usually preserved systolic function. Doppler echocardiography may be used to estimate the degree of stenosis using the planimetry technique (Fig. 32-7). It also can be used to assess valve thickening and calcification, as well as reduced leaflet motion. Distinction between bicuspid and tricuspid valve is often possible, particularly when the amount of calcification is small. Left ventricular hypertrophy can be estimated by calculating left ventricular mass. Transvalvular pressure gradient and valve area can be calculated with Doppler studies.

The normal area of the adult aortic valve measures, on average, 3.0 to 4.0 cm^2; this reduction of the normal area usually does not produce symptoms until the valve reaches one-fourth of its normal dimension. Currently accepted criteria for the gradation of AS define:

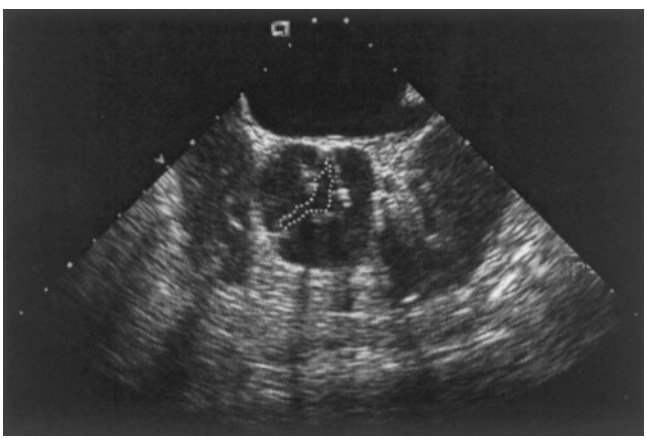

Figure 32-7. Transesophageal echocardiographic image of severely calcified aortic stenosis. Dotted lines highlight the significantly reduced aortic valve orifice.

1. Mild AS as area >1.5 cm^2
2. Moderate AS as area of 1 to 1.5 cm^2
3. Severe AS as area <1.0 cm^2

Doppler echocardiography is also used to determine diastolic dysfunction by the presence of abnormal left ventricular relaxation. Patients with AS are known to have diastolic dysfunction. Moderate to severe diastolic dysfunction does not increase early mortality but may increase late mortality after AVR.[46] *Asymptomatic diastolic dysfunction* is used to refer to asymptomatic patients with normal ejection fraction and an abnormal echo-Doppler pattern of left ventricular filling. Stress echocardiography is used in patients with normal left ventricular function (LVF) to demonstrate the presence of diastolic dysfunction (i.e., signs of elevated left ventricular filling pressure) as the cause of symptom development during exercise. Diastolic dysfunction in patients with normal LVF may cause exercise intolerance for several reasons: First, elevated left ventricular diastolic and pulmonary venous pressures increase the work of breathing and cause dyspnea; second, patients with LVH exhibit a limited ability to use the Frank-Starling mechanism during exercise, resulting in a decrease in cardiac output during exercise; third, elevated left ventricular diastolic and pulmonary venous pressures result in abnormalities in the diastolic properties of the ventricle. Combining transmitral flow velocity with annular velocity obtained at the level of the mitral annulus with tissue Doppler (E/E') has been used to assess left ventricular filling pressures that combine the influence of transmitral driving pressure and myocardial relaxation.[47] Patients with rest E/E' can be classified as having elevated filling pressure, whereas E/E' of less than 8 represents normal filling pressure. Filling pressures between 8 and 15 represent a gray zone.

Echocardiographic follow-up studies should be frequent to identify left ventricular dysfunction, LVH, and mitral regurgitation. Studies should be performed yearly in patients with severe AS, every 2 years in patients with moderate AS, and every 5 years in patients with mild AS.[48]

Exercise testing

Traditionally, severe AS has been regarded as a relative contraindication to exercise testing.[49] Indeed, it should be avoided in symptomatic patients with AS. More recent reports, however, have indicated that quantitative exercise Doppler echocardiography can be performed safely in asymptomatic patients with AVAs of less than 1 cm^2.[50] An increase in mean transaortic pressure gradient by 18 mm Hg or more during exercise, an abnormal exercise test, and an AVA of <0.75 cm^2 predict higher risk for cardiac events (i.e., death or heart failure) by multivariate analysis in a subset of asymptomatic patients with AS. Dobutamine stress echocardiography is often a useful modality to estimate valve area and gradient at a higher cardiac output. It is particularly useful in patients with moderate to severe AS with a low gradient and depressed LVF.[51,52]

Cardiac catheterization

Cardiac catheterization is useful to determine the transvalvular gradient and to evaluate LVF from the left ventriculogram. Coronary artery disease may be present in up to 25% of patients with AS who do not have angina. Thus, coronary angiography is performed in most patients to assess coronary anatomy and evaluate the need for combined AVR and myocardial revascularization. Right-sided heart catheterization is also used to calculate the AVA based on the Gorlin equation, as described earlier. Cardiac catheterization also may provide information about the presence or absence of other valve lesions.

Cardiac computed tomography

The ability of computed tomography (CT) to detect and quantify calcification has been applied recently to aortic valve stenosis. Electrocardiographically gated multidetector row CT has shown high accuracy and reproducibility in quantifying aortic valve calcification and its progression.[53] This may develop into clinical applications with respect to the prognostic relevance of aortic valve sclerosis, as well as the problem of calcification of the bioprosthesis.

Magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) may be used in assessing left ventricular volume, function, and mass. MRI also may be useful in quantifying the severity of AS. Valve area can be assessed by direct planimetry using a cross-sectional plane immediately downstream from the valve. Cardiac MRI is useful when acoustic windows in the echocardiogram are poor or when there is discordant imaging and catheterization results. Bicuspid aortic valves or fused valve leaflets can be identified readily. Moreover, after AVR for stenosis, cardiac MRI is used to demonstrate improvement in LVF, myocardial metabolism, and diastolic function, as well as reduced hypertrophy.[54]

Indications for Surgery

Symptomatic patients

There is no effective medical therapy for aortic valve stenosis. Diuretics and digitalis may improve the symptoms of CHF. ACE inhibitors are relatively contraindicated in patients with AS. Afterload reduction therapy is contraindicated in patients with AS because it can reduce coronary perfusion pressure. Prophylactic antibiotics are recommended prior to any dental or surgical procedures as a prevention strategy for endocarditis. Percutaneous balloon aortic valvotomy is indicated mainly in the treatment of children with AS and as a temporary maneuver in some symptomatic adults who are poor surgical candidates. Aortic valve repair for aortic valve stenosis has yielded poor results compared with aortic valve repair.[55] Aortic valve replacement is indicated in patients with symptomatic AS. Patients who present with angina, syncope, or symptoms of heart failure should undergo AVR.

Percutaneous AVR represents a novel, less invasive approach to the treatment of AS. This approach has been applied successfully in high-risk patients with severe symptomatic AS who were not deemed to be candidates for conventional surgery.

Asymptomatic patients

Aortic valve replacement in asymptomatic patients is currently controversial. The decision to operate on asymptomatic patients with severe AS remains difficult.[57,58] Considering the high rate of cardiac events and sudden death in previous reports, early elective surgery could be indicated in a high-risk subset of patients, such as those with an AVA of <0.75 cm^2, an abnormal exercise test, or an increase in transaortic gradient during exercise. Other patients with a poor prognosis are those with moderate or severe valvular calcification and a rapid increase in aortic jet velocity between two echocardiographic studies.[58] Asymptomatic patients with an AVA of <0.8 cm^2 or a peak aortic gradient of 40 mm Hg may benefit from AVR. Moreover, any evidence of impaired LVF as demonstrated by depressed ejection fraction (EF), left ventricular dilatation, or significantly elevated left ventricular diastolic pressure (LVDP) at rest or during exercise is an indication for AVR. Patients with CAD and AS with a mean transvalvular gradient of more than 40 mm Hg undergoing coronary artery revascularization should undergo coronary artery bypass with concomitant AVR. Combined coronary artery bypass grafting (CABG) and AVR generally is indicated in patients with CAD and at least moderate AS, higher transvalvular gradients, and calcified valves.[59] In patients with low EF and a small transvalvular gradient, AVR results in improvement in only 50% of patients, the other 50% being complicated by perioperative death or CHF.[60] Controversy currently exists as to whether asymptomatic patients with mild AS also should undergo AVR at the time of CABG.

AORTIC REGURGITATION

Aortic regurgitation (AR) is a diastolic reflux of blood from the aorta into the left ventricle owing to failure of coaptation of the valve leaflets during diastole. The presentation varies depending on the acuity of onset, severity of regurgitation, compliance of the ventricle and aorta, and hemodynamic conditions prevalent at the time. Whereas chronic AR is well tolerated for years, acute AR can be debilitating and life-threatening if not treated emergently.

Prevalence and Etiology

AR has numerous causes, which can be grouped according to the structural components of the valve affected. The valve leaflets may be distorted, thereby preventing proper valve coaptation. Calcific aortic disease, idiopathic degenerative disease, active or chronic aortic valve endocarditis, rheumatic disease, a biscuspid aortic valve, and myxomatous proliferation of aortic valve tissue all prevent the valve cusps from closing properly.[62,63] More recently, anorectic medications, such as fenfluramine and phentermine, have been found to cause aortic valve distortion from accelerated degeneration of valve leaflets, leading to regurgitation similar to that seen in carcinoid syndrome. Aortic annular dilatation will prevent the aortic cusps from closing properly, as well as leading to valve insufficiency. Aortic dissection; trauma; chronic systemic hypertension; aortitis from syphilis, viral syndromes, or other systemic arteritides (e.g., giant cell and Takayasu); and connective tissue disorders such as Marfan syndrome, Reiter disease, Ehlers-Danlos syndrome, osteogenesis imperfecta, and rheumatoid arthritis all lead to annular dilatation and valvular insufficiency.[61,64–69] Pure AR is rare and is seen commonly only in aortic dissection or in pathophysiologic processes causing annular dilatation. Most commonly, aortic valvular insufficiency is seen in combination with AS, as is often seen in aortic disease, rheumatic valvular disease, or myxomatous degenerative disease.

Pathophysiology

The pathophysiology of AR varies according to the onset and duration of the disease process.

Acute aortic regurgitation

By definition, acute AR is a hemodynamically significant aortic incompetence of sudden onset across a previously competent aortic valve into a left ventricle not previously subjected to volume overload. The inability to adapt is worse for concentrically thickened hypertrophic myocardium typically seen in those with chronic hypertension.

Disease states that typically present in this acute fashion include endocarditis, trauma, and aortic dissection. Even small regurgitant volumes result in a dramatic increase in left ventricular end-diastolic pressures. The mitral valve may close earlier in late diastole to reduce the amount of left atrial blood entering the ventricle, thereby preventing backflow into the left atrium and pulmonary veins. Pulmonary wedge pressure increases with resulting pulmonary edema. The normally widened pulse pressure of chronic AR is attenuated or nonexistent in the acute AR owing to the rapid rise in diastolic pressure.[70] Effective cardiac output is less than that of the chronic state because compensatory dilatation has not occurred, and, hence, left ventricular end-diastolic volume (LVEDV) remains larger than normal but small in comparison with effective stroke volume. Compensatory changes in heart rate occur, higher than those of chronic AR, to augment cardiac output. Overall, the hemodyamic effects of acute aortic insufficiency produce a low effective cardiac output with an elevated LVDP and heart rate, which are maintained in a precarious balance leading to the onset of early CHF with any perturbation in diastolic filling or heart rate.

Patients with acute AR and decreased cardiac output often present with chest pain that is a result of decreased coronary blood flow from changes is diastolic perfusion

pressures and an increase in myocardial oxygen consumption. In acute AR, coronary blood flow occurs in systole.

Chronic aortic regurgitation

In contrast, chronic AR is a slow and insidious process, which sets in motion numerous compensatory mechanisms. The left ventricle accommodates increased volume and pressure caused by the regurgitant flow by eccentric ventricular hypertrophy, with a consecutive increase in LVEDVs. Left ventricular end-diastolic pressure does not approach aortic diastolic pressure, as can occur in acute insufficiency, leading to a widened pulse pressure, which is an associated physical sign of this disease. Cardiac output is maintained with the aid of the autonomic nervous system. This increase in stroke volume (SV) is responsible for the wide pulse pressure and hypertension seen in AR.

AR also impairs early diastolic function because eccentric hypertrophy leads to impaired left ventricular relaxation during later stages of the disease process.[71] Unlike acute aortic insufficiency, premature closure of the mitral valve does not occur. However, flutter of the anterior leaflet of the mitral valve may occur owing to a Bernoulli effect. AR leads to changes in diastolic perfusion pressure, and coronary blood flow may be reduced, leading to chest pain in patients. Myocardial oxygen demands are high in hearts with aortic insufficiency due to large end-diastolic volumes and pressures, which lead to increased ventricular wall tension according to Laplace's law. With only a moderate reduction in aortic diastolic perfusion pressure, myocardial blood flow usually is adequate to meet the metabolic demands of the myocardium. However, with a severe reduction in diastolic pressure, a decrease in diastolic coronary perfusion occurs that is compensated only partially by increased coronary arterial flow during systole. With decreased diastolic pressure, coronary perfusion is now unable to meet the oxygen demands of the overloaded ventricular myocardium. In experimental models, diastolic aortic pressures of 40 mm Hg or less dramatically reduce coronary artery blood flow and increase myocardial ischemia, as measured by lactate production.[72] Severe regurgitant flow even may lead to a reversal of diastolic coronary arterial flow. This is seen more often in degenerative and bicuspid valve disease because the various valve shapes allow for more regurgitant flow than for valves made incompetent by rheumatic disease.[73] Left ventricular hypertrophy not only increases myocardial oxygen demand but also reduces coronary artery vascular reserve in proportion to the degree of hypertrophy likely by compression of capillary blood flow.[74] Superimposed CAD only exacerbates the effect of decreased diastolic coronary perfusion pressure and myocardial hypertrophy.

As seen from the hemodynamic effects of aortic insufficiency, effective forward cardiac output is enhanced by any physiologic changes that decrease afterload or increase heart rate, which in and of itself increases cardiac output and decreases diastolic filling time and hence regurgitant flow time. The peripheral vasodilatation and increased heart rate that accompany exercise increase effective cardiac output in this manner.[75] This is the physiologic basis for vasodilator therapy for the treatment of acute and chronic aortic insufficiency. It also becomes clear why bradycardia and negative inotropic and chronotropic agents are to be used carefully or avoided in AR because increased filling times lead to increased regurgitative flow and pulmonary congestion.

As aortic insufficiency progresses, the preload reserve of the left ventricle is reached eventually. Thereafter, any further increase in afterload creates afterload mismatch. In general, patients with aortic insufficiency have slightly depressed ventricular function when compared with normal subjects if ventricular function is evaluated in terms of end-systolic pressure-volume relationships (ESPVRs). A depressed ejection fraction with a near-normal ESPVR indicates afterload mismatch.[76] Hence, EF may not be a good indicator of ventricular function.[77] However, a depressed EF with a depressed ESPVR indicates intrinsic myocardial disease, especially in patients with large end-systolic and end-diastolic volumes. At this stage, prolonged aortic insufficiency has led to further increases in wall stress without compensatory hypertrophy, leading to eventual myofibrillar slippage. Subsequent molecular events lead to fibrosis and irreversible changes in ventricular function.

It is at this point in the natural history of aortic insufficiency that AVR will not improve cardiac function. Identifying these patients is somewhat difficult at the clinical level. Ejection fraction alone is a poor indicator of postoperative functional recovery because it depends on preload and afterload. Irreversible changes decrease both the EF and the ability to develop peak systolic stress in relation to chamber size. Attempts to identify these patients include studies illustrating that patients with left ventricular end-systolic volumes (LVESVs) exceeding 60 mL/m^2 remain in New York Heart Association (NYHA) functional class IV postoperatively. Other studies have suggested that when the ratio of chamber volume to wall thickness exceeds 3.8, postoperative recovery may be compromised.[78] This ratio is indicative of progressive dilatation with myofibrillar slippage. Some echocardiographic studies have found that an end-systolic left ventricular dimension of $>$55 mm and a fractional shortening of $<$25% are associated with decreased ventricular recovery postoperatively and increased mortality.[79] This is based on the belief that LVESV is an indicator of LVF. Other studies have refuted this finding, but current guidelines recommend AVR in asymptomatic patients when LVESV is $>$55 mL/m.[46]

Signs and symptoms

Physical examination findings of AR vary with the chronicity of the disease process. The widened pulse pressure seen in chronic AR results from the augmentation of total cardiac output that leads to the distention of the peripheral arterial system followed by a quick collapse from regurgitant flow. This leads to many classic physical findings such as a "water-hammer" pulse (Corrigan pulse), head bobbing with each heart beat (DeMusset sign), and capillary pulsations at the lips and fingers (Quincke pulses). Other findings are associated

with CHF if present (e.g., rales, S_3, etc).[80] Many of the classic signs and symptoms of chronic aortic insufficiency are absent in the acute manifestation of this valvular disorder. In acute insufficiency, as discussed earlier, pulse pressure is not widened, and, hence, the signs associated with this pathologic physiology are absent. Instead, the signs of acute CHF predominate.

Patients with compensated AR remain asymptomatic for prolonged periods of time. However, with ventricular decompensation occurring with large regurgitant volumes, patients may experience palpitations; an awareness of each heartbeat, especially at the ventricular apex; or atypical chest pain syndromes.[80] Chest pain is rare in aortic insufficiency, unlike AS. The eccentric hypertrophic myocardium of compensated aortic insufficiency is by no means as thick as that of AS, leading to lower degrees of increased oxygen requirement and a maximally dilated coronary circulation. However, turbulent flow patterns and diminished diastolic perfusion pressure at some point may lead to insufficient coronary and myocardial perfusion. Most symptoms of aortic insufficiency occur from underlying heart failure and pulmonary congestion as the ventricle decompensates.

Diagnostic Evaluation

Often the signs and symptoms of aortic insufficiency are all that are needed to make the diagnosis. However, if the diagnosis is unclear or the desire is to quantify the severity of disease, other diagnostic tests can be employed, including an electrocardiogram (ECG), echocardiography (ECHO), cardiac catheterization, and MRI, which are discussed below.

ECG

Chronic AR results in left axis deviation. Q waves in leads I, V_1, and V_3 to V_6 are indicative of diastolic volume overload.[81] Left ventricular conduction defects usually are associated with left ventricular dysfunction. The QRS complex amplitude is linearly correlated with left ventricular mass. The finding of a strain pattern in relation to a reduction in the QRS complex amplitude is indicative of severe depression of EF and contractility.[82] Overall, the ECG is not an accurate predictor of the severity of AR.

Echo

Echocardiography is the most useful diagnostic modality in both the initial diagnosis and continued monitoring of patients with AR. Transthoracic echocardiography (TTE) is the most commonly used imaging tool. Transesophageal echocardiography is invasive and used only when patient body habitus does not allow for adequate assessment of valvular function or when evaluation of the aortic valve and ascending aorta is needed in a patient with suspected aortic dissection (Fig. 32-8). Transthoracic echocardiography is indispensable in the diagnosis of the presence and degree of aortic insufficiency, its etiology, valve morphology and presence of vegetations and calcification, quantification of pulmonary hypertension, and determination of ventricular function. Most important, though, it allows for the noninvasive monitoring of valvular disease and LVF in asymptomatic patients. This is critically important in determining the timing of surgery in asymptomatic patients prior to the onset of permanent ventricular decompensation.

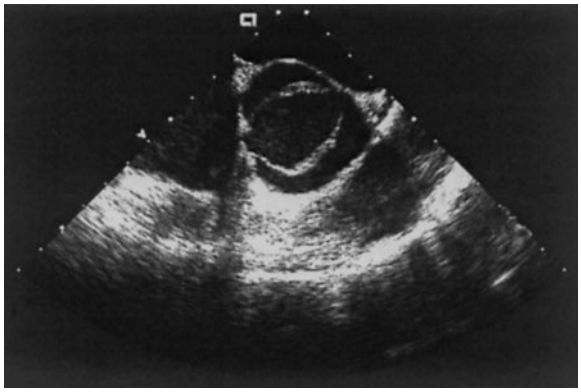

Figure 32-8. Transesophageal echocardiographic image of bicuspid aortic valve. Noncoronary cusp (at the tip of the viewing triangle) is freestanding, Left and right coronary cusps are fused.

The etiology of aortic insufficiency is defined by failure of leaflets to coapt versus stiffness of fibrotic or calcified leaflets. The quality of the regurgitant murmur is evaluated by color-flow techniques. Measurements of end-systolic and end-diastolic volumes, as well as measurement of wall thickness, can be obtained. These measurements are useful for determining irreversible changes in LVF. Two-dimensional (2D) echocardiography, along with Doppler color-flow mapping, has been used routinely to diagnose and assess the severity of AR.[83–85] The color-flow jets typically are composed of three segments: (1) proximal flow convergence zone (area of acceleration into the orifice), (2) vena contracta (the narrowest and highest-velocity region of the jet), and (2) the jet itself distal to the orifice in the left ventricular cavity. The severity of AR can be defined by the ratio of the proximal jet width to LVOT width, with a ratio of less than 25% consistent with mild AR and a ratio of greater than 65% diagnostic of severe AR.

Quantitative Doppler flow measurements use the total stroke volume (i.e., flow at the aortic valve level) and the forward stroke volume (i.e., flow at the mitral valve level) to calculate the AR volume and fraction.[86] The effective regurgitant orifice (ERO) area can be calculated by dividing the regurgitant volume by the velocity time integral of the AR jet calculated by continuous-wave Doppler.[87]

Premature closure of the mitral valve, as seen in acute AR, can be recognized. Fluttering of the anterior mitral leaflet from regurgitant flow also may occur during diastole and can be appreciated. This is a sensitive indicator of both acute and chronic AR. Although fluttering of the open mitral valve is seen classically during diastole, fluttering also may occur with the mitral valve closed. Fluttering of the posterior mitral valve leaflet is also described.[88] Measurement of left ventricular dimension and function by echocardiography

is essential and plays a significant role in management decisions.

Catheterization

Cardiac catheterization is important to estimate the severity of aortic insufficiency if echocardiographic studies are equivocal or if there is concomitant CAD. The amount of regurgitant flow can be determined by calculating the angiographic stroke volume minus a measured fixed stroke volume. The difference between these two measured volumes divided by the angiographic stroke volume determines the regurgitant fraction. In general, a regurgitant fraction of less than 20% is 1+ aortic insufficiency. An increase in regurgitant fraction to 60% corresponds to 4+ insufficiency.[92] Left ventricular end-diastolic pressure is measured directly, and EF is estimated roughly. Radionucleotide imaging with ventriculography can be substituted for angiography if there is a contradiction to cardiac catheterization or serial follow-up of patients is required.[54] This imaging modality, like echocardiography, allows for noninvasive monitoring of aortic insufficiency and ventricular function, although it does not visualize the valvular apparatus directly.

MRI

With current improvements in MRI technology, MRI cineangiography is able to provide some of the same information provided by TTE and TEE. MRI in some aspects provides superior resolution of the valves and better quantification of regurgitant flow and LVF. The regurgitant volume can be calculated by quantitative assessment, wherein aortic flow is subtracted from the ventricular stroke volume measured by volumetric technique. It also can be assessed using flow mapping downstream from the aortic valve by measuring the retrograde volume flow after valve closure. This method is more reproducible and is used more frequently for follow-up studies. However, MRI is costly, and expertise is not available in most centers. Future improvements in technology may reduce costs and increase its availability, thereby making it a standard imaging modality along with or in substitution for echocardiography.[90–92]

Indications for Surgery

Acute AR is treated by early valve replacement. With inadequate time for the left ventricle to compensate by myocardial hypertrophy, progressive CHF, tachycardia, and diminished cardiac output occur rapidly.

Compensated chronic AR is well tolerated by most patients.[93–94] Aortic valve replacement is currently not recommended for patients who are asymptomatic, even with severe chronic AR. These patients, however, must have normal ventricular function and good exercise tolerance. In asymptomatic patients, AVR is indicated for deteriorating ventricular function.[46,95] An EF of less than 55% with a diastolic diameter approaching 75 mm or an end-systolic diameter approaching 55 mm is an indication for operation.[46,82,96–99]

Predictive indicators of impending symptoms in asymptomatic patients are not available. One potential indicator is measurement of left ventricular wall stress at rest and after exercise. Some studies have shown that patients with increased wall stress during exercise develop decompensated left ventricular failure within 5 years.[100] Aortic valve replacement is indicated if patients develop symptoms of CHF or decreased exercise tolerance. However, decreased EF during exercise is not a good measure to indicate the need for valve replacement in asymptomatic patients with normal systolic function at rest. The lack of correlation between exercise EF and the need for operation lies in that exercise EF depends on multiple factors, and no studies have shown conclusive proof linking exercise EF with mortality preoperatively or to be of prognostic value postoperatively.

Ideally, AVR should be performed before irreversible myocardial damage from myocyte apoptosis with resulting fibrosis occurs. Although patients with impaired ventricular function are at an increased perioperative risk, survival is prolonged when compared with patients undergoing medical management. Nonoperative management of patients with severe AR and abnormal LVF is associated with a 50% mortality in 1 year.[101] Risk factors for postoperative mortality include a radius-to-wall-thickness ratio of 3.8 or greater.[80–102] However, despite AVR, impaired LVF may continue in some patients. These patients are difficult to identify preoperatively, and their hearts, as expected, show increased interstitial fibrosis.

In patients in whom ventricular remodeling occurs after AVR, the regression of left ventricular dimension and cross-sectional area can take as long as 3 years. The best predictor for persistent postoperative left ventricular enlargement is preoperative enlargement of the end-diastolic dimension, but this predictor is not always predictive of outcome. Duration of symptoms of left ventricular dysfunction preoperatively is also an indicator for poor reversibility of ventricular function postoperatively.[103]

Early postoperative studies of left ventricular size and function reveal that end-diastolic volumes decrease significantly with valve replacement. With the decrease in preload, subsequent EF decreases; however, if the operation is timed correctly, EF eventually recovers to near-normal values in selected patients.[104] Further recovery includes regression of myocardial hypertrophy, reduction in left ventricular size, normalization of the mass:volume ratio, and increased diastolic coronary flow.[105,106] If improvement is going to occur after AVR, it occurs within the first 6 months as the ventricular end-diastolic dimension decreases. A decrease in the peak systolic wall stress and an increase in EF also occur within the first 6 months.[107–109]

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CHAPTER 33

Aortic Valve Replacement with a Mechanical Cardiac Valve Prosthesis

Robert W. Emery • Ann M. Emery • Amy Knutsen • Goya V. Raikar

In 1931, Paul Dudley White stated "There is no treatment for aortic stenosis." Even today the medical therapy of aortic stenosis has not significantly advanced (Fig. 33-1).[1] Conversely, patients may tolerate aortic insufficiency for many years, but as the ventricle starts to dilate, a progressive downhill course begins and early operation is warranted.[2] Definitive therapy for aortic valve disease was unavailable until the advent of cardiopulmonary bypass. Innovative cardiovascular surgeons then began to develop cardiac valve prostheses. Over the subsequent 50 years,[3] the variety of prostheses that have become available for use have expanded greatly. Available aortic valve substitutes include: mechanical valve prostheses, stented biologic valve prostheses, stentless biologic valve prostheses, human homograft tissue (both as isolated valve replacement and aortic root replacement), and a combination of a biologic valve utilizing a pulmonary autograft and pulmonary outflow tract replacement with heterograft prostheses (Ross procedure). This chapter will focus on the use of mechanical valve replacement in the aortic position.

HISTORY

In 1952, Hufnagel used an aortic valve ball and cage prosthesis heterotopically in the descending thoracic aorta to treat aortic insufficiency.[4] After the advent of cardiopulmonary bypass, initial attempts at aortic valve replacement (AVR) consisted of replacement of the individual aortic cusps with Ivalon gussets sewn to the annulus. When successful, these prostheses often calcified and results were short-lived. Shortly thereafter, surgical pioneers Starr, Braunwald, and Harkin began replacement of the aortic valve in the orthotopic position. First-generation aortic valve prostheses, the ball and cage, became the standard for AVR for over a decade (Fig. 33-2). Many of these prostheses have remained durable for up to 40 years.[5,6] Multiple modifications ensued including: changing the material of the ball from Silastic to Stellite, changes in the shape of the cage, depression of the ball occluder, the addition of cloth coating to the sewing ring and the cage, and changes in the sewing ring itself. These valves, however, required intense anticoagulation.[7] Hemodynamic performance was compromised, as there were three areas of potential outflow obstruction: the annular size of the sewing ring (the effective orifice area of the valve), the distance between the cage and the walls of the ascending aorta (particularly in the small aortic root), and obstruction to outflow by the ball itself distal to the tissue annulus. Flow patterns were also abnormal (Fig. 33-3). These problems led to the development of the next generation of aortic valve prostheses: the tilting disc valve. Innovators such as Bjork, Hall, Kastor, and Lillehei developed three models of tilting disc prostheses that became the second generation of commonly implanted aortic valve replacement devices between 1968 and 1980. The low-profile configuration simplified surgical implantation (Fig. 33-4). Problems with the tilting disc valve included stasis and eddy current formation at the minor flow orifice (see Fig. 33-3), and sticking or embolization of the leaflet, the latter leading to discontinuation of the Bjork prosthesis in spite of otherwise good long-term results.[8] The Lillehei-Kastor prosthesis has evolved into the Omniscience valve. The Medtronic Hall valve, the third tilting disc prosthesis, continues to be used globally (Fig. 33-5).

Kalke and Lillehei developed the first rigid bileaflet valve, but it had very limited clinical use. In 1977, the St. Jude Medical (SJM) prosthesis was developed and implanted by Nicoloff and associates (Fig. 33-6).[3,9] Over the following decades, the dramatic step of a bileaflet prosthesis nearly obviated the use of all other kinds of mechanical prosthetic valves in the United States and to a large extent elsewhere. The SJM valve demonstrated low aortic gradients, minimal aortic insufficiency, and low rates of thromboembolism (TE) (Fig. 33-7).[9–11] Anticoagulation continued to be necessary but to a lesser extent than with previous design models.[12] Because of the low-profile design and lesser need for

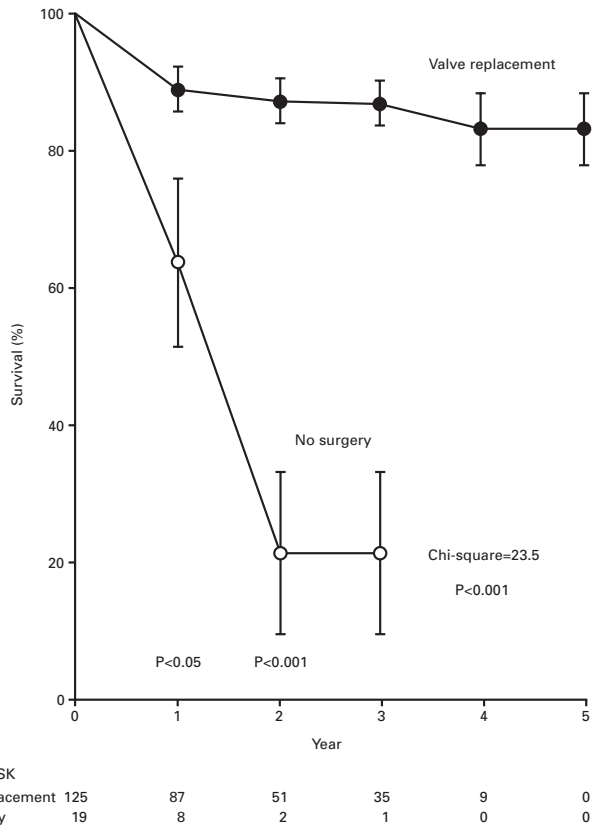


Figure 33-1. Survival of patients having aortic valve replacement compared to those not having valve replacement. (*Reproduced with permission from Carabello.*[1])

orientation, surgical implant was further simplified. Following the introduction of the SJM valve, several other third-generation models of bileaflet prostheses were introduced, including the Sulzer CarboMedics valve (Fig. 33-8), the ATS Medical prosthesis (Fig. 33-9), and the On-X prosthesis (Fig. 33-10). Since the introduction of the bileaflet valve, over 2 million implants on a global basis have been accomplished and extensive literature has developed. Surgeons have become more confident in earlier aortic valve replacement and guidelines for anticoagulation necessary for all mechanical valves have been developed for each generation of prosthesis at progressively decreasing target levels.[12]

Figure 33-2. Prototype model of a ball and cage valve, an early Starr-Edwards model.

Over the past 25 years, design and configurational changes have been made in bileaflet prostheses. The ATS Medical valve changed the "rabbit ears" pivot style of other bileaflet prostheses, incorporating a convex or open-pivot design allowing more complete washing of the moving parts

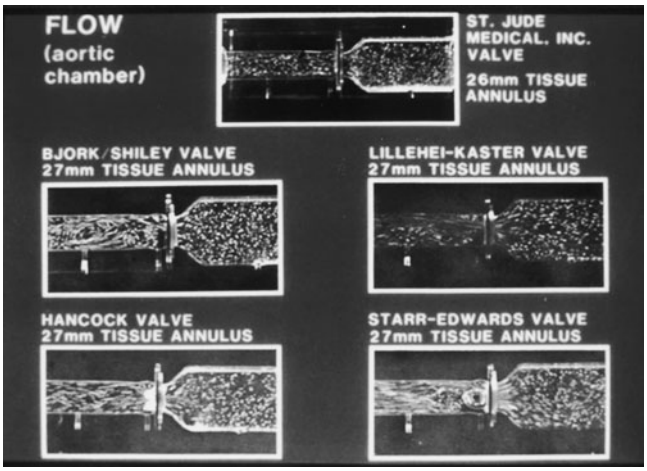


Figure 33-3. Prosthetic valve flow patterns utilizing the Weiting CBA-77-03 pulse duplicator with high-speed photography and resin particles. Note the laminar flow with the bileaflet aortic valve as opposed to other clinically available prostheses and the flow similarity between the bileaflet valve and the tissue valve in the lower left corner. Tilting disk valves show directional flow, stasis at the minor flow orifice, and eddy current formation distally. The ball valve demonstrates stasis beyond the ball and eddy current formation around the ball itself. Note that the ball is obstructive to outflow, as is the proximity of the ball cage to the walls of the outflow chamber. (*Reproduced with permission from Emery et al.*[10])

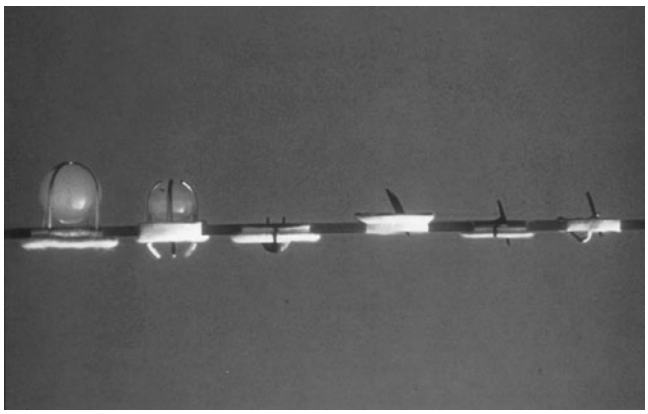


Figure 33-4. Low-profile prostheses simplify the surgical implant. The lowest profile is that of the bileaflet valve, and orientation of the leaflets is most commonly not necessary, as compared to tilting disc prostheses, for which the major flow orifice should be directed along the greater curvature of the aorta.

of the valve and possibly a quieter valve closing.[13,14] The sewing ring of the SJM valve has changed (SJM HP) to allow a larger valve size implantation for any given tissue annulus, as has ATS Medical with its AP design. The sewing ring of the Sulzer CarboMedics valve has been modified such that this valve is implanted in a supravalvular position (top hat model). The On-X valve incorporates advanced pyrolytic carbon technology using a purer, more flexible coating to allow flanging of the inflow portion of the valve housing, mimicking the normal flow pattern.

The most recent development in bileaflet valve design was the introduction of the SJM Regent valve (Fig. 33-11). This valve model not only modified the sewing ring, but also redefined the external profile in a nonintrinsic structural portion of the valve, increasing the effective flow orifice area.

Figure 33-5. The Medtronic Hall valve.

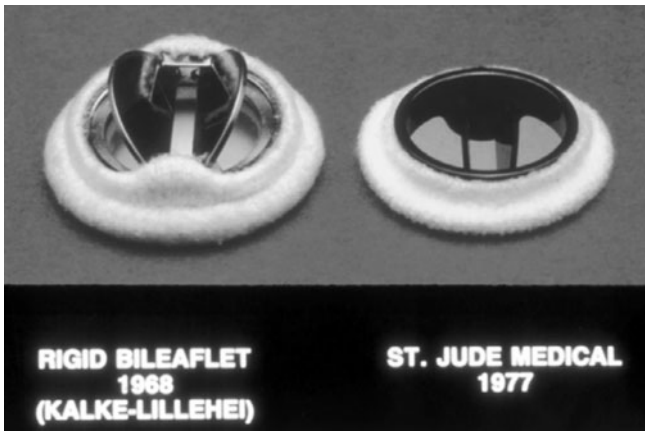


Figure 33-6. The original Kalke-Lillehei bileaflet valve as compared to the St. Jude Medical valve introduced nearly a decade later.

Thus, a larger prosthesis could be implanted for any given tissue annulus diameter. This was the first mechanical prosthesis to demonstrate left ventricular mass regression across all valve sizes.[15,16] The Regent valve is seated supra-annular with only the pivot guards protruding into the aortic annulus.[17]

PATIENT SELECTION

As with any medical therapy, AVR with a mechanical prosthesis is not indicated for all patients. Several prospective randomized studies have shown no difference in survival in patients having biologic or mechanical valve prostheses or among mechanical prostheses per se.[18–22] However, follow-up was limited. Conversely, in other nonrandomized studies of patients followed over longer time frames, freedom from all valve-related events and from reoperation were improved in patients with mechanical valve prostheses as compared to patients with biologic prostheses.[8,23]

While the advantages of large effective flow orifice and durability with a mechanical valve are paramount, the

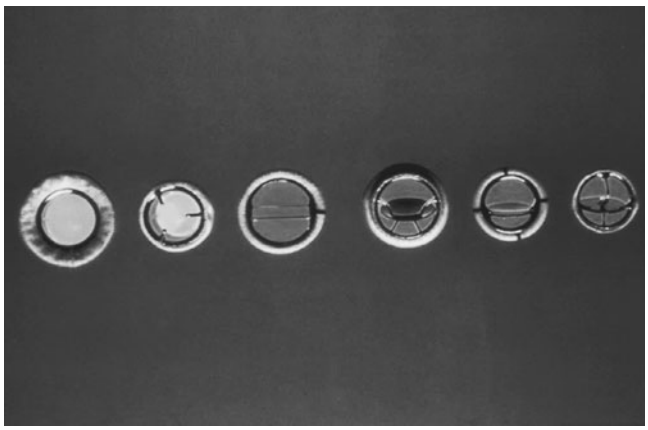


Figure 33-7. The increased flow orifice of the bileaflet valve is clearly shown as compared to ball valves and tilting disc valves available at the time of introduction of the bileaflet bioprosthesis.

Figure 33-8. CarboMedics Top Hat valve.

confounding effects resulting from the necessity for anticoagulation continue. Patients that are transient, noncompliant, or incapable of managing medications are not good candidates for long-term chronic anticoagulation, nor are those with dangerous lifestyles or hobbies.[24] Patients with higher levels of education, and those from geographic areas with a sophisticated medical infrastructure and a static population have better compliance with necessary medication and anticoagulant monitoring.[25]

A mechanical valve prosthesis is recommended to patients having second valve reoperations regardless of the nature of the first procedure, as re-reoperative risks are substantial.[26,27] Some studies report low mortality for reoperation of patients with failed biologic valves, but failures can occur abruptly, creating more risk.[28] Reoperative risk is also higher in those patients having combined procedures[26,29] or after prior coronary bypass.

Many surgeons have opted for an age of >70 years as the indication for bioprosthetic AVR, based on data by Akins.[26] In patients younger than 60 years of age, most would opt for a mechanical prosthesis based on prosthesis durability.[30]

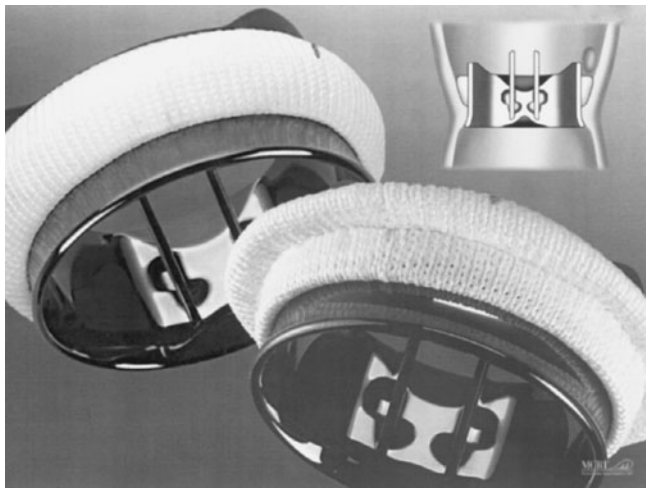


Figure 33-10. On-X valve. Note the flange of the inflow portion of the valve housing which seats in the left ventricular outflow tract.

In the decade between 60 and 70 years of age, other factors have to be taken into account.[31,32]

SURGICAL TECHNIQUES

Implantation of mechanical valve prostheses has been previously described and is straightforward.[11] Historically, high-profile aortic valve prostheses can be difficult to implant, particularly in small aortic roots. In such cases, a hockey-stick aortotomy is used to "unroll" the aorta and expose the annulus. While the implantation of low-profile bileaflet prostheses is simpler, problems can still arise in the small aortic root. If a tilting disc prosthesis is utilized, orienting the major flow orifice toward the greater curve of the aorta is necessary. Because bileaflet prostheses are the most commonly utilized, the surgical technique for implantation of these devices is described: A midline incision and sternotomy

Figure 33-9. ATS Medical valve. Note the open pivot design maintaining leaflet insertion.

Figure 33-11. St. Jude Medical Regent valve.

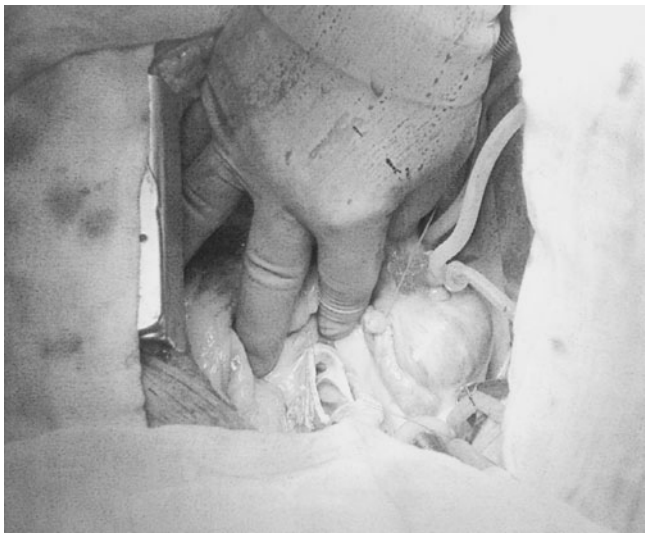


Figure 33-12. A transverse aortotomy has been made above the level of the sinotubular ridge. The diseased valve can readily be visualized and excised in toto.

is made and a pericardial well created. Alternatively, a right anterior thoracotomy approach with femoral cannulation has been reported. A partial sternotomy is also an alternative in thin patients, creating a sternal "T" at the fourth interspace. This alternative technique is particularly amenable to the implantation of low-profile aortic valve prostheses. The patient is cannulated via the aorta and a single atrial venous cannula. Most commonly, retrograde cardioplegic solution is utilized and a left ventricular vent is placed via the right superior pulmonary vein to maintain a dry operative field. After cross-clamping of the aorta, a transverse aortotomy is made approximately 1 cm above the take off of the right coronary artery, slightly above the level of the sinotubular ridge (Fig. 33-12). The incision is extended three-quarters of the way around the aorta, leaving the posterior one-quarter of the aorta intact allowing excellent visualization of the

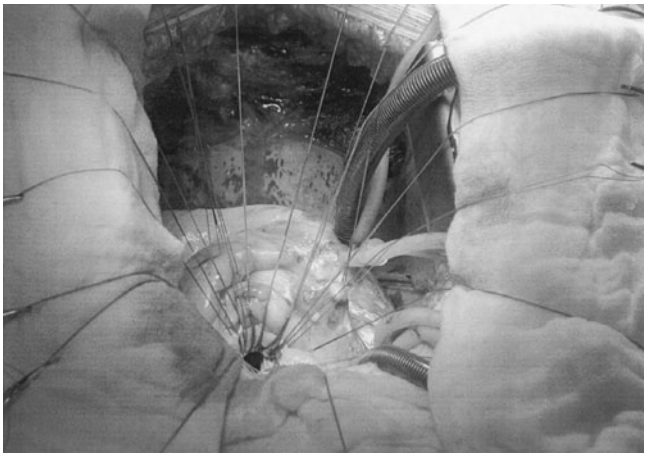


Figure 33-13. The annulus has been encircled with multiple interrupted pledgeted mattress sutures of 2-0 braided suture. The annulus can be readily visualized and all calcification has been extensively débrided.

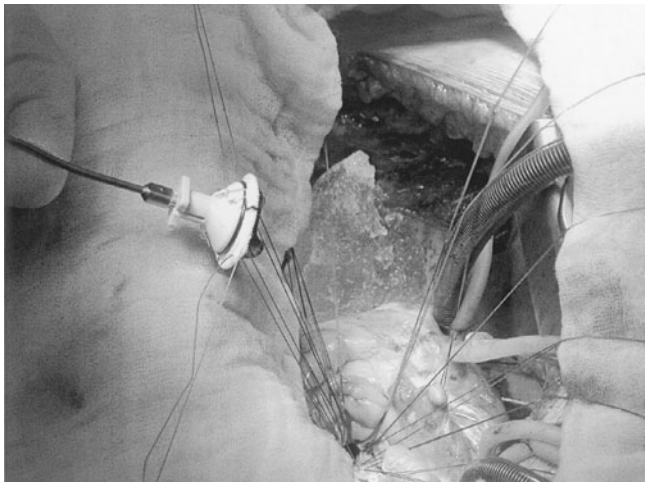


Figure 33-14. The pivot guard sutures have been placed aligning the pivot guards with the right and the left coronary artery.

native aortic valve and annulus. The leaflets of the aortic valve are excised to the level of the annulus and the annulus is thoroughly débrided of any calcium. Extensive de-calcification will minimize the risk of paravalvular leak, particularly in newer-generation prostheses with thinner sewing rings, and allows for better seating of the valve prosthesis. Braided 2-0 sutures with pledgets are utilized. Beginning at the noncoronary commissure, the annulus is encircled with interrupted mattress sutures (Fig. 33-13) extending from the aortic to the ventricular surface (everting). Alternatively, multiple single interrupted sutures may be placed. After placement, the suture bundles are divided into two equal portions and two individual sutures placed into the sewing ring at the level of the pivot guards, orienting the pivot guard toward the ostia of the left and right coronary artery (Fig. 33-14). Next, each half of the suture bundles are implanted in the sewing ring and the prosthesis seated (Figs. 33-15 and 33-16).

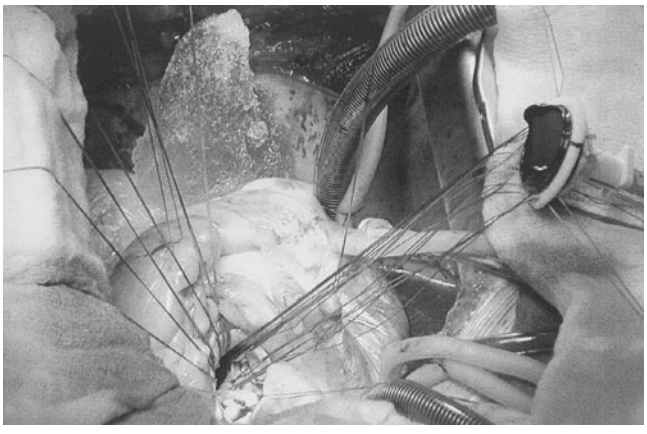


Figure 33-15. The first half of the remaining suture bundles has been passed through the sewing ring of the valve. The valve has been moved to the opposite side of the patient and the remaining suture bundle is to be placed.

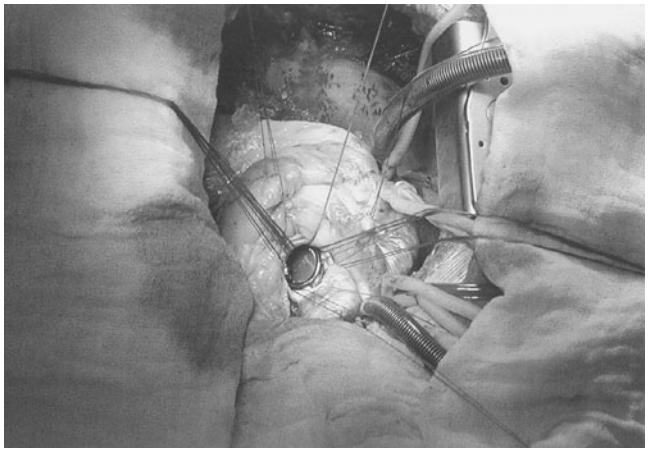


Figure 33-16. All sutures have been passed through the sewing ring and the valve is lowered to the aortic annulus and seated appropriately by placing gentle leverage on the valve sewing ring and traction on the suture bundles.

The pivot guard sutures are tied first followed by the sutures beginning at the left coronary cusp extending to the mid-portion of the right coronary cusp. Lastly, the sutures of the noncoronary cusp are secured, seating the valve appropriately. In a small aortic root, should a valve not be able to be seated, paravalvular leak can be prevented if the unseated area of the valve is in the noncoronary cusp. External aortic sutures can be placed from outside the aorta to the valve sewing ring, securing the prosthesis and preventing regurgitation. Because of the low-profile nature of the leaflets, opening and closing can still occur unimpeded. Leaflet motion should always be checked and the surgeon must be assured that the coronary arteries are not obstructed. The aortotomy is closed with a double layer of polypropylene suture consisting of an underlying mattress suture and a more superficial over-and-over suture. The patient is placed in the Trendelenburg position and the heart filled with blood and cardioplegic solution, vented, and the cross-clamp removed. After resuscitation and de-airing of the heart, the procedure is completed and the patient transferred to the intensive care unit. On the first postoperative day the chest tubes are removed if output is less than 125 mL in the previous 8 hours. Following the removal of the chest tube, the patient is begun on subcutaneous heparin (5000 U every 8 hours) or low-molecular-weight heparin (1 mg per kg twice a day), and warfarin therapy started. Valve implantation can usually be accomplished in under 40 minutes of aortic cross-clamping and with cardiopulmonary bypass times of approximately 1 hour, allowing limited coagulopathic and homeopathic alterations.

When coronary bypass grafting is indicated, the order of the operation changes. The diseased valve is excised, distal vein or free arterial grafts constructed, the valve is replaced, and the aortotomy closed. Proximal anastomoses are then completed, with one left untied for de-airing. The distal anastomoses of pedicled grafts (internal maxillary artery, IMA) are then completed. De-airing is accomplished through the untied proximal anastomosis.

ANTICOAGULATION

The durability and function of mechanical valve prostheses, particularly those of the modern generation, is unquestioned.[23,30,33–36] It is the process of anticoagulation that is key and drives long-term success. International Normalized Ratio (INR) is the standard to which anticoagulation levels should be targeted.[24,37] Anticoagulation is begun slowly following removal of the chest tubes, as the danger of overshooting target INR to dangerous levels is common.[38] Current data on anticoagulant regimens indicate that a one-size-fits-all recipe is inadequate to obtain excellent long-term results.[25] Horstkotte noted that complications occur during fluctuations in the INR, and less often during steady-state levels, be they high or low.[39] When levels of INR increase, bleeding episodes become more common, and when levels of INR decrease, thromboembolic episodes become more common, both on the slope of the change. These events are opposite ends of the continuum of anticoagulation-related complications. The presence of a mechanical valve prosthesis is also not the only risk factor for TE.[25,40] Traditional risk factors for TE listed in Table 33-1 predispose patients to thromboembolic episodes, and as such higher therapeutic INRs are warranted. Similarly, as shown in Table 33-2, nontraditional risk factors for thromboembolism will also predispose patients to embolic events.[25,40] Butchart has noted that the more of these risk factors patients have, the greater the incidence of events and the greater the need for a higher target INR (Fig. 33-17).[25] Thus, it is imperative in the modern era that patient risk factors be taken into account and the INR individualized for a given patient. Recommendations for INR target levels in our practice are shown in Table 33-3. These levels are more liberal than those offered by the American College of Cardiology/American Heart Association (ACC/AHA) and the American College of Chest Physicians (ACCP) guidelines, but more conservative than those recommended by the European self-anticoagulation trials.[41–43] These later reports are especially

Table 33–1.

Traditional Risk Factors for Thromboembolism

• Atrial fibrillation
• Increased left ventricular cavity size
• Regional wall motion abnormality
• Depressed ejection fraction
• Hypercoagulability
• Increased age

Table 33–2.

Nontraditional Risk Factors for Thromboembolism

• Cancer
• Systemic infection
• Diabetes
• Prior event
• IgA against Chlamydia pneumoniae (CP)
• Eosinophilia
• Hypertension

(*Reproduced with permission from Butchart et al.*[25])

relevant, because they demonstrate that a lower INR is consistent with a lower incidence of TE if patients are maintained in the therapeutic target range.[41,44] Patients with home testing were maintained in the therapeutic range a substantially greater percentage of the time than those whose status was monitored at anticoagulation clinics.[41,44] Starting self-management early after mechanical valve replacement further reduced valve-related events.[38] In the United States, home testing has not become commonplace or popular. However, home testing could certainly be expected to lower the incidence of valve-related thromboembolic and bleeding events. It has recently been approved for reimbursement for weekly testing in patients with a mechanical valve prosthesis or atrial fibrillation.

A recent report of patients followed over 25 years noted that approximately 40% of the bleeding episodes occurred in the first year following surgery. It is thus important during this initial postoperative time frame when the patient's anticoagulant levels are more likely to fluctuate that INR be measured more frequently.[30] In the early postoperative period, INR can occasionally jump to supratherapeutic levels and result in significant bleeding events. This is an

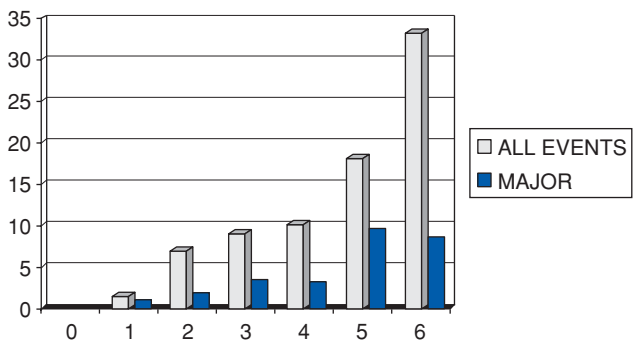


Figure 33-17. The correlation of number of risk factors to thromboembolic events. (*Reproduced with permission from Butchart et al.*[25])

Table 33–3.

Target INR Recommendations

1. Normal ejection fraction and cavity size, NSR: INR 1.82.0, ASA
2. Any single factor: INR 2.0–2.5, ASA
3. Multiple factors or atrial fibrillation: INR 2.5–3.5
4. ? Antiplatelet only

ASA = aspirin; INR = International Normalized Ratio; NSR = normal sinus rhythm.

independent risk factor for mortality at 60 days.[45] Furthermore, the most important independent predictor of reduced survival is anticoagulant variability.[24] We and others therefore recommend in the early postoperative period that one proceed slowly to bring the INR to target levels while the patient is under the protection of subcutaneous enoxaparin (100 IU/kg twice a day) or heparin (5000 U every 8 hours) until the INR is therapeutic.[12,30,46,47]

The addition of aspirin to a warfarin regimen can be expected to result in a lower incidence of TE at any given therapeutic INR with a low probability for bleeding events and so is recommended.[48,49]

An educational program to teach patients how to manage their anticoagulation is an important part of the overall operative process. Patients should be instructed on the influence of alcohol and diet on anticoagulant levels, the need for regular dosing, and the potential impact of travel and gastrointestinal illnesses on fluctuations in anticoagulant levels. Warfarin is well known to be high-risk, as is insulin, yet both drugs can be managed with proper compliance and education so that the impact on lifestyle and quality of life is minimal.[7,50] Patient age does not appear to be a risk factor for anticoagulation[50–53] as long as there are no specific contraindications to anticoagulation. The presence of a mechanical valve is not a risk factor for long-term neurocognitive dysfunction.[54] The importance of regular testing cannot be overstated.

Newer antithrombin agents may obviate several of the issues discussed above. These agents are showing promise in the treatment of atrial fibrillation, with a lower incidence of embolism and bleeding complications. The drugs are expensive, require multiple administrations per day, and may cause hepatic dysfunction, yet they do not require blood testing or physician visits to maintain the therapeutic effect.[55] Their application to mechanical valve prostheses is as yet unknown.

RESULTS

Outcomes from aortic valve replacement with mechanical valve prostheses vary among reports depending on the patient population. Patients with higher risk factors for TE and those

with risk factors for anticoagulation will have a higher incidence of valve-related events, making meta-analyses less meaningful.[56] Older patients are at higher risk for valve-related events, particularly thromboembolic episodes, because of the greater number of risk factors that accumulate with aging.[25] The incidence of valve-related events is also determined by the intensity with which the investigators follow their patients. A higher incidence of early hemorrhagic events may also be diluted over the longer periods of follow-up.[57] Compliance is key to good long-term outcomes. Traditional and nontraditional risk factors for embolism and risk factors for anticoagulation and valve-related events must be considered.[25,40] Several trials have indicated no significant differences in events among various mechanical prostheses, but follow-up was short.[19,21,23,58] There are, however, certain standards within which one should expect a mechanical valve to perform, and within which the medical decisions for anticoagulation must be made. The majority of valve-related morbidity is related to TE and anticoagulation-related hemorrhage.[36] The sections below deal with specific valve-related complications and acceptable current incidence.

Valve Type

Freedom from all valve-related events over the long term is shown in Fig. 33-18. In the early follow-up period, anticoagulation-related hemorrhage is the most common untoward event for mechanical valve prostheses. Thus, over the first 10 years of follow-up there is a higher incidence of valve-related events in patients with mechanical prostheses as opposed to those with biologic valves.[23] However, over the subsequent period of 10 to 20 years, the incidence of biologic valve failure changes this ratio such that the valve-related complications of biologic prostheses become more common than those with mechanical valve prostheses. In a series of aortic reoperations, Potter has noted that the time to biologic valve failure was only 7.6 years.[28] This failure rate will increase over time.[23,59] Overall, freedom from valve-related events is more strongly influenced by pre-existing comorbidities than the presence of a mechanical prosthesis per se.[23,25,30,36]

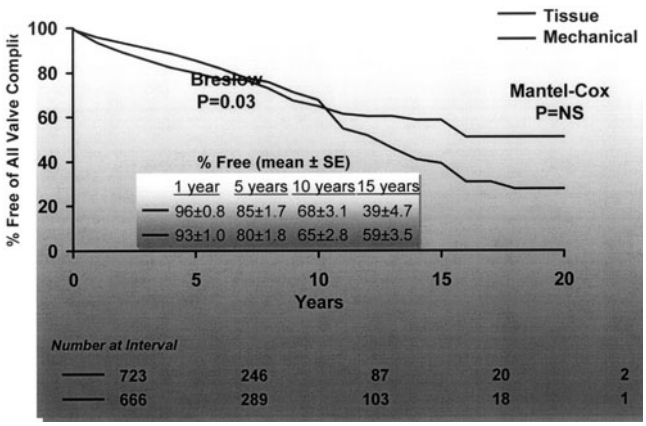


Figure 33-18. Freedom from all valve-related complications over 20 years. Note that in the first 10-year period of follow-up, complications related to mechanical valves exceeded those of tissue valves. The lines cross at approximately 10 years, and over the following period, complications from tissue valves were more frequent than those from mechanical valves. (*Reproduced with permission from Khan et al.*[23])

Anticoagulant-Related Hemorrhage

Anticoagulation -related hemorrhage (ARH) is the most common valve-related event. The more intense the anticoagulation regimen, the higher the incidence of valve-related hemorrhage. Most commonly ARH will occur during fluctuations in INR values commonly related to changes in warfarin dosing or medical or drug interactions.[39] The most common site for ARH is the gastrointestinal tract, the second being the central nervous system.[30] ARH also accounts for the highest incidence of patient mortality for valve-related events. Acceptable ARH rates range from 1.0 to 2.5% per patient-year in long-term reports.[8,23,30,33–36] These long-term reports dilute the short-term impact, as ARH risks are higher early after valve replacement.[30,36,57] With individualized and home monitored anticoagulant regimens, both related events TE and ARH are diminished.[41] Freedom from anticoagulation at 10 and 20 years are 75 to 80% and 65 to 70%, respectively. Importantly, one long-term study noted that nearly 40% of all ARH that occurred over a 25-year follow-up period occurred during the first 6 months of anticoagulation (Fig. 33-19), indicating that a slow increase to therapeutic levels, coupled with close follow-up during this early period is warranted.[30,45,46] Results of the European self-anticoagulation study indicate that a lower INR target is appropriate if home testing is initiated, as a greater time is spent in the therapeutic range.[41] Mortality more commonly occurs in relation to bleeding events than in relation to thromboembolic events.[30]

Thromboembolism

Thromboembolic episodes are the second most common valve-related event and are the reason that chronic anticoagulation is warranted. Khan and associates reported in a large series of patients that the incidence of thromboembolic events between bioprostheses and mechanical prostheses are the same (Fig. 33-20), but the mechanical valve patients are on warfarin.[23] Acceptable thromboembolic rates range between 0.8 and 2.3% per patient-year.[8,23,30,33–36,60] Approximately one-half of these events are neurologic events, 40% are transient, and 10% peripheral.[30] Freedom from thromboembolic events at 10 and 20 years is approximately 80 to 85% and 65 to 70%, respectively.

Thromboembolism is a continuous risk factor that is present throughout the life of the mechanical valve prosthesis. As patients age, risk factors for TE increase, so one must be on guard to maintain therapeutic anticoagulant levels. Changes in the target INR may be necessary as individual risks increase.

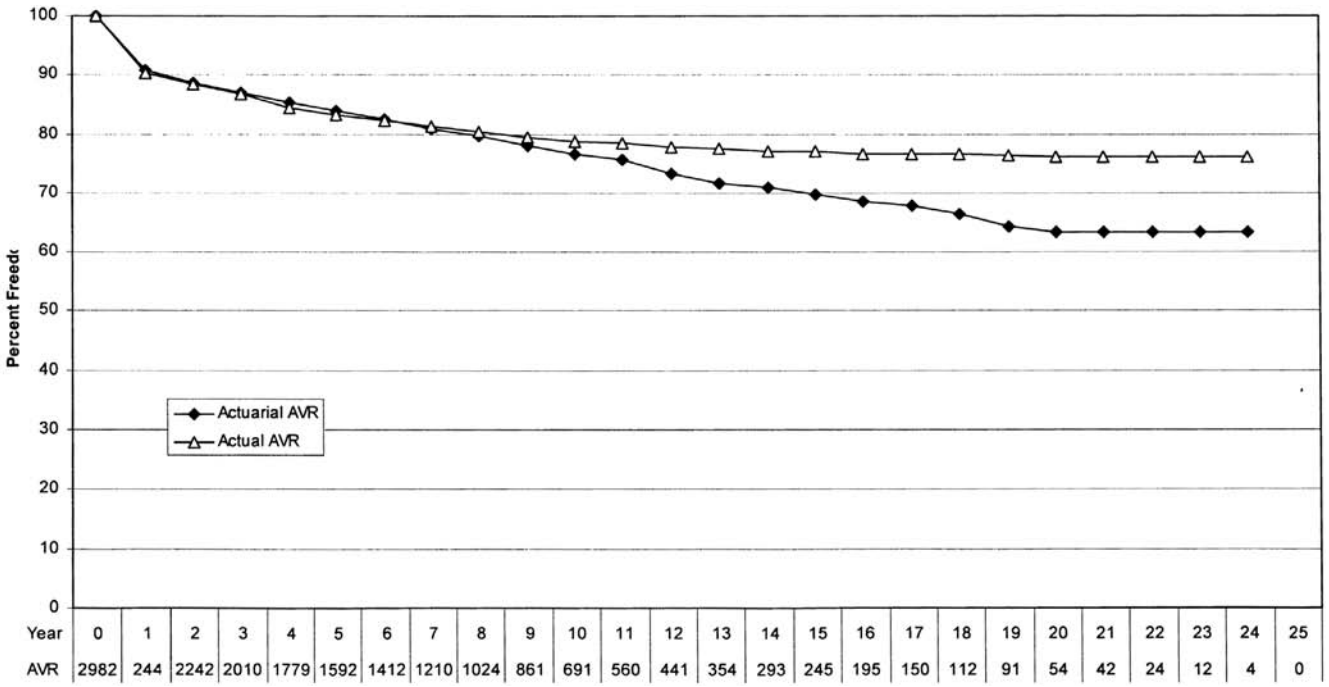


Figure 33-19. Kaplan-Meier curve of freedom from anticoagulation-related hemorrhage for patients having aortic valve replacement. (*Reproduced with permission from Emery et al.*[30])

Valve Thrombosis

Valve thrombosis in the aortic position is an unusual event that occurs late after valve replacement and is most commonly due to inadequate anticoagulation or noncompliance.[61,62] In bileaflet valves, thrombus formation impinging valve function occurs at the pivot guards and in the crevices of the valve. Only one bileaflet design does not have convexities into which the leaflets fit.[63] In tilting disc valves, thrombus is most common at the minor flow orifice. The incidence of thrombosis is approximately <.3% per patient-year and freedom from valve thrombosis at 20 years is >97%.[8,23,30,33–36]

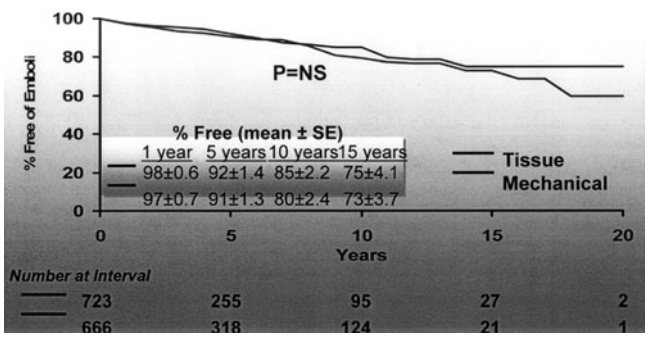


Figure 33-20. Freedom from thromboembolism in patients followed for 20 years. Note that there is no difference in the incidence of thromboembolic events between mechanical and tissue valves. (*Reproduced with permission from Khan et al.*[23])

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis is also a rare event in the modern era with prophylactic antibiotics. Approximately 60% of events occur early and are associated with staphylococci. The mortality for this event is high. The remainder appear late (>60 days). Prosthetic valve endocarditis is also a continuous variable, and patients must be cautioned to take prophylactic antibiotics for any invasive procedure. Freedom from endocarditis with mechanical valve prostheses is 97 to 98% at 20 to 25 years.[30,36]

Paravalvular Leak

Paravalvular leak is an operative complication and is related to operative technique and to endocarditis. With annular decalcification and closely placed sutures, these events can be minimized. The Silzone experience showed an increased incidence of paravalvular leak wherein the silver impregnated in the sewing ring not only impeded bacterial growth, but also healing of the annular ring, doubling the accepted rate of this complication.[64] The Silzone coated sewing ring was removed from the market. There may be an anatomic predisposition to paravalvular leak in the area of the annulus extending from the right and noncoronary commissure, one-third the distance along the right coronary cusp, and two-thirds the distance to the noncoronary cusp, due to intrinsic weakness in this area of the annulus.[65] The acceptable range of paravalvular leak is approximately <.1% per patient-year, with early postoperative occurrence predominating.

Structural Failure

Structural failure of bileaflet aortic prostheses due to wear has not been observed or reported in long-term studies totaling more than 50,000 patient-years of follow-up. This indicates the high structural integrity of these modern aortic devices.[23,30,36] In a single study totaling 21,742 patient-years with 94% complete follow-up, there was no structural failure.[46]

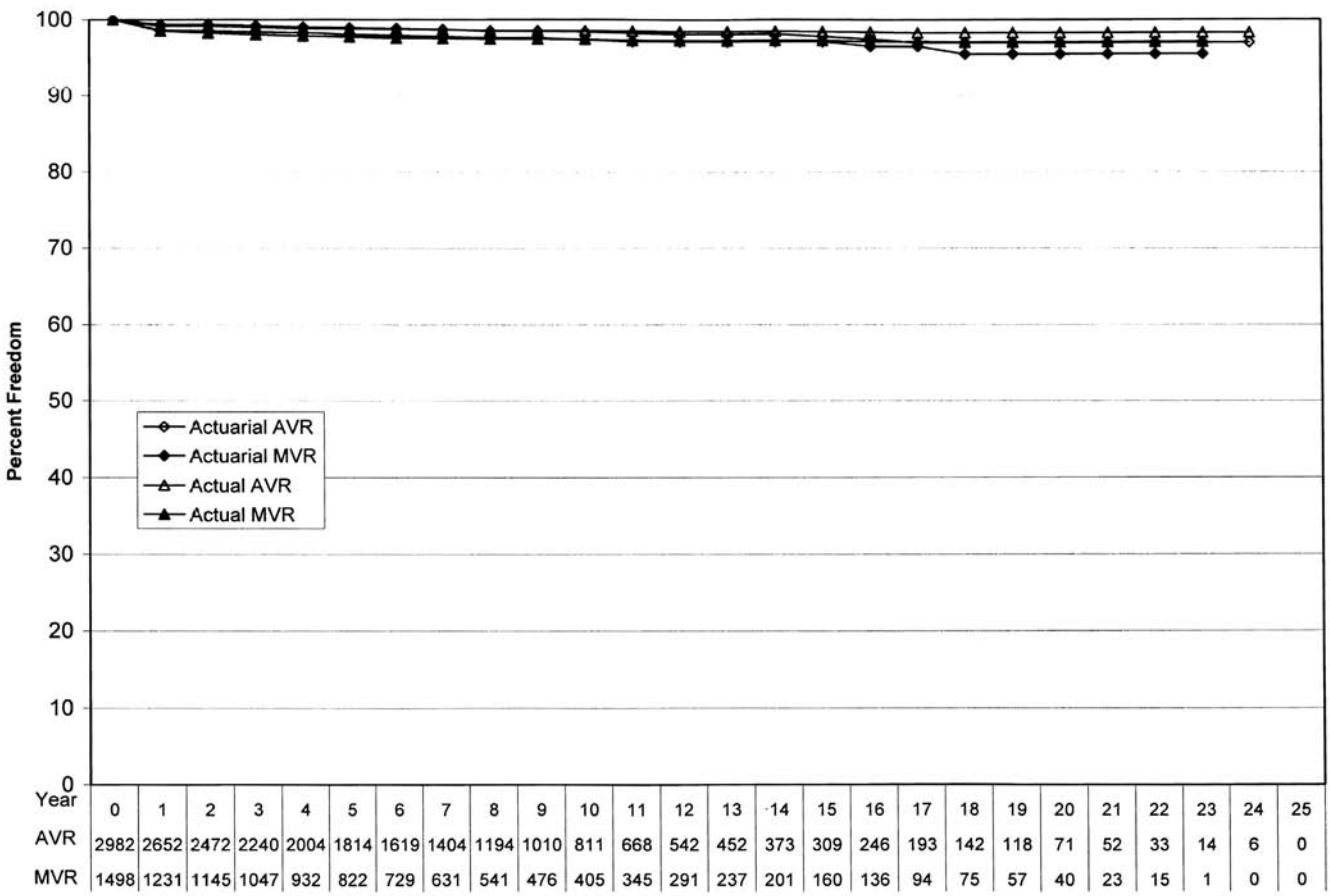
Freedom from Reoperation

The long-term durability of modern mechanical valve prostheses is excellent, and a valve replacement rate of less than 2% over 25 years (Fig. 33-21) can be expected, and re-reoperation after AVR replacement is even more rare.[27] Subvalvular pannus formation is rare with bileaflet valves.[30,36] The most common reasons for prosthetic valve reimplantation are pre- and postoperative endocarditis, paravalvular leak, and valve thrombosis.

SPECIAL CIRCUMSTANCES

Technical Considerations

While the technique of implanting a mechanical valve prosthesis is very straightforward, special circumstances arise. Because of the large size of the valve housing of the St. Jude Medical Regent valve compared to the tissue annulus, entry into the aorta can sometimes be difficult. Occasionally, patients have the smallest diameter of their aortic root at the sinotubular ridge. While the sizer will pass readily through the aortic annulus, seating the Regent valve itself into the annulus can sometimes be difficult and frustrating. It is important to gently rock the valve back and forth through the sinotubular ridge, tilting the valve circumferentially through the narrowest part. Once the valve is below the level of the sinotubular ridge, it will seat readily in the annulus if sizing has been correct. When tying the valve into the annulus, sutures in the pivot guards and the left and right coronary cusps should be first completed. The last sutures ligated are those of the noncoronary cusp for two reasons. It may seem like the Regent valve will not seat because of the large-sized valve housing; however, with gentle persistence seating can be completed as long as sizing has been correct. The Regent valve sits supra-annular and only the pivot guards lie inside the annulus (Fig. 33-22). Therefore one should leave the last sutures to be tied in the mid-part of the noncoronary cusp with the valve oriented so the leaflets are parallel to the ventricular septum.[66] With proper annular decalcification and flexibility of the annulus, we have not seen a Regent valve that has not been able to be seated properly.



Year	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
AVR	2982	2652	2472	2240	2004	1814	1619	1404	1194	1010	811	668	542	452	373	309	246	193	142	118	71	52	33	14	6	0
MVR	1498	1231	1145	1047	932	822	729	631	541	476	405	345	291	237	201	160	136	94	75	57	40	23	15	1	0	0

Figure 33-21. Freedom from reoperations in patients having mechanical valve replacement followed over 25 years. Note that the rate of reoperation in patients with aortic valve replacement is less than 2% in over 21,000 patient-years of follow-up. (*Reproduced with permission from Emery et al.*[30])

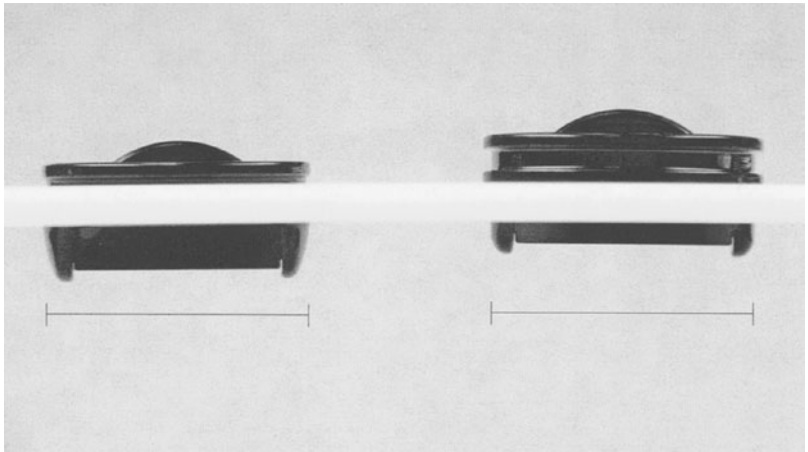


Figure 33-22. The St. Jude Medical Regent valve on the right as compared to the St. Jude Medical HP valve on the left. With the Regent valve only the pivot guards insert into the annulus, allowing a larger valve housing for any given tissue annulus diameter. (*Reproduced with permission from Emery et al.*[30])

Similarly, when using the On-X valve one has to be sure that the flare of the valve inflow is seated properly in the left ventricular outflow tract. Gentle manipulation and patience may be necessary. Walther and colleagues note that exact sizing requires some experience.[20]

If an oversized bileaflet valve has been implanted purposefully in a small aortic root, the valve can be tilted and will still function without coronary obstruction as long as the highest portion of the valve is in the noncoronary cusp. Pledgeted sutures placed from outside the aorta through the sewing ring of the valve can prevent paravalvular leak, and opening and closing can still occur due to the low-profile nature of the prosthetic valve. In our review of nearly 3000 bileaflet aortic valve replacements, no annular enlarging procedures were completed.[46]

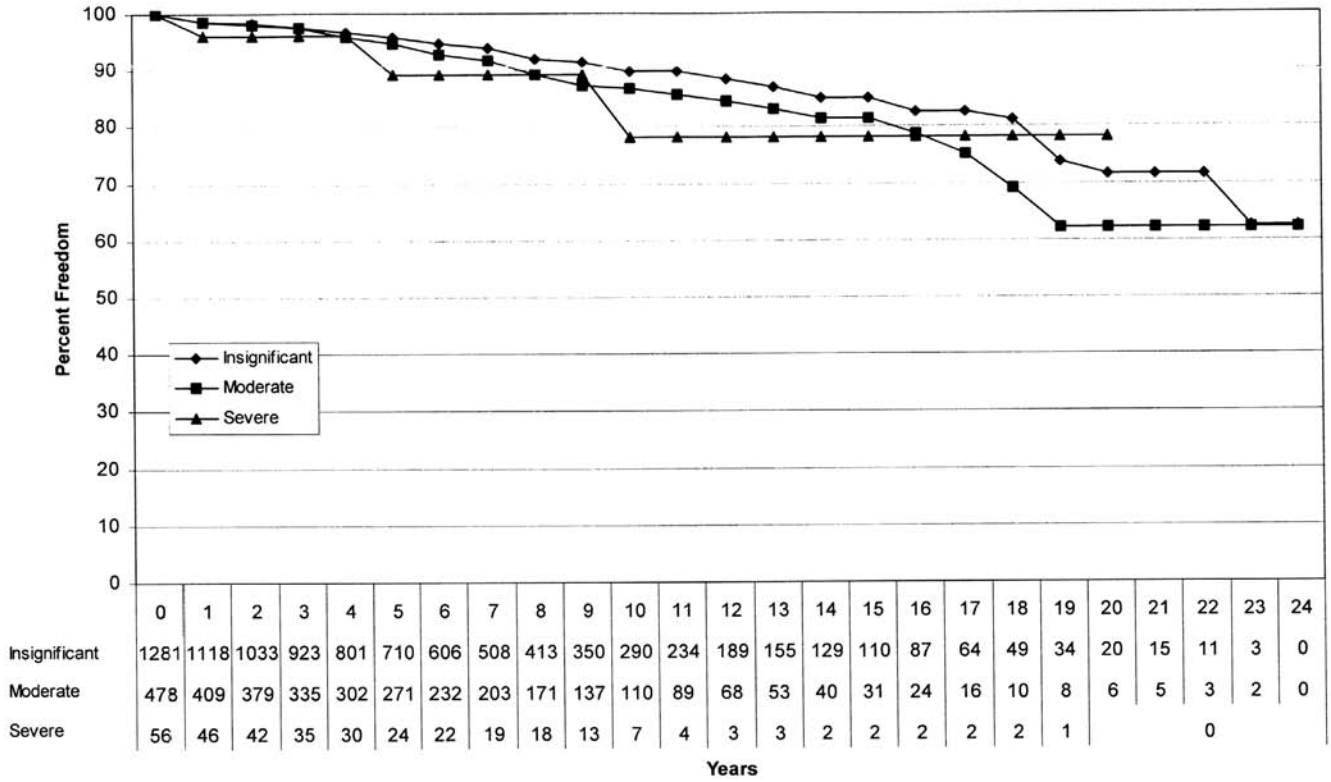
Patient-Prosthesis Mismatch

Patient-prosthesis mismatch (PPM) is a concept first described by Rahimtoola and popularized by Pibarot and Dumesnil.[67,68] Unfortunately, views are varied on the importance of PPM.[69–72] This is due to the fact that virtually all contributions to the literature study mixtures of mechanical and biologic prostheses and varying types of each. In a 25-year follow-up of patients with a single model mechanical valve prosthesis, no difference was found in overall valve-related mortality for patients who had severe PPM, moderate PPM, or insignificant PPM according the criteria described by Blais and associates.[71] This similarity in long-term survival was sustained whether the effective area was measured by in vitro (internal geometric valve area) or in vivo criteria (echo-calculated valve area) as shown in Figs. 33-23 and 33-24. This study also found no difference in valve-related events, including operative mortality, long-term cumulative mortality, anticoagulant-related hemorrhage, TE, valve thrombosis, paravalvular leak, or diagnosis of congestive heart failure. Follow-up in this study was 94% complete and extended over 13,000 patient-years.[73] Therefore, with bileaflet mechanical valve prostheses, PPM does not appear to be an issue. This study was limited in that it did not address patient age (i.e., younger versus older), patient activity, or ventricular function. Thus, it is likely that PPM is important in patients with small biologic prostheses, because as the valve leaflets stiffen, clinical aortic stenosis becomes prominent early in the postoperative follow-up period, affecting symptoms and survival. If one is, however, concerned about PPM, the indexed effective orifice area can be calculated for any given prosthetic valve and a determination made whether an annular enlarging procedure or a different model prosthesis with a larger effective orifice area is warranted.[74] PPM has been minimized by the new-generation Regent valve and is very rare with this prosthesis.[16,46]

Off Anticoagulation

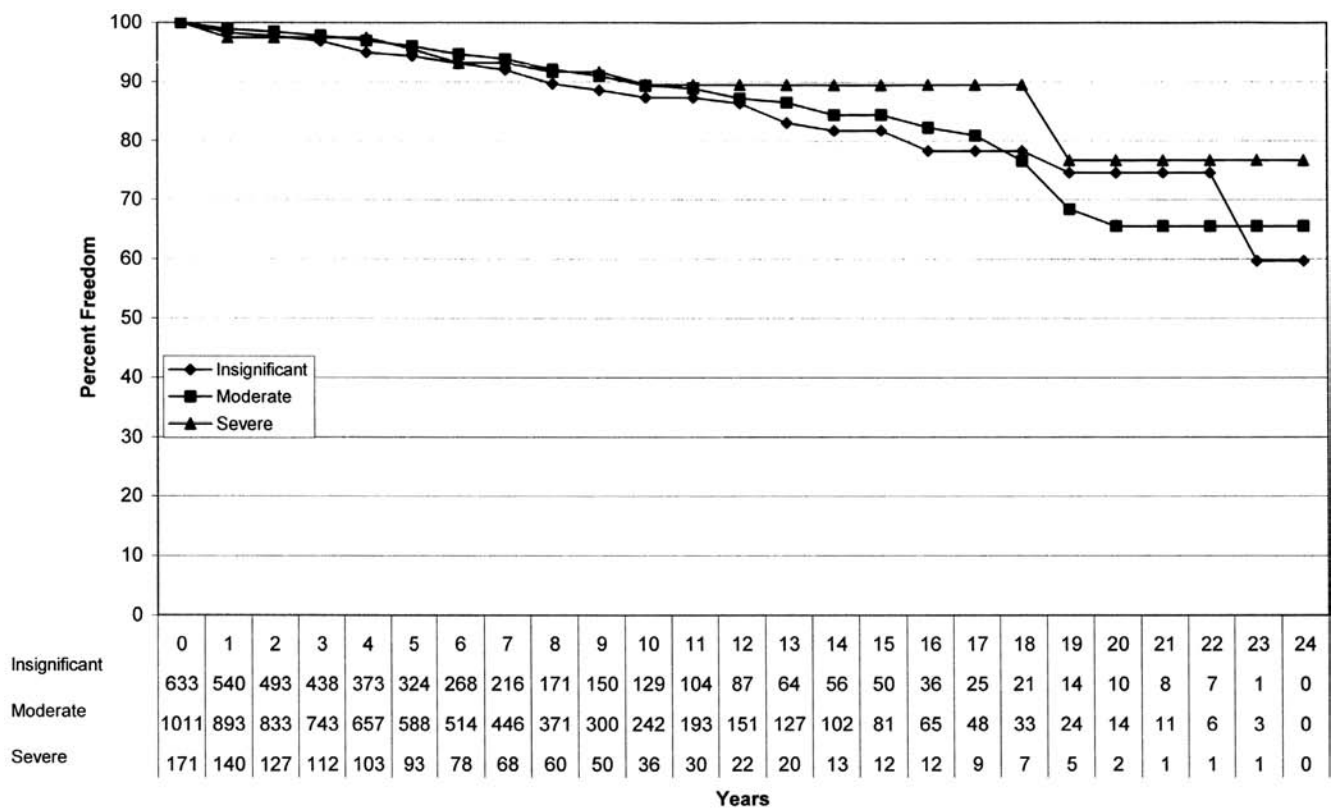
Anticoagulation is recommended in all patients with mechanical valve prostheses. Limited trials have been undertaken with low-risk patients, but only after a several-month course of systemic anticoagulation. An increased incidence of valve thrombosis but with little increase in the incidence of TE has been reported in patients not taking chronic anticoagulation if antiplatelet agents are utilized.[61,75,76] One study found no significant differences in valve-related events in patients on warfarin as compared to antiplatelet therapy alone, but follow-up was limited.[77] One prospective study is currently ongoing consisting of a randomized trial of antiplatelet therapy versus warfarin after 3 months of formal anticoagulation, but the results are not yet available.[78] Certainly one can expect that highly selected patients with mechanical valve prostheses will do well off warfarin on antiplatelet agents, but this is unproven.[17,79]

When anticoagulation requires reversal electively, as for scheduled surgery, the INR is allowed to slowly drift toward normal over 5 days and the patient is admitted for intravenous heparin therapy 24 hours prior to the procedure. Anticoagulation is restarted after the procedure with antiplatelet therapy, and subcutaneous heparin with



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Insignificant	1281	1118	1033	923	801	710	606	508	413	350	290	234	189	155	129	110	87	64	49	34	20	15	11	3	0
Moderate	478	409	379	335	302	271	232	203	171	137	110	89	68	53	40	31	24	16	10	8	6	5	3	2	0
Severe	56	46	42	35	30	24	22	19	18	13	7	4	3	3	2	2	2	2	2	1			0		

Figure 33-23. Kaplan-Meier determination of valve-related late mortality in patients having insignificant, moderate, or severe patient-prosthesis mismatch according to the criteria of Pibarot and colleagues. After implant of a bileaflet prosthesis, in vitro determination is calculated from the geometric flow orifice by the manufacturer. Note there is no difference in these three curves. Numbers at the bottom of the figure represent patients available for follow-up.



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Insignificant	633	540	493	438	373	324	268	216	171	150	129	104	87	64	56	50	36	25	21	14	10	8	7	1	0
Moderate	1011	893	833	743	657	588	514	446	371	300	242	193	151	127	102	81	65	48	33	24	14	11	6	3	0
Severe	171	140	127	112	103	93	78	68	60	50	36	30	22	20	13	12	12	9	7	5	2	1	1	1	0

Figure 33-24. Kaplan-Meier determination of valve-related late mortality in patients having insignificant, moderate, or severe patient-prosthesis mismatch by the in vivo criteria according to Blais and associates determined echocardiographically. There is no difference in the survival curves after implant of a bileaflet prosthesis. The numbers at the bottom of the graph represent patients available for follow-up.

warfarin is restarted on postoperative day one. Abrupt reversal of INR in patients who have bleeding episodes may be warranted, but carries increased risk of TE. Fresh frozen plasma will gently reverse INR when necessary, but it is best to avoid the use of vitamin K. Frequent INR checks are warranted.

Following ARH episodes, when feasible, because of the high incidence of recurrent bleeding, anticoagulant therapy is withheld up to 2 weeks or until the source of the bleeding has been identified and definitively treated, using antiplatelet agents only.[76] For those patients in whom anticoagulant therapy cannot be restarted, antiplatelet therapy is warranted, but the patient should be informed of an increased incidence of thromboembolism to approximately 4% per patient-year and that of valve thrombosis to 2% per patient-year with bileaflet valves.[61,75,76,80]

Mechanical Valve Replacement in the Younger Patient

A major deterrent to mechanical valve replacement in the younger patient is the impact of long-term anticoagulation. Mechanical valves are, however, more ideal for younger patients due to their excellent durability characteristics. Most importantly, younger patients (i.e., patients under the age of 50 years) are a low-risk subset for valve-related events. These individuals have very few risk factors for TE, and thus anticoagulation can be run at the lower end of the therapeutic target range, decreasing the incidence of anticoagulant-related hemorrhage without altering the incidence of TE. In fact, many infants and children have been managed with only aspirin with quite good long-term results.[81] While this is not recommended in patients older than infancy, it is a feasible alternative. A recent study in patients under 50 years of age followed 254 patients for up to 20 years and found an exceedingly low rate of valve-related events (Table 33-4), an exceptional long-term overall survival of nearly 88%, and event-free survival probability of 92% at 19 years.[82]

The longest surviving patient in a series of bileaflet valve replacement patients is currently over 27 years from his procedure, which was completed in his early forties and has been without complication.[30] The low incidence of valve-related complications in younger patients should drive a discussion of the alternative prostheses available for such individuals, especially with new aggressive antiplatelet drugs. Operative mortality increases with each succeeding procedure; therefore discussion of durability with patients becomes mandatory.[26–28]

Follow-Up

With the use of any valve prosthesis, long-term follow-up is a key factor. Ten years is certainly not long enough to ascertain the true durability of a prosthesis. Grunkemeier reviewed several types of biologic prostheses and found that the 10-year durability was excellent, but between 12 and 18 years durability fell off and prosthetic replacement was necessary.[59] These data were echoed by Khan and colleagues.[23] Valve-related failure of all biologic alternatives including stented prosthetic replacements, stentless prostheses, and homograft and autograft replacements have all shown long-term durability to be less than that of modern mechanical valve prostheses.

Even with some mechanical valve prostheses, durability after 10 years has not been adequate. In recommending mechanical valve replacement, one should be assured to have clinically available data on the prostheses that extend beyond 15 years.

In conclusion, with proper selection of patients for mechanical valve replacement, one can expect excellent long-term results, long-term survival, and a low incidence of valve-related complications. Current indications for recommending aortic valve replacement with mechanical prostheses are shown in Table 33-5.

Table 33–4.

Valve-Related Events with the St. Jude Medical Prosthetic Valve

Event	No. of events	Percent per patient-year	No. deaths
Endocarditis	3	0.15	0
Paravalvular leak	6	0.30	2
Embolism	6	0.30	0
Valve thrombosis	23	0.10	0
Bleeding	6	0.10	2
Structural failure	0	0	0

Source: Data from Emery et al.[82]

Table 33–5.

Indications for Mechanical Valve Replacement

- High probability for anticoagulant use
- Need for chronic anticoagulation (any age)
- Preferences of patient
- Surgical risk for reoperation
- Age <60 years
- Age 60–70 years with patient discussion
- Reoperations
- Good medical infrastructure

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CHAPTER 34

Bioprosthetic Aortic Valve Replacement: Stented Pericardial and Porcine Valves

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This chapter provides an overview of aortic valve replacement (AVR) with stented bioprostheses. The indications for aortic valve surgery are reviewed with an emphasis on current evidence-based guidelines and currently available stented aortic bioprostheses are described. Clinical and physiologic outcomes of aortic valve surgery are critically examined to create a rational basis for prosthesis selection.

NATURAL HISTORY AND INDICATIONS FOR OPERATION

Aortic Stenosis

Natural history

Aortic stenosis (AS) may be caused by degenerative calcification, congenital malformations, or rheumatic fever. It may also be found in association with systemic diseases such as Paget's disease of bone and end-stage renal disease. Congenital malformations include unicommisural, and more commonly, bicuspid valves. Detailed descriptions of these pathologies are presented elsewhere in this volume. Degenerative calcification is common in the elderly population and although limited calcific deposits often do not have any clinical significance, severe degenerative calcification is the most common pathology among patients undergoing AVR. Regardless of the initial pathology, there is a progressive reduction of orifice cross-sectional area caused by calcification of the cusps that resembles atherosclerotic processes that include inflammation and lipid accumulation.[1,2] Commissural fusion is typically seen in rheumatic AS but not in degenerative calcification of tricuspid or bicuspid valves. The normal human aortic valve has an area between 3.0 and 4.0 cm^2. Mild, moderate, and severe AS are defined as aortic valve areas (AVAs) greater than 1.5 cm^2, 1.0 to 1.5 cm^2, and less than 1.0 cm^2, respectively.[3] This corresponds to a mean gradient of 25 mm Hg and peak jet velocity of less than 3.0 m/s in mild cases, a mean gradient of 25 to 40 mm Hg and peak jet velocity of 3.0 to 4.0 m/s in moderate cases, or a mean gradient of greater than 40 mm Hg and peak jet velocity of greater than 4.0 m/s in severe cases. In the presence of normal cardiac output, transvalvular gradient is usually greater than 50 mm Hg when the AVA is less than 1.0 cm^2.[4] There is a rapid increase in transvalvular gradient when the AVA is less than 0.8 to 1.0 cm^2.

Exposure to elevated intracavitary pressures causes increased wall stress leading to parallel replication of sarcomeres and concentric hypertrophy.[5,6] These mechanisms compensate for the obstruction to flow created by the reduced orifice area of the aortic valve in order to maintain normal cardiac output. With progressive hypertrophy, the compliance of the ventricle decreases and end-diastolic pressure rises.[7,8] In this situation, the contribution of atrial contraction to preload becomes more significant and loss of sinus rhythm may lead to rapid progression of symptoms.[6]

Symptomatic patients

Hemodynamically significant AS is initially counteracted by left ventricular hypertrophy (LVH). Progression of outflow obstruction and ventricular hypertrophy lead to the cardinal symptoms of AS: angina, syncope, and congestive heart failure (CHF). The average AVA is 0.6 to 0.8 cm^2 at the onset of symptoms.[6] Classic natural history studies have shown that the average life expectancy in patients with hemodynamically significant AS is 4 years if anginal symptoms are present, 3 years if they have experienced syncope, and 2 years with the onset of CHF.[9] Symptomatic patients should therefore undergo AVR in a timely fashion.[10] Excessive waiting periods for AVR in symptomatic patients are associated with increased mortality and the rate of sudden death is >10% per year in these symptomatic patients. Once a patient is symptomatic, average

survival is less than 3 years.[11–14] The typical modes of death in untreated severe AS are sudden death from ventricular arrhythmia or CHF.

Asymptomatic patients

Managing asymptomatic patients with hemodynamically significant AS can be a challenging problem, as there is often a prolonged latent period before symptoms emerge. During the latent period, there is a progression of concentric LVH as the ventricle adapts to elevated chamber pressures. Studies by Otto and colleagues have shown that up to 7% of asymptomatic patients experience death or aortic valve surgery 1 year after diagnosis.[15] After 5 years, the incidence of death or aortic valve surgery increases to 38%. The average decrease in AVA is 0.12 cm^2 per year, while the average increase in transvalvular pressure is often 10 to 15 mm Hg per year.[16] Sudden death is quite uncommon in the asymptomatic patient and occurs at a rate of 0.4% per year. The vast majority of patients who experience sudden death will become symptomatic in the months immediately prior to the fatal event.[17,18]

There is considerable variation in the rate of disease progression and many patients do not experience any change in gradient for several years. To provide improved guidance on which asymptomatic patients need closer follow-up or early operation, a study by Rosenhek and colleagues identified that asymptomatic patients with an increase in peak velocity jet greater than 0.45 m/s per year on serial echocardiography were substantially more likely to need operation than patients with lesser changes in jet velocity.[19]

Low-gradient severe aortic stenosis

The significance of AS is often unclear in patients with very poor ventricular function (ejection fraction <20%) who have severely stenotic valves but small (<30 mm Hg) transvalvular gradients. The compromised left ventricular function (LVF) in these patients may be caused by afterload mismatch created by the stenotic valve or by intrinsic cardiomyopathy, particularly in the setting of chronic ischemia from diffuse coronary disease. In these patients, measurement of transvalvular gradient and valve area at rest and with positive inotropy (i.e., dobutamine infusion) may distinguish whether cardiomyopathy or true valvular stenosis is the most responsible lesion. Although some patients with a preponderance of cardiomyopathy do not experience significant benefit from valve replacement,[20] a recent study by Pereira and colleagues suggests that in a balanced, propensity matched comparison, patients with poor LVF and severe AS experience a significant survival benefit from valve replacement[21] (Fig. 34-1). Hwang and colleagues, using a multivariate analysis to determine factors that predict poor LVF after AVR for AS, identified that poor preoperative LVF was the most significant predictor, indicating suboptimal outcome in the low-gradient group of patients.[22]

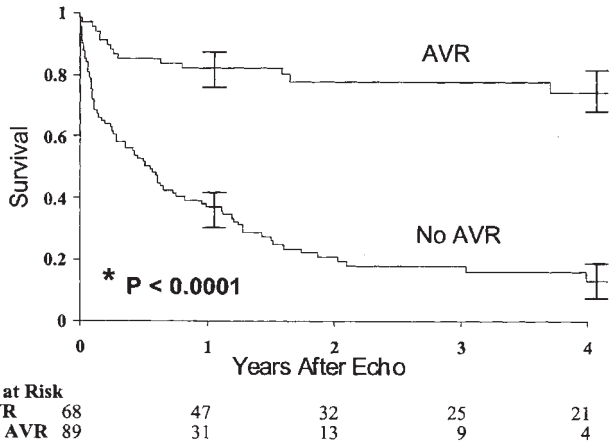

Figure 34-1. Impact of aortic valve replacement on survival in patients with low-gradient aortic stenosis. Survival by Kaplan-Meier analysis among all propensity-matched patients in the aortic valve replacement (AVR) and control (No AVR) groups (p <0.0001). The number of patients at risk during follow-up is shown on the x axis. (*Reproduced with permission from Pereira et al.*[21])

Medical therapy

No known medical therapy has been shown to alter the natural history of AS. Although several small nonrandomized studies have shown a reduction in disease progression with antilipid therapy,[23–25] a recent prospective randomized clinical trial of aggressive antilipid therapy with atorvastatin did not demonstrate decreased rates of disease progression as determined by changes in aortic jet velocity or valve calcification score[26] (Fig. 34-2).

Indications for operation

In 1998, a joint task force of the American College of Cardiology (ACC) and the American Heart Association(AHA) developed evidence-based consensus guidelines for management of valvular heart disease.[27] These were updated in 2006.[28] Their recommendations for AVR in the setting of AS are summarized in Table 34-1. A class I recommendation indicates there is good evidence and general agreement that the treatment is beneficial, useful, and effective. Class IIA recommendation indicates there may be disagreement but the weight of evidence supports the usefulness/efficacy of the treatment in that setting, Class IIB recommendation indicates that the usefulness/efficacy of the treatment is less well established, and class III recommendation indicates that the treatment is either not useful/effective or potentially harmful.

Aortic valve replacement is indicated in all symptomatic patients with severe AS or patients with severe asymptomatic AS who require concomitant coronary bypass, aortic surgery, or other valve replacement. It is our practice to perform AVR on patients with moderate AS requiring concomitant cardiac surgery. We do not routinely perform AVR in patients with mild AS undergoing concomitant cardiac

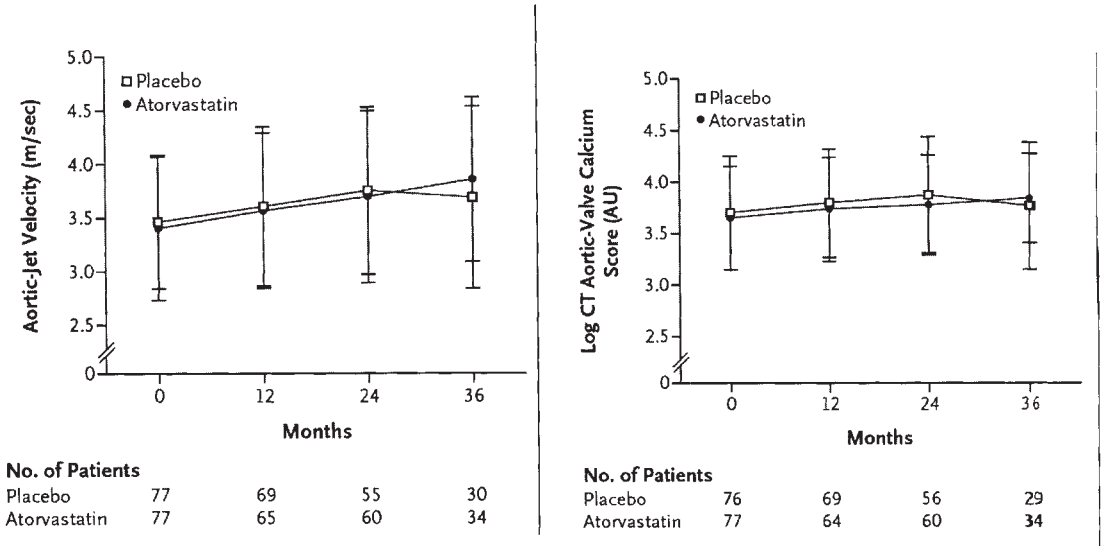

Figure 34-2. Progression of aortic valve jet velocity and calcification in patients treated with intensive atorvastatin therapy or matched placebo. (*Reproduced with permission from Cowell et al.*[26])

Table 34–1.

ACC/AHA Guidelines for Aortic Valve Replacement in Patients with Aortic Stenosis (AS)

Indication	Class
1. Symptomatic patients with severe AS	I
2. Patients with severe AS undergoing coronary bypass surgery	I
3. Patients with severe AS undergoing surgery on the aorta or other heart valves	I
4. Patients with severe AS and left ventricular systolic dysfunction (ejection fraction <50%)	I
5. Patients with moderate AS undergoing coronary artery bypass or other aortic or valvular surgery	IIA
6. Asymptomatic patients with severe AS and:	
a. Abnormal response to exercise (hypotension)	IIB
b. Likelihood of rapid progression (age, calcification, or coronary artery disease)	IIB
c. Ventricular tachycardia	IIB
d. Valve area <0.6 cm^2, mean gradient >60 mm Hg, jet velocity >5.0 m/s	IIB
7. Patients with mild AS and moderate to severe valve calcification undergoing coronary bypass surgery	IIB
8. Prevention of sudden death in an asymptomatic patient with none of the findings in 5–7.	III

Source: Adapted with permission from Bonow RO, Carabello BA, Chatterjee K, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Valvular Heart Disease). Available at: http://www.americanheart.org.

surgery unless the aortic valve is heavily calcified and the stenosis likely to rapidly progress. Aortic valve replacement is commonly performed in otherwise asymptomatic patients with severe AS and severe left ventricular dysfunction (LVD), exercise-induced symptoms, significant hypertrophy, or ventricular arrhythmia. Asymptomatic patients with very high transvalvular gradients (>60 mm Hg) or highly stenotic valves (valve area <0.6 cm^2) are at higher risk for progression to symptoms and should have valve replacement prior to significant ventricular decompensation or sudden death.

Aortic Regurgitation

Acute aortic regurgitation

Acute aortic regurgitation (AR) may be caused by acute dilatation of the aortic annulus preventing adequate cusp coaptation or by disruption of the valve cusps themselves. This typically occurs in the setting of acute aortic dissection, infective endocarditis, trauma, active connective tissue disease, aortic cusp prolapse associated with ventricular septal defects (VSDs), aortitis (syphilitic or giant cell), Marfan syndrome, Ehlers-Danlos syndrome, or iatrogenically after aortic balloon valvotomy.[6] The heart cannot readily tolerate acute AR, as the normal left ventricle is unable to compensate for the sudden increase in end-diastolic volume caused by the large regurgitant volume load, thereby overwhelming the Frank-Starling mechanism.[29] A dramatic reduction in forward stroke volume then occurs. If there is poor left ventricular compliance from hypertrophy prior to the onset of acute AR, hemodynamic decompensation is significantly more dramatic.

To compensate for the acute decline in forward stroke volume, tachycardia ensues. Volume overload causes the left ventricular diastolic pressure to acutely rise above left atrial pressure resulting in early closure of the mitral valve.[30] Although early mitral valve closure protects the pulmonary venous circulation from high end-diastolic pressures, rapid progression of pulmonary edema and cardiogenic shock are often unavoidable.

Death is the common endpoint of all etiologies of acute AR. Progressive cardiogenic shock and malignant ventricular arrhythmias are common causes of death. Urgent surgical treatment is warranted for all causes of hemodynamically significant acute AR.

Chronic aortic regurgitation

Chronic AR is caused by either slow enlargement of the aortic root or dysfunction of the valve cusps. Common etiologies include congenital abnormalities, calcific cusp degeneration, rheumatic fever, endocarditis, degenerative aortic dilatation as seen in the elderly, Marfan syndrome, Ehlers-Danlos syndrome, myxomatous proliferation, osteogenesis imperfecta, ankylosing spondylitis, Behçet syndrome, Reiter syndrome, psoriatic arthritis, severe systemic hypertension, and idiopathic aortic root dilatation.[6] The anorectic drugs fenfluramine and dexfenfluramine have been implicated in left- and right-sided valvular disease, including AR.[31,32] Bicuspid aortic valve is the most common congenital abnormality but unicommissural, quadricuspid, and fenestrated valves may also occur.[33]

Chronic AR causes a chronic volume overload of the left ventricle. The volume load leads to progressive chamber enlargement without increasing end-diastolic pressure during the asymptomatic phase of the disease.[34] Progressive chamber enlargement is accompanied by eccentric hypertrophy, with sarcomere replication and elongation of myocytes. The combination of chamber dilatation and hypertrophy leads to a massive increase in left ventricular mass. Initially, the ratio of wall thickness to chamber diameter, ejection fraction (EF), and fractional shortening are all maintained.[35] However, this degenerates into a repetitive cycle of enlarging chamber radius with continually increasing wall stress. This wall stress is compensated by ventricular hypertrophy. Interstitial fibrosis limits the ability of the ventricle to further dilate and this cycle becomes overwhelmed, leading to elevated end-diastolic pressure, left ventricular systolic dysfunction, and CHF.[36] Vasodilator therapy may delay progression of ventricular dysfunction by decreasing afterload and decreasing regurgitant flow. Vasodilator therapy is currently indicated in asymptomatic patients with hypertension; asymptomatic patients with severe AR, ventricular dilatation, and preserved systolic function; and for short-term hemodynamic tailoring prior to operation.[37] This therapy is not recommended in patients with severe AR and LVD, as it does not improve survival but may be used in these patients if they are not considered operable.[38]

Symptomatic chronic aortic regurgitation

The time course from diagnosis of AR to the development of symptoms is highly variable. Since symptoms, such as angina and dyspnea, develop only after significant ventricular decompensation has occurred, surgery is advocated prior to the symptomatic phase of the disease. Symptomatic patients experience >10% mortality per year without surgical management.[38,39]

Asymptomatic chronic aortic regurgitation

Natural history studies of asymptomatic AR show that symptoms, LVD, or both develop in <6% of patients per year.[40] Progression to LVD without symptoms occurs in <4% of patients per year. Sudden death occurs in <0.2% per year.[41] Age, left ventricular end-systolic dimension, rate of change in end-systolic dimension, and rest EF are all independent predictors of progression to symptoms, LVD, or death in asymptomatic patients.[42] Asymptomatic patients with left ventricular systolic dysfunction experience onset of symptoms at a rate exceeding 25% per year.[43]

Indications for operation

In cases of isolated AR, timing of surgery on the asymptomatic patient is predicated on the identification of subtle changes in myocardial function before they become irreversible and negatively affect the patient's long-term prognosis. Unfortunately, such changes are often recognized by current

imaging modalities only after irreversible damage and fibrosis has occurred. Patients with more severe LVD have decreased perioperative and late survival due to irreversible changes to the ventricle including hypertrophy and interstitial fibrosis.[43–45] The decision to operate on such patients is dependent on individual variables since the outcomes are poor with surgery or medical therapy. Advances in imaging such as cardiac magnetic resonance imaging (MRI) may allow identification of candidates for AVR prior to the onset of LVD.[46]

A summary of the revised ACC/AHA Task Force guidelines for AVR for chronic AR is presented in Table 34-2.[28] Aortic valve replacement is indicated in all symptomatic patients with severe AR, regardless of LVF, and in all asymptomatic patients with severe AR with left ventricular ejection fraction (LVEF) <50%. Aortic valve replacement is also recommended in asymptomatic patients with normal LVF but significant left ventricular dilatation (end-diastolic diameter >75 mm or end-systolic diameter >55 mm). Aortic valve replacement is recommended in patients with moderate to severe AR who require concomitant coronary artery bypass surgery (CABS) or ascending aortic surgery.

Asymptomatic patients with severe AR and an enlarged left ventricle with end-systolic diameter <50 mm, and those with end-diastolic dimension >70 mm should have AVR if there is evidence of serial deterioration of ventricular function or exercise intolerance.

CORONARY ANGIOGRAPHY AND AORTIC VALVE REPLACEMENT

Many patients requiring AVR have coexistent coronary artery disease (CAD). In North America, more than one-third of AVR procedures are accompanied with coronary bypass

Table 34–2.

ACC/AHA Recommendations for Aortic Valve Replacement (AVR) in Chronic Severe Aortic Regurgitation (AR)

Indication	Class
1. AVR is indicated for symptomatic patients with severe AR irrespective of left ventricular systolic function	I
2. AVR is indicated for asymptomatic patients with chronic severe AR and left ventricular systolic dysfunction (ejection fraction ≤0.50) at rest	I
3. AVR is indicated for patients with chronic severe AR while undergoing coronary artery bypass graft or surgery on the aorta or other heart valves	I
4. AVR is reasonable for asymptomatic patients with severe AR with normal left ventricular systolic function (ejection fraction >0.50) but with severe left ventricular dilatation (end-diastolic dimension >75 mm or end-systolic dimension >55 mm)*	IIA
5. AVR may be considered in patients with moderate AR while undergoing surgery on the ascending aorta	IIB
6. AVR may be considered in patients with moderate AR while undergoing coronary artery bypass graft surgery	IIB
7. AVR may be considered for asymptomatic patients with severe AR and normal left ventricular systolic function at rest (ejection fraction >0.50) when the degree of left ventricular dilatation exceeds an end-diastolic dimension of 70 mm or end-systolic dimension of 50 mm, when there is evidence of progressive left ventricular dilatation, declining exercise tolerance, or abnormal hemodynamic responses to exercise.*	IIB
8. AVR is not indicated for asymptomatic patients with mild, moderate, or severe AR and normal left ventricular systolic function at rest (ejection fraction >0.50) when the degree of dilatation is not moderate or severe (end-diastolic dimension <70 mm, and those with end-diastolic dimension >70 mm should have aortic valve replacement if there is evidence of serial deterioration of ventricular function or exercise intolerance.).*	III

**Consider lower threshold values for patients of small stature of either gender.*

Source: Adapted with permission from Bonow RO, Carabello BA, Chatterjee K, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Valvular Heart Disease). Available at: http://www.americanheart.org.

graft surgery. This proportion may increase as the surgical population continues to age. Risk assessment for ischemic heart disease is complicated in patients with aortic valve disease since angina may be related to true ischemia from hemodynamically significant coronary lesions, or other causes such as left ventricular wall stress with subendocardial ischemia or chamber enlargement in the setting of reduced coronary flow reserve. Since traditional coronary risk stratification is unreliable in aortic valve patients, it is our practice to routinely perform diagnostic coronary angiography on all patients over the age of 35. ACC/AHA Task Force guidelines for preoperative angiography are presented in Table 34-3.[28]

Technique of Operation

Myocardial protection and cardiopulmonary bypass

Isolated AVR is performed using a single two-stage venous cannula inserted into the right atrium for venous return and a standard arterial cannula into the ascending aorta for systemic perfusion of oxygenated blood. A retrograde cardioplegia cannula may be placed into the coronary sinus via the right atrium. A left ventricular vent cannula is placed through a purse-string suture in the right superior pulmonary vein and advanced into the left ventricle to ensure a bloodless field and to prevent ventricular distention if there is aortic insufficiency. Once cardiopulmonary bypass (CPB) is initiated, the aorta and pulmonary artery are dissected to expose the anterior aortic root to the left coronary artery. Careful dissection of the pulmonary artery from the aorta ensures that the cross-clamp will be fully occlusive on the aorta and prevents inadvertent opening of the pulmonary artery with the aortotomy incision. Pulmonary artery injuries may be difficult to repair, as this tissue is substantially more friable than the aorta.

After the cross-clamp is applied, myocardial protection is initially delivered as a single dose of high potassium blood through the ascending aorta.[47–49] This will achieve

Table 34–3.

ACC/AHA Task Force Guidelines on Coronary Angiography in Patients with Valvular Heart Disease

Indication	Class
1. Before valve surgery (including infective endocarditis) or mitral balloon commissurotomy in patients with: a. Chest pain b. Other objective evidence of ischemia c. Decreased left ventricular systolic function d. History of coronary artery disease e. Coronary risk factors (including advanced age)	I
2. Patients with apparently mild to moderate valvular heart disease but with: a. Progressive (class II or greater) angina b. Objective evidence of ischemia c. Decreased left ventricular systolic function d. Overt congestive heart failure	I
3. Before valve surgery in men aged 35 and older, premenopausal women aged 35 years or older who have coronary risk factors, and postmenopausal women	I
4. Surgery without coronary angiography is reasonable for patients having emergency valve surgery for acute valve regurgitation, aortic root disease, or infective endocarditis	IIA
5. Patients undergoing catheterization to confirm the severity of valve lesions before valve surgery without pre-existing evidence of coronary artery disease, multiple coronary risk factors, or advanced age	IIB
6. Coronary angiography is not indicated in young patients undergoing nonemergent valve surgery when no further hemodynamic assessment by catheterization is deemed necessary and no coronary risk factors, no history of coronary artery disease, and no evidence of ischemia are present	III
7. Patients should not undergo coronary angiography before valve surgery if they are severely hemodynamically unstable	III

Source: Adapted with permission from Bonow RO, Carabello BA, Chatterjee K, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Valvular Heart Disease). Available at: http://www.americanheart.org.

prompt diastolic arrest unless there is moderate to severe AR. Myocardial protection is maintained by continuous infusion of cold or tepid oxygenated blood cardioplegia delivered via direct cannulation of both coronary ostia after the aorta has been opened.[50] Many surgeons do not routinely use retrograde cardioplegia for aortic valve cases, but this strategy is helpful in patients with significant AR or severe concomitant coronary disease.[51] In cases in whom the retrograde cannula cannot be placed into the coronary sinus, conversion to bicaval cannulation and opening the right atrium to directly place the cannula into the coronary sinus is possible. If retrograde perfusion is employed, this is also used in a continuous manner. Right ventricular myocardial protection may be inadequate with only retrograde cardioplegia and can lead to significant right ventricular dysfunction after CPB is discontinued. This may be avoided by ensuring that the retrograde cannula is not placed beyond the origin of the right coronary vein ostium in the coronary sinus.[52–55] The patient's systemic body temperature is allowed to drift downward, but active cooling for noncirculatory arrest cases is unnecessary.

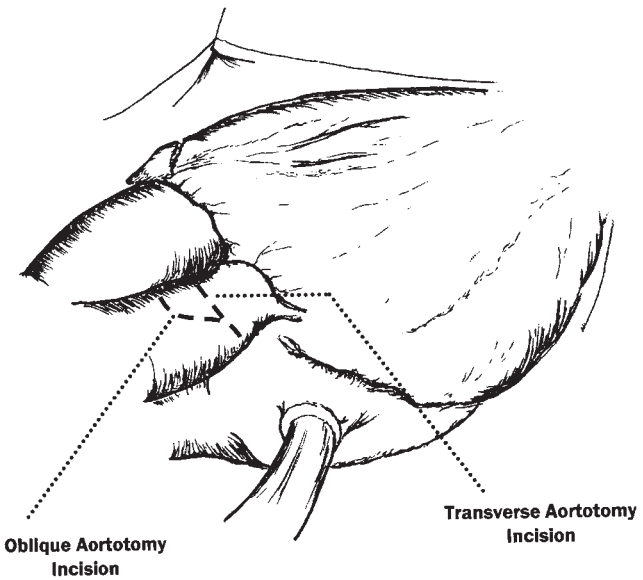

Figure 34-3. Exposure and aortotomy incision. A two-stage venous cannula is in place in the right atrial appendage. The aortotomy (dashed line) may be made in the transverse or oblique direction.

Aortotomy, valve excision and débridement

After the cross-clamp has been applied and cardioplegic arrest has been achieved, the aorta is opened either with a transverse or oblique aortotomy. The low transverse aortotomy is a common approach to the aortic valve when using stented bioprostheses or mechanical valves. The aortotomy is started approximately 10 to 15 millimeters above the origin of the right coronary artery (RCA) and extended anteriorly and posteriorly. The initial transverse incision over the RCA may also be extended obliquely in the posterior direction into the noncoronary sinus or the commissure between the left and noncoronary cusps (Fig. 34-3). The oblique incision is often used in patients with small aortic roots, in whom root enlargement procedures may be required (see below) and may also be used to tailor a larger ascending aorta.

Morphology of the valve is then inspected (Fig. 34-4). Excision of the valve cusps starts with scissors to incise into the right cusp between the right coronary ostium and the commissure between the right coronary and noncoronary cusps (Fig. 34-5). Mayo scissors or special right-angled valve scissors are usually used at this stage and the calcific deposits are squeezed away from the aortic wall. One to two millimeters of tissue is left behind to provide a sewing surface. Right cusp excision is carried first toward the left coronary cusp and then toward the noncoronary cusp and the cusp is removed as a single piece if possible. Excision is then carried toward the left and noncoronary commissure along the noncoronary cusp and then the left coronary cusp. A moistened radiopaque sponge is placed into the outflow area to catch debris, and the surgeon must ensure that this is removed before placing the valve sutures. Thorough decalcification is then performed with a scalpel or rongeur.

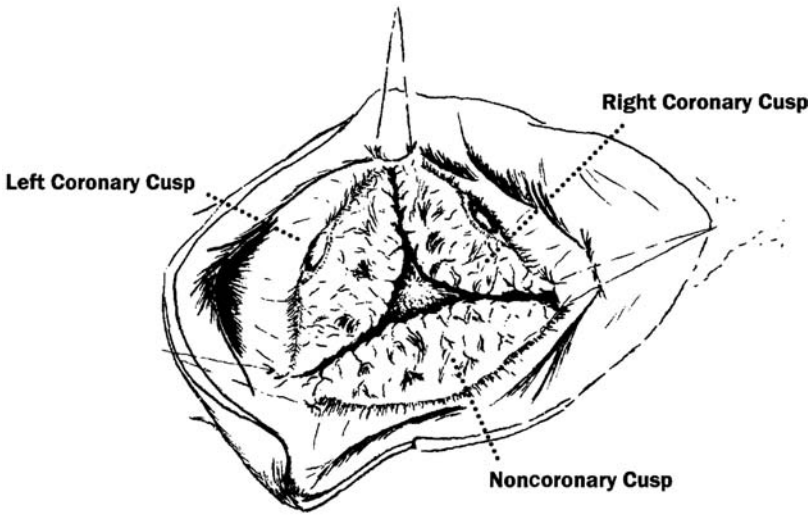

Figure 34-4. The exposed aortic valve.

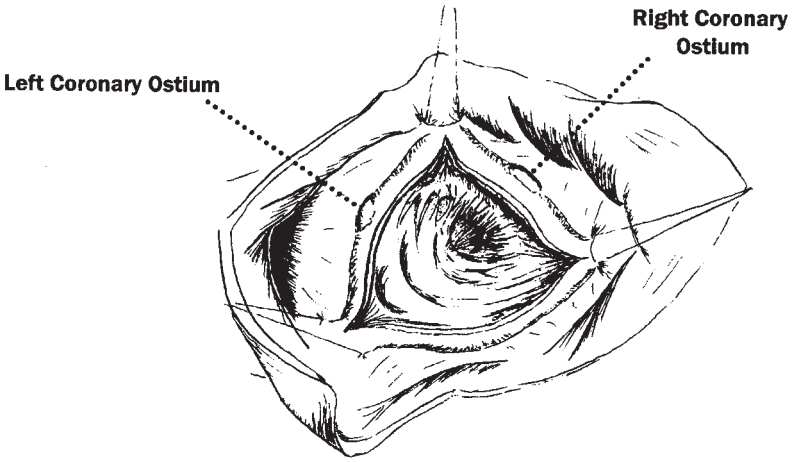

Figure 34-5. The aortic valve after leaflet excision.

Débridement of all calcium deposits back to soft tissue improves seating of the prosthesis and decreases the incidence of paravalvular leak and dehiscence.

Care must be taken to prevent aortic perforation while calcific deposits are débrided from the aortic wall, particularly at the commissure between the left and noncoronary cusps, where perforation is most likely. Several anatomic relationships must be respected during valve excision (Fig. 34-6). The bundle of His (conduction system) is located below the junction of the right and noncoronary cusps in the membranous septum. Deep débridement in this area can result in permanent heart block. The anterior leaflet of the mitral valve is in direct continuity with the left aortic valve cusp. If it is damaged during decalcification, an autologous pericardial patch is used to repair the defect.

Once débridement is completed, the aortic root is copiously flushed with saline while the left ventricular vent is stopped. To prevent pushing debris into the left ventricle, saline in a bulb syringe is flushed through the left ventricular vent and out the aortic valve in an antegrade manner instead of retrograde through the valve. The irrigation solution is suctioned with the external wall suction and not into the cardiotomy suction.

Valve implantation

After the native valve has been excised, the annulus is sized with a valve-sizer designed exactly for the selected prosthetic device. The valve is secured to the annulus using 12 to 16 double-needled interrupted 2-0 synthetic braided pledgeted sutures that are alternating in color. The pledgets can be left on the inflow/ventricular side or the outflow/aortic side of the aortic annulus (Figs. 34-7 and 34-8). Placing the pledgets on the inside of the annulus allows supra-annular placement of the valve and generally will allow implantation of a

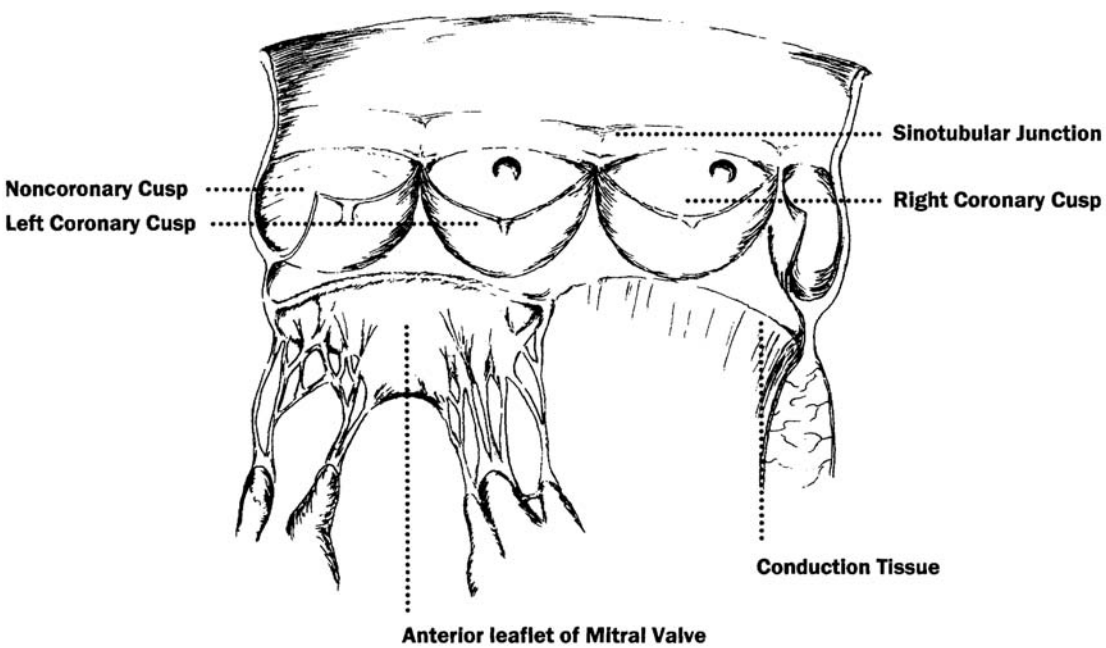

Figure 34-6. Anatomic relationships of the aortic valve.

slightly larger prosthesis. In cases in whom the coronary ostia are close to the annulus, supra-annular placement may only be possible along the noncoronary cusp. Mattress sutures are first placed in the three commissures and retracted to assist visualization. Some surgeons will place the commissural suture between the right and noncoronary cusps from the outside of the aorta (i.e., the pledget is left on the outside of the aorta) to prevent injury to the conduction system. Pledgeted mattress sutures are then placed in a clockwise fashion typically starting in the noncoronary cusp. Sutures may be placed into the sewing ring of the prosthetic valve with each annular suture or after all annular sutures are placed. The sutures for each of the three cusps are held separately with three hemostats and retracted while the prosthesis is slid into the annulus. Sutures are then tied down in a balanced fashion alternating among the three cusps.

Aortic closure and de-airing

The aorta is closed with a double row of synthetic 4-0 polypropylene sutures. The first suture line is started on the right side at the posterior end of the aortotomy and the double-needled suture is secured slightly beyond the incision to ensure there is no leak in this region. One end of the suture is run as a horizontal mattress anteriorly to the midpoint of the aortotomy, and then the second end of the suture is run anteriorly, slightly superficial to the horizontal mattress suture, in an over-and-over manner. On the left side, a similar technique is performed, the aorta is de-aired (described below), and the two sutures are tied to themselves and to each other at the aortotomy midpoint.

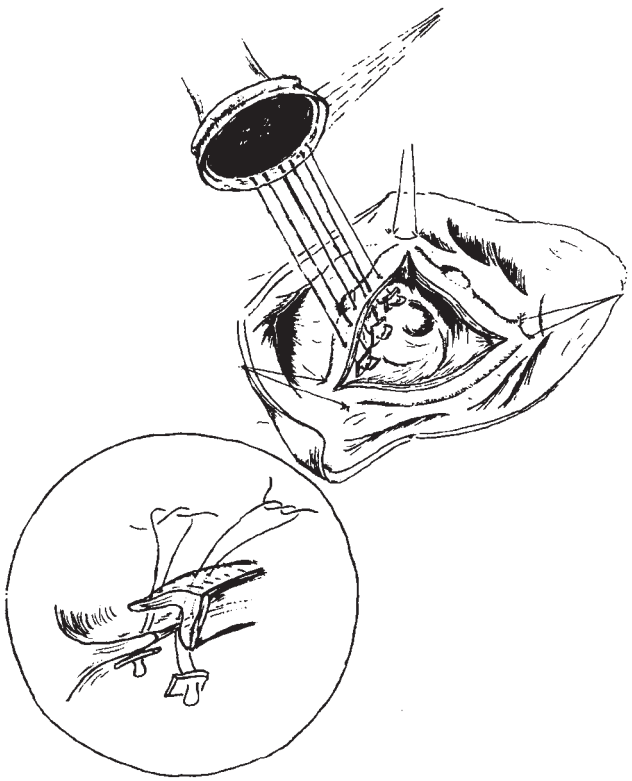

Figure 34-7. Placement of sutures with pledgets below the annulus.

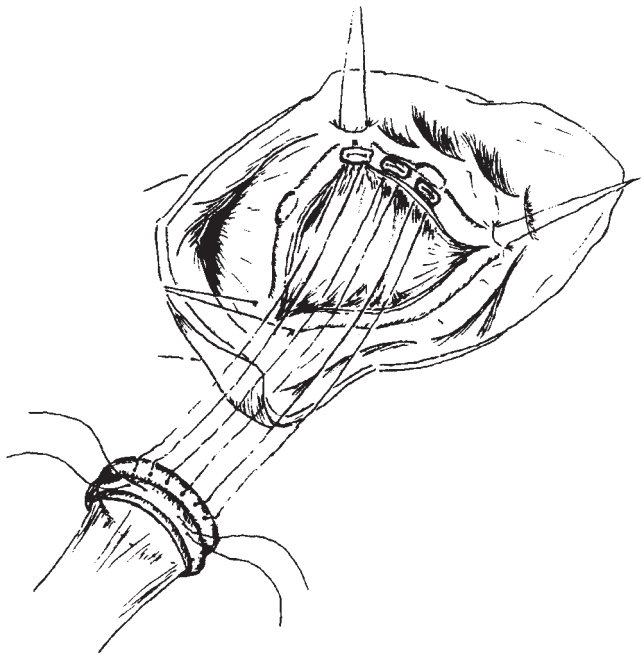

Figure 34-8. Placement of sutures with pledgets above the annulus.

During AVR, air is entrained into the left atrium and ventricle, and aorta. This must be removed to prevent catastrophic air embolization. Immediately prior to tying the suture of the aortotomy, the heart is allowed to fill, the vent in the superior pulmonary vein is stopped, the lungs are inflated, and the cross-clamp is briefly partially opened. The subsequent influx of blood should expel most air from these cavities out of the partially open aortotomy. Closure of the aortotomy is then completed and the cross-clamp is fully removed. The cardioplegia cannula in the ascending aorta and the left ventricular vent are then placed on suction to remove any residual air as the heart begins electrical activity. A small needle (21-gauge) is used to aspirate the apex of the left ventricle and the dome of the left atrium. To prevent air entrainment, the left ventricular vent must be removed while the pericardium is filled with saline irrigation. De-airing maneuvers are verified with transesophageal echocardiographic visualization to verify that all air has been removed from the left side of the heart. Vigorous shaking and careful manual compression of the heart while suctioning through the aortic vent (i.e., cardioplegia tack) is helpful to remove air trapped within trabeculations. Once de-airing is complete, the aortic vent is removed. The patient is then weaned from CPB and decannulated in the standard fashion.

Concomitant coronary artery bypass grafting

Operative technique is modified when there is concomitant CAD to optimize myocardial protection. Distal anastomoses are performed prior to AVR so that antegrade cardioplegia

may be administered through these grafts during the operation. The left internal thoracic artery should be used for revascularization of the left anterior descending artery, as this may improve long-term survival in aortic valve patients.[56] This anastomosis is performed after the aortotomy is closed to ensure that the coronary circulation is not exposed to systemic circulation during cardioplegic arrest and to prevent trauma to the anastomosis during manipulation of the heart.

Concomitant ascending aortic replacement

In general, the ascending aorta is replaced electively when maximal diameter exceeds 5.5 to 6.0 cm in patients without Marfan syndrome, and 4.5 to 5.0 cm in patients with Marfan syndrome. In the setting of concomitant aortic valve replacement, aortic replacement is advised if the ascending aortic diameter is >5.0 cm. Recent data suggest that patients with bicuspid aortic valves have an underlying aortopathy that leads to significant risk of late ascending aortic complications, and these patients should have replacement of their ascending aorta if its diameter exceeds 4.5 cm at the time of AVR[57] (Fig. 34-9).

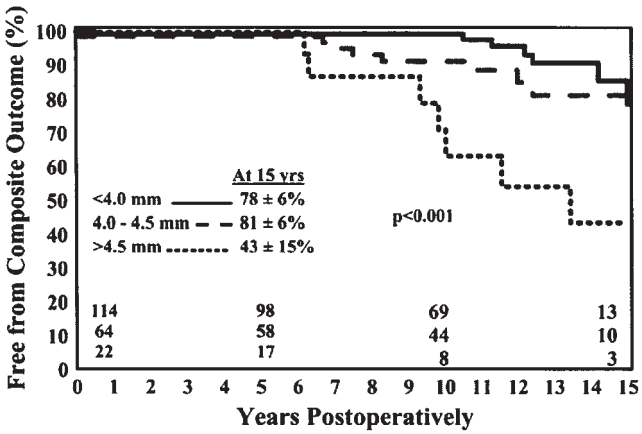

Figure 34-9. Freedom from ascending aortic complications for patients with a bicuspid aortic valve with an ascending aortic diameter of <4 cm, 4.0 to 4.5 cm, and 4.5 to 4.9 cm at the time of aortic valve replacement. (*Reproduced with permission from Borger MA, et al: Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? J Thorac Cardiovasc Surg 2004; 128:677.*)

Aortic root enlargement procedures

Detailed descriptions of aortic root enlargement procedures are presented in a later chapter. Either an anterior or posterior annular enlargement procedure may be performed in a patient with a small aortic root to allow for implantation of a larger valve. The posterior approach is the most commonly used aortic root enlargement procedure in adults and can increase the annular diameter by 2 to 4 mm. Nicks and colleagues in 1970 described a technique of root enlargement in which the aortotomy is extended downward through the noncoronary cusp, through the aortic annulus to the anterior mitral leaflet.[58] In 1979 Manouguian and Seybold-Epting described a procedure extending the aortotomy incision in a downward direction through the commissure between the left and noncoronary cusps into the interleaflet triangle and into the anterior leaflet of the mitral valve.[59,60] The anterior approach is generally used in the pediatric population. Described by Konno and colleagues in 1975, this technique, which is also known as aortoventriculoplasty, is used when more than 4 mm of annular enlargement is required.[61] Instead of a transverse incision, a longitudinal incision is made in the anterior aorta and extended to the right coronary sinus of Valsalva and then through the anterior wall of the right ventricle to open the right ventricular outflow tract. The ventricular septum is incised, allowing significant expansion of the aortic annulus and left ventricular outflow tract.

Reoperative aortic valve surgery

Repeat sternotomy after AVR may be performed for valve-related complications, progressive ascending aortic disease, or CAD. Valve-related causes include structural valve deterioration, prosthetic endocarditis, prosthesis thrombosis, or paravalvular leak. Chest re-entry is the most hazardous portion of any repeat cardiac procedure. It is our routine practice to obtain an adequate lateral chest x-ray and computed tomography (CT) scan to determine the proximity of cardiac structures to the posterior sternum. Cardiopulmonary bypass is instituted through the femoral vessels when there is concern about chest re-entry. An oscillating saw is used to open the sternum and the dissection is kept as limited as possible. Extreme caution must be employed during dissection when there are patent bypass grafts. When only the aortic valve needs reoperation, advanced port-access technologies such as percutaneous coronary sinus cannulation and pulmonary artery venting can allow the operation to proceed with only a limited upper sternotomy.

Once cardioplegic arrest is established, the old prosthesis is excised with sharp dissection. Care must be taken to remove all sutures and pledgets from the annulus. Annular injuries caused while excising the prosthesis are repaired with pledgeted interrupted sutures. Removal of stentless prostheses may be particularly difficult in this regard. In the setting of endocarditis, aggressive débridement of infected tissue must be performed with appropriate annular reconstruction with pericardium when root abscesses are present.[62,63] All foreign graft material, including Dacron aortic grafts, must be excised in the presence of active endocarditis.[64]

In the presence of a Dacron prosthesis in the ascending aorta, chest re-entry may be extremely hazardous since exsanguination will occur if the graft is accidentally opened during dissection. To limit the systemic consequences of exsanguination at normothermia, the patient should be placed on femoro-femoral CPB and cooled to 20°C prior to chest reentry.[65] If the Dacron graft is accidentally opened, local control of the bleeding is established and CPB is stopped. Under circulatory arrest, atrial venous cannulation

is instituted and the graft is controlled distal to the tear. Cardiopulmonary bypass may then be restarted. In all repeat aortic procedures, rigorous myocardial protection must be applied since these procedures often have very long ischemic times. Antegrade cold blood cardioplegia is usually employed in a continuous fashion throughout the case by selective cannulation of the coronary ostia. Retrograde cardioplegia may have benefit in the setting of patent old saphenous vein grafts.[66]

Aortic balloon valvotomy

Aortic balloon valvotomy may be performed percutaneously via a femoral artery puncture in the interventional angiography suite to treat AS.[67] Inflation of the balloon within the valve orifice can stretch the annular tissue and fracture calcified areas or open fused commissures. There is no role for valvotomy in the patient with significant AR, as this will become significantly worse after the procedure.[68–70] Balloon valvotomy is rarely successful if significant calcification is present and carries a prohibitive risk of stroke from calcific emboli.[71,70] The long-term outcomes of this procedure in adult patients are dismal, with restenosis usually occurring within 1 year.[70,72,73] Patients with severe symptomatic AS who are too hemodynamically unstable to tolerate operation or have comorbid illnesses, such as advanced malignancy, which contraindicate operation, may benefit from palliative balloon valvotomy.[74–77] More recently, techniques have developed in implant prosthetic valves using transcatheter approaches. These procedures are discussed later in this chapter.

POSTOPERATIVE MANAGEMENT

Special consideration must be given to the underlying pathologic changes to the ventricle during the immediate postoperative period. The severely hypertrophied, noncompliant left ventricle found in AS is highly dependent on sufficient preload for adequate filling. Filling pressures should be carefully titrated between 15 and 18 mm Hg with intravenous volume infusion. Maintenance of sinus rhythm is also essential since up to one-third of cardiac output is derived from atrial contraction in a noncompliant ventricle. Up to 10% of patients will experience low cardiac output syndrome in the immediate postoperative period.[78] If pacing is required postoperatively, synchronous atrioventricular pacing is beneficial in preventing low cardiac output syndrome. If patients are pacemaker-dependent when weaned from CPB in the operating room, it is recommended to insert atrial pacing wires to allow for synchronous atrioventricular pacing.

In cases of severe hypertrophy, subvalvular left ventricular outflow obstruction with systolic anterior wall motion of the mitral valve may occur. Intravenous beta-adrenergic blockade may relieve this obstruction by decreasing inotropy. In extreme cases reoperation and surgical myectomy may be required.[79]

Profound peripheral vasodilation, often seen in patients with aortic insufficiency, is treated with vasoconstrictors including alpha-adrenergic agonists or vasopressin. Adequate filling of the dilated left ventricle may also require volume infusion.

Complete heart block occurs in 3 to 5% of AVR patients. This complication may be due to suture placement or injury from débridement near the conduction system. Transient complete heart block caused by perioperative edema usually resolves in 4 to 6 days. After this time, insertion of a permanent pacemaker is recommended if there is no resolution. Echocardiographic evaluation of valve function should be performed in the operating room with transesophageal echocardiography (TEE) and then at discharge, at 3 months, and yearly with transthoracic echocardiography (TTE).

STENTED BIOPROSTHETIC AORTIC VALVE REPLACEMENT DEVICES

Stented biologic prostheses may be constructed of porcine aortic valves or bovine pericardium. Over the past 40 years, advances in tissue fixation methodology and chemical treatments to prevent calcification have yielded improvements in the longevity of bioprostheses. All heterograft valves are preserved with glutaraldehyde, which cross-links collagen fibers and reduces the antigenicity of the tissue. Glutaraldehyde also reduces the rate of in vivo enzymatic degradation and causes the loss of cell viability, thereby preventing normal turnover and remodeling of extracellular matrix tissues.[80,81] Calcification occurs when nonviable glutaraldehyde-fixed cells cannot maintain low intracellular calcium.[81] Calcium phosphate crystals form at the phospholipid-rich membranes and their remnants, and the collagen matrix also calcifies.[82]

Glutaraldehyde fixation of porcine valves can be performed at high pressure (60 to 80 mm Hg), low pressure (0.1 to 2 mm Hg), or zero-pressure (0 mm Hg). Pericardial prostheses are fixed in low- or zero-pressure conditions. Porcine prostheses fixed at zero pressure retain the collagen architecture of the relaxed aortic valve cusp.[83] Higher fixation pressures cause tissue flattening and compression with loss of transverse cuspal ridges and collagen crimp, which may lead to earlier calcification.[84,85]

Multiple chemical treatments have been proposed to decrease the calcification process that invariably leads to material failure and valvular dysfunction. These include sodium dodecyl sulfate, polysorbate-80, Triton X-100, N-lauryl sarcosine, amino-oleic acid, aminopropane-hydroxydiphosphonate, toluidine blue, controlled-release diphosphonates, ferric chloride, aluminum chloride, and phosphocitrate.[86–100]

When comparing various bioprostheses, it is important to be aware of lack of standardization in methodologies for labeling valve sizes by the different manufacturers. In general, label sizes refer to either the internal or external

diameter of the stent, not the external diameter of the sewing cuff or the maximal opening diameter of the valve leaflets. Thus, the same aortic annulus will likely fit different sized valves from different manufacturers, depending on the convention they use and the size of their sewing cuff. Figure 34-10 compares internal and external sizes for a variety of prostheses.

First-Generation Prostheses

First-generation bioprostheses were preserved with high-pressure fixation and were placed in the annular position. They include the Medtronic Hancock Standard and Modified Orifice (Medtronic, Minneapolis, MN), and Carpentier-Edwards Standard porcine prostheses (Edwards Life Sciences, Irvine, CA).

Second-Generation Prostheses

Second-generation prostheses are treated with low- or zero-pressure fixation. Several second-generation prostheses may also be placed in the supra-annular position, which allows placement of a slightly larger prosthesis. Porcine second-generation prostheses include the Medtronic Hancock II valve (Medtronic, Minneapolis, MN), the Medtronic Intact porcine valve (Medtronic, Minneapolis, MN), and the Carpentier-Edwards Supraannular valve (SAV) (Edwards Life Sciences, Irvine, CA). Second-generation pericardial prostheses include the Carpentier-Edwards Perimount (Edwards Life Sciences, Irvine, CA), and the Pericarbon (Sorin Biomedica, Saluggia, Italy) prostheses.

Third-Generation Prostheses

Newer-generation prostheses incorporate zero- or low-pressure fixation with anti-mineralization processes that are designed to reduce material fatigue and calcification. Stents have become progressively thinner, have a lower profile, and are more flexible, and sewing rings have become scalloped for supra-annular placement. The Medtronic Mosaic porcine valve (Medtronic, Minneapolis,

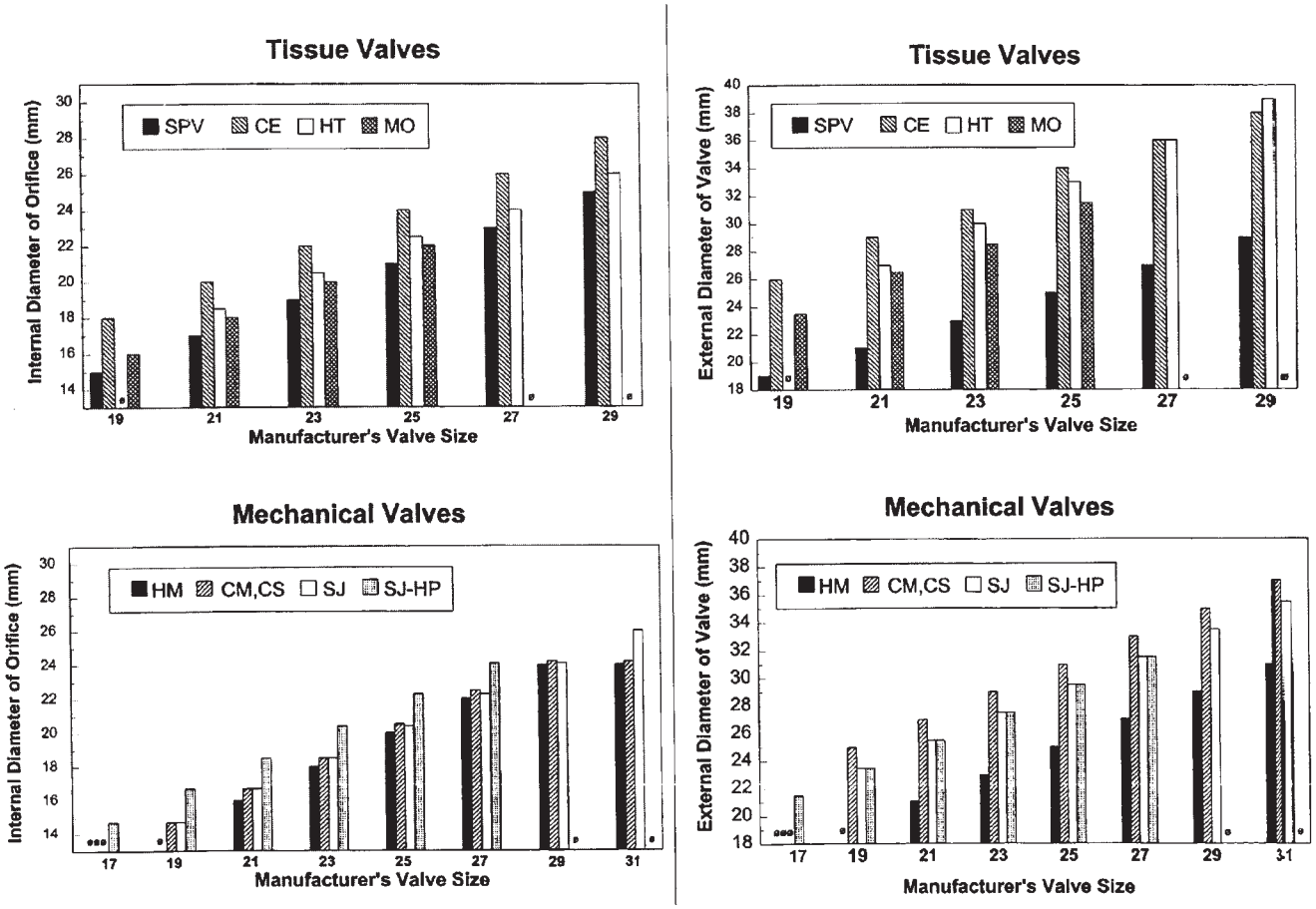

Figure 34-10. Comparison of the internal and external diameter of prosthetic aortic valves to the manufacturers' labeled size of each valve. No two manufacturers' valves have the same internal diameter for a given labeled size. (CE = Carpentier-Edwards Pericardial valve; CM = Carbomedics Standard valve; CS = Carbomedics Supra-annular valve; HM = Medtronic Hall valve; HT = Hancock II Bioprosthesis; MO = Hancock Modified Orifice Bioprosthesis; SJ = St. Jude Standard valve; SJ-HP = St. Jude Hemodynamic Plus valve; SPV= stentless porcine valve.) (*Reproduced with permission from Christakis GT, et al: Inaccurate and misleading valve sizing: a proposed standard for valve size nomenclature. Ann Thorac Surg 1998; 66:1198.*)

MN) is fixed in a "physiologic" environment with equal pressure (40 mm Hg) applied to the ventricular and aortic sides of the leaflets, resulting in net zero pressure on the leaflets themselves (Figs. 34-11 and 34-12). By pressurizing the root without placing pressure on the leaflets, this process stabilizes the root to maintain its anatomic shape. Alpha-amino oleic acid, which permanently covalently binds to free aldehyde groups, is used as the anticalcification treatment.

The St. Jude Medical Epic valve (St. Jude Medical Inc., Minneapolis, MN) is a porcine valve with a very low stent post and base profile to minimize protrusion into the aortic wall and facilitate coronary clearance (Fig. 34-13). The valve is composed of three separate porcine leaflets matched to size and low-pressure fixed in glutaraldehyde. A proprietary anticalcification treatment is used on the leaflet tissue. The outflow edge of the stent is covered with pericardium to prevent leaflet contact with the fabric of the sewing cuff.

The Carpentier-Edwards Magna valve (Edwards Life Sciences, Irvine, CA) is the evolution of the Perimount pericardial valve, with a narrower sewing cuff and scalloped

Figure 34-12. The Medtronic Mosaic porcine aortic prosthesis. (*Figure courtesy Medtronic Inc., Minneapolis, MN.*)

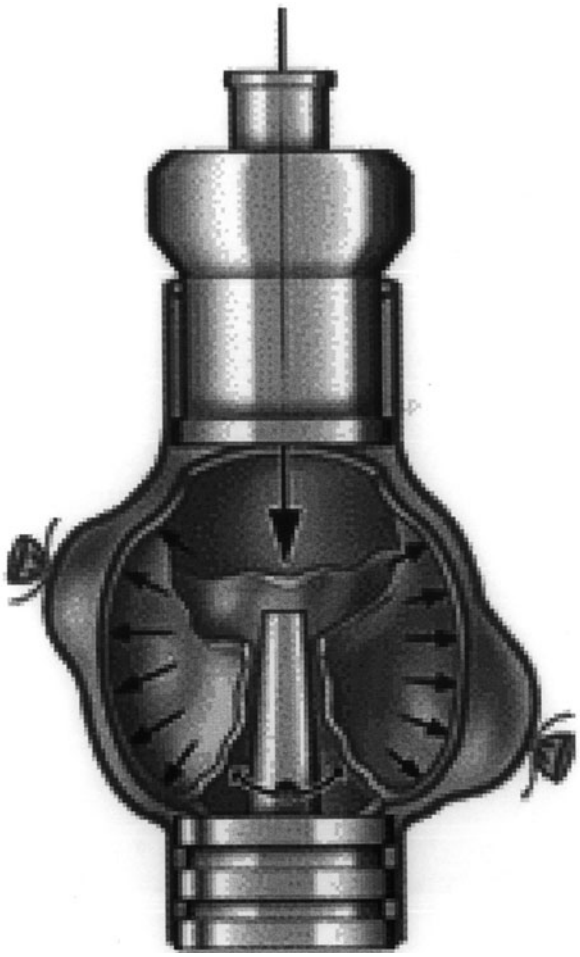

Figure 34-11. "Physiologic" fixation process. Simultaneous application of pressure to the inflow and outflow portions of a porcine bioprosthesis place zero net pressure on leaflets within a pressurized root. (*Figure courtesy of Medtronic Inc., Minneapolis, MN.*)

design for supra-annular placement (Fig. 34-14). The bovine pericardial leaflets are fixed at low pressure and treated with proprietary treatments to eliminate phospholipids and unstable and residual glutaraldehyde molecules, which are calcium-binding sites.

The Mitroflow Pericardial aortic prosthesis (Carbomedics, Austin, TX) is a pericardial valve that is unique in that the pericardium is placed around the exterior of the stent, presumably allowing for a larger opening diameter (Fig. 34-15). Although the current version does not have anticalcification treatment, this is being developed for future iterations.

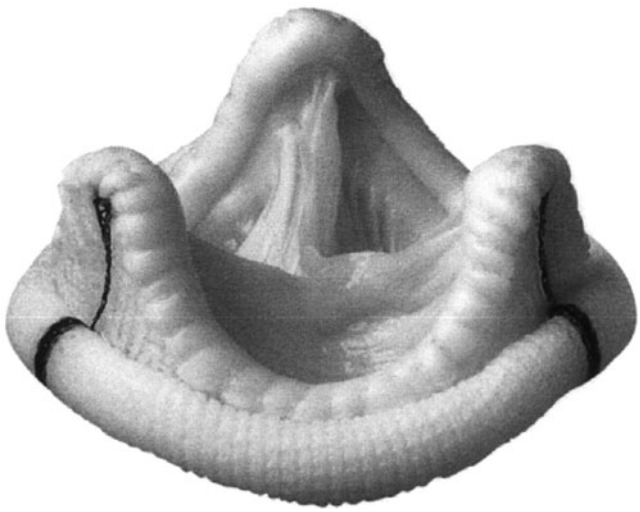

Figure 34-13. The St. Jude Epic porcine aortic prosthesis. (*Figure courtesy of St. Jude Medical Inc., Minneapolis, MN.*)

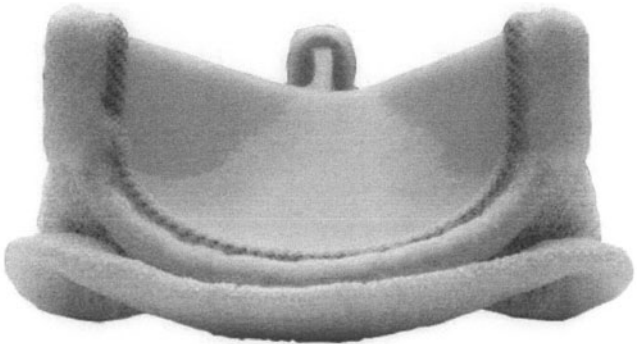

Figure 34-14. The Carpentier-Edwards Magna pericardial prosthesis. (*Figure courtesy of Edwards Life Sciences Inc., Irvine, CA.*)

Transcatheter Stented Bioprostheses

Transcatheter valve replacement technologies are evolving and have recently become a clinical reality, applied to high-risk patients who are not operative candidates. Valves comprised of equine pericardium have been mounted onto stents which can be delivered by three different techniques (Fig. 34-16). The antegrade approach involves femoral venous access, transseptal puncture, dilation of the atrial septum, guiding a flotation balloon through the mitral valve, antegrade cannulation of the aortic valve, snaring of a guidewire from opposite the femoral artery with exteriorization of an arteriovenous wire loop, balloon dilatation, and device delivery.[101] Initial results of this technique were associated with many mechanical and arrhythmic complications and a high periprocedural mortality, leading to virtual abandonment of this technique.[102–105] The retrograde femoral approach involves percutaneous femoral artery access, retrograde cannulation of the aortic valve, balloon dilatation, and device delivery. This technique has been applied with acceptable early results in elderly and high-risk patients, and represents an emerging option for nonoperative candidates.[106]

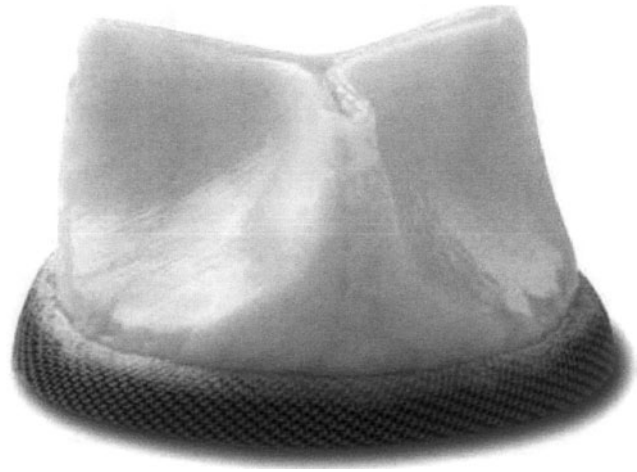

Figure 34-15. The Mitroflow Pericardial aortic prosthesis (*Figure courtesy of Carbomedics Inc., Austin, TX.*)

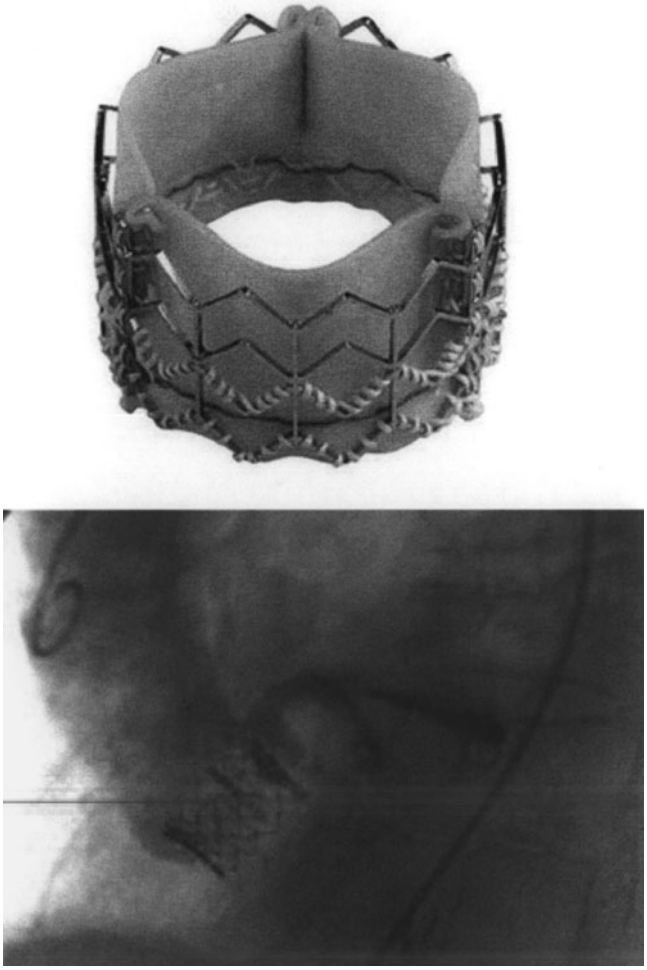

Figure 34-16. The Cribier-Edwards aortic percutaneous heart valve (upper panel) and fluoroscopic view of this prosthesis deployed in the aortic root (lower panel). (*Figure courtesy of Edwards Life Sciences, Irvine, CA.*)

The third approach is transapical transcatheter valve delivery. Performed in the operating room under general anesthesia, this technique involves creating a small thoracotomy, direct cannulation of the left ventricular apex, and passing of a wire under fluoroscopic guidance through the aortic valve.[107] The stent-mounted valve is then deployed with fluoroscopic and echocardiographic guidance. This technique avoids CPB and may be particularly beneficial for previous prosthetic valve failure, since the sternotomy incision may be avoided and the new prosthesis is placed inside the failed prosthesis. All three techniques require rapid ventricular pacing to ensure there is no cardiac output during device deployment.

The ultimate role of these catheter-based techniques of AVR has yet to be determined. Questions regarding prosthesis durability, periprocedural stroke, coronary artery injury, and hemodynamic performance remain unanswered, and will continue to evolve with successive iterations of the technology. At present, these techniques are enabling very high-risk patients to experience some relief of

their symptoms without undergoing a complex operation. Given the excellent current results of open operative AVR, the use of these procedures in lower-risk patients is not currently warranted.

OUTCOMES OF AORTIC VALVE REPLACEMENT

Operative Mortality

Operative mortality is defined as all-cause mortality within 30 days of operation or during the same hospital admission.[108] Contemporary series describe a very low operative mortality for isolated AVR. The mortality from AVR varies between 1 and 8%, depending on the patient population, the presence of coronary disease, and the era of study.[109–120] A publication from the Society of Thoracic Surgeons' (STS) database reviewing the results of 86,580 valve procedures found an overall mortality of 4.3% for isolated AVR, and 8.0% for AVR with CABS.[121] Aortic valve replacement with ascending aortic aneurysm repair had an operative mortality of 9.7%.[121] The results of this study are summarized in Table 34-4. It is important to note that information in this database is voluntarily submitted and includes both low-volume and high-volume centers.

Advanced patient age, poor preoperative LVF, New York Heart Association (NYHA) class IV symptoms, concomitant CAD, severe preoperative renal dysfunction, active endocarditis, female gender, emergent or salvage operation, and previous AVR have been associated with increased operative mortality in several series.[121–130] In the absence of major comorbidities and preserved LVF, isolated AVR can be performed with an expected mortality of less than 2%.[131] Kouchoukos and colleagues have shown that operative mortality is not further increased if simple resection of an ascending aortic aneurysm is performed concurrently at an experienced center.[132] Concomitant CABS is associated with approximately double the operative mortality of isolated AVR.[131–137] Table 34-5 presents the preoperative risk factors of operative mortality derived from the Society of Thoracic Surgeons database. Most early deaths are attributable to postoperative low cardiac output syndrome, neurologic injury, or infection. In Table 34-6, mortality data from a recent update of the Society of Thoracic Surgeons' database are presented describing the operative risk of isolated and combined valve procedures.[138] Isolated AVR was the valve procedure associated with the lowest perioperative mortality.

Long-Term Survival

Longitudinal analysis shows that there is no difference in survival between patients receiving mechanical and bioprosthetic valves when they are implanted in similar age cohorts over 10 years of follow-up.[139] However, at 15 years' follow-up, structural valve deterioration in bioprosthetic valves leads to a survival benefit for patients with mechanical valves. In a prospective trial by Hammermeister and colleagues, 11-year mortality was 62 and 57% for bioprosthetic and mechanical valves,

Table 34–4.

Operative Mortality Rates for Aortic Valve Replacement (AVR) Procedures from the Society of Thoracic Surgeons' Database

Operative category	Number	Operative mortality (%)
AVR (isolated)	26,317	4.3
Multiple valve replacement	3840	9.6
AVR + coronary artery bypass	22,713	8.0
Multiple valve replacement + coronary artery bypass	1424	18.8
AVR + any valve repair	938	7.4
Aortic valve repair	597	5.9
AVR + aortic aneurysm repair	1723	9.7
AVR + other*	356	8.4

**Other includes left ventricular aneurysm, ventricular septal defect, atrial septal defect, congenital defect, cardiac trauma, cardiac transplant, permanent pacemaker, automatic implanted cardioverter-defibrillator, aortic aneurysm, or carotid endarterectomy. Isolated aortic valve replacement and aortic aneurysm are not included in aortic valve replacement + other.*

Source: Adapted from Jamieson WR, Edwards FH, Schwartz M, et al: Risk stratification for cardiac valve replacement. National Cardiac Surgery Database. Database Committee of the Society of Thoracic Surgeons. Ann Thorac Surg 1999; 67:943.

Table 34–5.

Independent Risk Factors for Operative Mortality (Odds Ratios) for Isolated Aortic Valve Replacement and Aortic Valve Replacement Plus Coronary Artery bypass from the Society of Thoracic Surgeons' Database

Aortic valve replacement			Aortic valve replacement plus coronary artery bypass		
Risk factor	**Odds ratio**	**CI**	**Risk factor**	**Odds ratio**	**CI**
Salvage status	7.12	4.69–10.68	Salvage status	7.00	4.74–10.33
DDRF	4.32	2.83–6.43	DDRF	4.60	3.10–6.70
ES	3.46	2.62–4.52	Reoperation	2.40	2.11–2.73
Multiple reoperations	2.27	1.57–3.21	NDRF	2.11	1.77–2.51
NDRF	2.20	1.76–2.73	ES	1.89	1.50–2.36
Resuscitation	1.77	1.05–2.91	Preoperative IABP	1.82	1.43–2.30
First reoperation	1.70	1.44–1.99	Female gender	1.61	1.45–1.80
CS	1.67	1.14–2.40	CS	1.57	1.14–2.13
NYHA IV	1.56	1.35–1.81	NYHA IV	1.36	1.21–1.52
Inotropic agent used	1.47	1.10–1.95	TVD	1.31	1.18–1.45
CVA	1.44	1.14–1.80	CVA	1.24	1.03–1.48
MI	1.36	1.12–1.65	Diabetes	1.23	1.10–1.38
Female gender	1.25	1.10–1.42	Obesity	1.23	1.04–1.44
US	1.25	1.05–1.48	COPD	1.21	1.06–1.37
Diabetes	1.23	1.04–1.44	LMD	1.20	1.04–1.38
CHF	1.22	1.07–1.40	PVD	1.17	1.00–1.36
Arr	1.16	1.01–1.31	Diuretics	1.16	1.05–1.29
Age (mean = 68.7)	1.03	1.03–1.04	MI	1.16	1.03–1.29
EF (mean = 49.9%)	0.99	0.99–1.00	Arr	1.14	1.01–1.29
			Age	1.04	1.03–1.05
			EF	1.00	0.99–1.00

Arr = arrhythmia; CHF = congestive heart failure; CI = 95% confidence interval; COPD = chronic obstructive pulmonary disease; CS = cardiogenic shock; CVA = cerebrovascular accident; DDRF = dialysis-dependent renal failure; EF = ejection fraction; ES = emergency status; IABP = intra-aortic balloon pump; LMD = left main disease; MI = myocardial infarction; NDRF = nondialysis-dependent renal failure; NYHA IV = New York Heart Association class IV; PVD = peripheral vascular disease; TVD = triple vessel disease; US = urgent status.

Source: Adapted from Jamieson WR, Edwards FH, Schwartz M, et al: Risk stratification for cardiac valve replacement. National Cardiac Surgery Database. Database Committee of the Society of Thoracic Surgeons. Ann Thorac Surg 1999; 67:943.

Table 34–6.

Distribution of Valve Procedures and Operative Mortality from the Society of Thoracic Surgeons' Database

	No.	% Concomitant		Unadjusted mortality
		CAB	"Other"	
Single valve				
A	216,245	50.0%	11.7%	5.7%
M	132,641	44.8%	11.6%	7.7%
T	3688	20.5%	41.9%	10.7%
P	819	16.1%	41.1%	4.4%
R	11,545	20.9%	64.5%	11.1%
Double valve				
A, M	24,608	38.3%	13.0%	11.5%
A, T	1183	29.6%	24.8%	14.0%
A, P	2574	10.2%	25.0%	3.1%
M, T	11,532	29.0%	23.4%	10.8%
M, P	43	27.9%	16.3%	9.3%
R, M	729	31.1%	52.3%	17.4%
T, P	186	9.1%	50.0%	6.0%
R, T	69	20.3%	40.6%	18.8%
R, P	248	10.9%	43.5%	2.8%
Triple valve				
A, M, T	3121	27.1%	20.5%	15.3%
A, M, P	92	20.7%	18.5%	5.4%
A, T, P	23	17.4%	26.1%	4.4%
M, T, P	33	39.4%	24.2%	9.1%
R, M, T	87	25.3%	49.4%	23.0%
R, M, P	6	0.0%	16.7%	0.0%
R, T, P	3	33.3%	33.3%	66.7%
Quadruple valve				
A, M, T, P	47	61.7%	27.7%	8.5%
R, M, T, P	2	0.0%	50.0%	100.0%
Total	409,524			

CAB = coronary artery bypass; A = aortic valve; M = mitral valve; P = pulmonic valve; R = aortic root reconstruction; T = tricuspid valve.
Source: Adapted from Rankin et al.[147]

respectively.[140] At 15 years, mortality in the bioprosthetic group rose to 79% while mortality in the mechanical valve group rose to 66%.[140] There were substantially more bleeding events in patients with mechanical valves. It is important to note that the effect of bioprosthetic structural deterioration on mortality in this series was influenced by the actual prosthesis used in the study (Medtronic Hancock porcine). This is a first-generation prosthesis and is more prone to structural failure than newer devices.[141,142]

In most published series, the expected survival after AVR is approximately 80 to 85% at 5 years, 65 to 75% at 10 years, and 45 to 55% at 15 years.[143–146] The outcomes of AVR are highly dependent on the functional status, comorbidities, and age of each individual patient.[146,147] The effect of age at the time of surgery on late mortality for a variety of prostheses is depicted in Fig. 34-17. Cohen and colleagues studied the impact of age, concomitant CAD, LVD, and poor functional status on middle to late survival after bioprosthetic AVR. Their results, presented in Table 34-7, show an additive risk for each of these comorbid factors.[148] Other studies have shown that concomitant renal disease, female gender, concomitant cardiac or vascular procedure, and atrial fibrillation are also risk factors for late mortality.[149–154] Studies of mechanical valves often show superior long-term survival, as these patients are significantly younger at the time of operation. No prospective series of comparable patients has

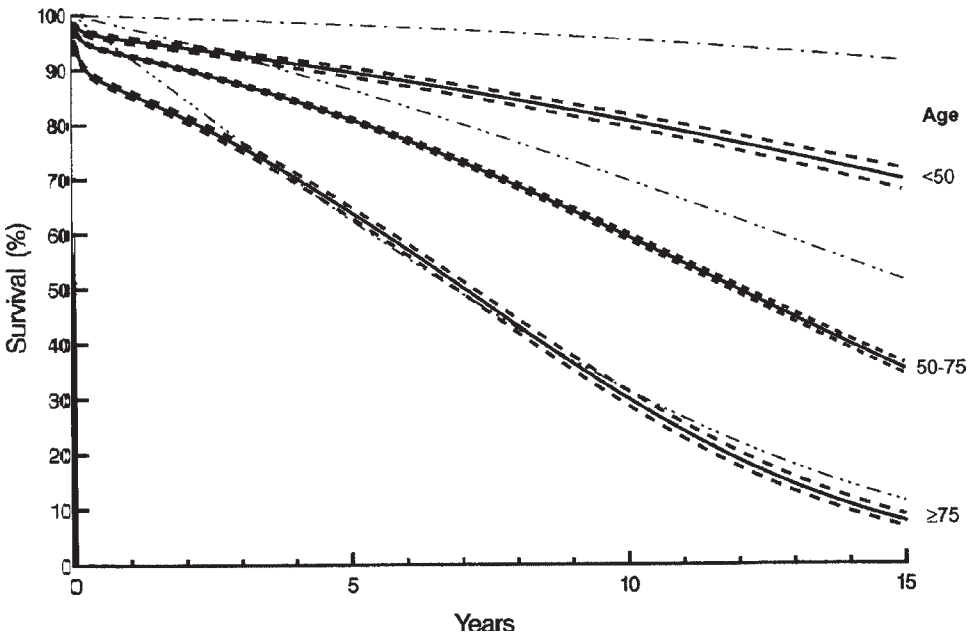

Figure 34-17. Projected long-term survival after aortic valve replacement stratified by age at time of surgery. For each age group the age-, race-, and ethnicity-matched population life table curve is shown as a dot-dashed line. Note that younger patients show more marked departure from normal life expectancy. (*Reproduced with permission from Blackstone et al.*[34])

shown any survival benefit comparing pericardial to porcine valves in similar eras.

Valve-Related Mortality

Long-term survival data distinguish between valve-related mortality, non–valve-related cardiac mortality, and mortality from other causes. A revised consensus document from the STS and the American Association of Thoracic Surgeons (AATS) was published in 1996 outlining a standardized method to report valve-related complications in prosthetic and repaired heart valves.[155] This panel defined valve-related mortality as all deaths caused by structural valve deterioration, nonstructural valve dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or death related to reoperation of an operated valve. Sudden, unexplained, unexpected deaths of patients with an operated valve are included as valve-related mortality. Deaths caused by progressive heart failure in patients with satisfactorily functioning cardiac valves are not included. In the Hammermeister series, valve-related deaths accounted for 37% of all deaths in patients with mechanical valves and 41% of all deaths in patients with bioprostheses at 15 years.[156] Nonvalvular cardiac deaths accounted for 17 and 21% of deaths at 15 years in patients with mechanical and bioprostheses, respectively.[156] There are no well designed prospective randomized series comparing the long-term outcomes of specific pericardial or porcine prostheses to each other.

Nonfatal Valve Events

The joint STS/AATS panel defined specific guidelines for reporting outcomes on structural and nonstructural valve deterioration, valve thrombosis, embolic events, bleeding events, and prosthetic endocarditis.[157] These definitions are summarized below.

1. Structural valve deterioration: Any change in function of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation, such as wear, leaflet tears, or suture line disruption of components.
2. Nonstructural dysfunction: Any abnormality of an operated valve resulting in stenosis or regurgitation that is caused by factors not intrinsic to the valve itself, such as pannus overgrowth, inappropriate sizing, or paravalvular leak.
3. Valve thrombosis: Any thrombus attached near an operated valve that interferes with valve function in the absence of infection.
4. Embolism: Any embolic event that occurs after the immediate postoperative period when perioperative anesthesia has been completely reversed. Emboli may be peripheral (noncerebral) or cerebral. Myocardial infarction is excluded unless the event occurs after the perioperative period and coronary artery embolus is unequivocally documented.
   Cerebral embolic events are subclassified into:
   a. Transient ischemic attacks: Fully reversible neurologic events lasting less than 24 hours.
   b. Reversible ischemic neurologic deficit: Fully reversible neurologic events lasting more than 24 hours and less than 3 weeks.
   c. Stroke: Permanent neurologic deficit lasting longer than 3 weeks or causing death.
5. Bleeding event: Any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury, or requires transfusion,

Table 34–7.

Survival Probability Calculated from an Accelerated Time Failure Model for Combinations of Risk Factors*

CAD	Age >65	NYHA class IV	Left ventricular grade III or IV	Predicted 5-year survival (%)	Predicted 10-year survival (%)
				89.1 (73, 100)	83.9 (73, 95)
X				83.4 (70, 97)	76.2 (67, 85)
	X			84.5 (71, 98)	77.7 (69, 86)
		X		83.6 (70, 97)	76.6 (68, 85)
			X	82.3 (69, 96)	74.8 (66, 84)
X	X			77.1 (66, 88)	68.2 (61, 75)
X		X		75.9 (65, 87)	66.8 (60, 74)
X			X	74.1 (63, 85)	64.6 (58, 72)
	X	X		77.4 (66, 88)	68.6 (62, 76)
	X		X	75.7 (65, 86)	66.5 (59, 74)
		X	X	74.5 (64, 85)	65.1 (58, 72)
X	X	X		67.8 (59, 77)	57.4 (52, 63)
X	X		X	65.7 (57, 75)	55.0 (49, 61)
	X	X	X	66.2 (57, 75)	55.5 (50, 61)
X	X	X	X	54.6 (47, 62)	43.5 (39, 48)

**Each of these four risk factors was entered into the model as a dichotomous variable (i.e., NYHA IV versus NYHA I, II, or III; left ventricular grades 3 or 4 versus left ventricular grades 1 or 2). The "X" indicates that the risk factor is present. These four risk factors are not present for the first row of estimates. The upper and lower 95% confidence interval for the predicted survival probabilities are given in parentheses.*

CAD = coronary artery disease; NYHA, New York Heart Association.

Source: Reproduced with permission from Cohen et al.[159]

regardless of the patient's anticoagulation status. This does not include embolic stroke followed by hemorrhagic transformation and intracranial bleed.

6. Operated valvular endocarditis: Any infection involving an operated valve; any structural or nonstructural valvular dysfunction, thrombosis, or embolic event associated with operated valvular endocarditis is included only in this category.

Time-related analysis of nonfatal complications is often expressed by the Kaplan-Meier actuarial method, or by the recently described cumulative incidence method proposed by Grunkemeier and Wu.[158] Cumulative incidence (or actuarial) reporting provides additional information, as it removes the impact of mortality on nonfatal outcomes. This is most relevant in higher-risk groups such as elderly patients, a group in which many patients will die from other causes prior to the occurrence of nonfatal events. Kaplan-Meier actuarial methods tend to overestimate nonfatal events by continuing to assume that patients who have died are still at risk for these nonfatal events.

Structural Valve Deterioration

Mechanical prostheses

Currently available mechanical prostheses are extremely resistant to material fatigue or structural valve deterioration (SVD). Very long-term follow-up of the Starr-Edwards caged-ball prosthesis, the Medtronic Hall tilting disc prosthesis, and the St. Jude bileaflet mechanical prosthesis show

that these valves are exceedingly resistant to structural failure. Some discontinued mechanical prostheses, such as the Bjork-Shiley convexo-concave valve, had high rates of structural failure due to fracture of the outlet strut.[159]

Stented bioprostheses

There are several large series describing long-term follow-up of first- and second-generation stented bioprostheses. These series are not comparable to each other since they took place in different patient populations or in different eras. Structural valve deterioration is the most common nonfatal valve-related complication in bioprosthetic aortic valves. Table 34-8 summarizes the long-term SVD outcomes of commonly used first- and second-generation stented bioprostheses. Long-term follow-up of currently available second-generation stented bioprostheses, including the Medtronic Hancock II porcine and Carpentier-Edwards pericardial valves, shows that these prostheses have a freedom from structural valve deterioration <90% at 12-year follow-up.[160–162] However, beyond 15-year follow-up, freedom from SVD falls rapidly.[163] There is no good evidence to suggest that comparable, well-established second-generation pericardial or porcine prostheses differ in longevity, and decisions to choose a specific prosthesis should be made based on surgeon comfort and familiarity with the prosthesis and its sizing and holding mechanisms. While newer third-generation prostheses with advanced tissue treatments may eventually be shown to have superior longevity, data about these prostheses are currently limited to 5- to 6-year outcomes, which appear comparable to those of the second-generation prostheses.[164]

Table 34–8.

Bioprosthetic Valve Failure 10 years After Valve Replacement According to the Patient's Age at the Time of Implantation

Patient's age (y)	Percentage with valve failure after 10 years
<40	42
40–49	30
50–59	21
60–69	15
>70	10

Source: Adapted from Vongpatanasin et al[166] based on data from Grunkemeier et al.[167]

There is an important predisposition for premature bioprosthetic structural valve deterioration in younger patients, particularly those under the age of 40 years.[165,166] Table 34-9 summarizes the effect of patient age on SVD. Structural valve deterioration may be less common in elderly patients due to decreased hemodynamic stress placed on the valve. The freedom from SVD may be underestimated in the literature since most series report SVD by the actuarial method instead of the actual or cumulative incidence

Table 34–9.

Structural Deterioration of Stented Bioprosthetic Valves in the Aortic Position: Long-term Follow-up Over 12–15 years

Study	Prosthesis	Number of patients	Mean age (years)	Mean follow-up (months)	Time of SVD estimate (years)	Actuarial freedom from SVD	Actuarial freedom from reoperation
David et al	Hancock II Porcine	723	65 ± 12	68 ± 40	12	94 ± 2	89 ± 5
Dellgren et al	CE Pericardial	254	71 ± 9	60 ± 31	12	86 ± 9	83 ± 9
Poirier et al	CE Pericardial	598	65*	57.7	12	93 ± 2	91 ± 2
					14	80 ± 5	72 ± 6
Corbineau et al	Medtronic Intact	188	72 ± 8	86.4 ± 50.4	13	91 ± 3.3	
Jamieson et al	CE SA Porcine	1657	65.5 ± 11.9	70.8 ± 58.8	12	83.4 ± 2.1	
					14	57.4 ± 9.2	52.9 ± 2.8
Burdon et al	Hancock I and MO	857	59 ± 11	87.6	15	63 ± 3	57 ± 3

CE = Carpentier-Edwards; MO = modified orifice; SA = supra-annular; SVD = structural valve deterioration

method.[167] Actuarial statistical analysis overestimates SVD in older patients since it assumes that patients who have died of other causes will continue to be at risk for SVD.[168]

Stentless bioprostheses

Longevity of stentless bioprostheses appears to be significantly dependent on the native valve pathology and implantation technique. Retrospective studies have shown that such valves are prone to early structural deterioration when used in the subcoronary position in patients with AR or bicuspid pathology as the primary indication for operation. In these patients, progressive root dilatation due to aortic pathology often leads to poor leaflet coaptation, leaflet tears, and recurrent AR.[169–171] Such modes of failure have not been observed when stentless valves are used as root replacements, which appear to have similar mid-term durability to the stented prostheses.[172,173]

Freedom from Reoperation

Freedom from reoperation for currently available mechanical valves is >95% at 10 years and >90% at 15 years.[174–180] Bioprostheses have a significantly higher rate of reoperation due to structural valve dysfunction. In large series, freedom from reoperation is >95% at 5 years, >90% at 10 years, but <70% at 15 years.[181–200] The long-term freedom from reoperation for several commonly available valves is presented in Table 34-9.

Optimal Antithrombotic Therapy

Mechanical valves

All mechanical valves require formal anticoagulation with warfarin for the lifetime of the patient since these valves are inherently thrombogenic. The overall linearized risk of thromboembolism in patients on warfarin therapy is 1 to 2% per year in most published series.[201–219] A meta-analysis of over 13,000 patients showed that the incidence of major embolism in mechanical valves without antithrombotic therapy was 4 per 100 patient-years.[220] With antiplatelet therapy this risk was 2.2 per 100 patient-years, and with warfarin therapy it was reduced to 1 per 100 patient-years. The incidence of thromboembolism was slightly higher in caged-ball prostheses than other mechanical prostheses.[221]

The embolic risk is highest in the first few months, before the exposed cloth sewing ring and valve components have fully endothelialized.[222] Antithrombotic therapy is initiated on the second postoperative day with oral warfarin. In the presence of complicating factors such as gastrointestinal or mediastinal bleeding or perioperative neurologic injury, anticoagulation may be held initially. If the target level of anticoagulation is not achieved by the fourth postoperative day, intravenous heparin is instituted to achieve a partial thromboplastin time between 60 and 90 seconds. If the patient is at high risk for thromboembolism, heparin is started concurrently with warfarin on the second postoperative day. High-risk patients include those with atrial fibrillation, intracardiac thrombus, left atrial enlargement, severe LVD, and history of systemic emboli or hypercoagulable state.[223]

The target level of anticoagulation for each individual patient is dependent on their thrombotic risk profile and the type of valve employed. It is our practice to establish an International Normalized Ratio (INR) of 3.0 (acceptable range 2.5 to 3.5) for high-risk patients with mechanical valves and additionally institute low-dose aspirin therapy (80 to 100 mg once daily). For lower-risk patients, the target INR is 2.5 (acceptable range 2.0 to 3.0) and low-dose aspirin is started on an individual basis.

Several articles suggest that caged-ball valves in the aortic position require a higher level of anticoagulation than tilting monoleaflet or bileaflet prostheses.[224,225] These valves should be anticoagulated to an INR of 3.5 to 4.5. Although older tilting monoleaftlet prostheses were associated with an increased rate of thromboembolism, currently available prostheses such as the Medtronic Hall valve do not appear to have an increased thromboembolism risk versus bileaflet prostheses and should have the same target INR.[226–228]

Aspirin, an antiplatelet agent, is routinely used at a low dose to minimize the risk of thromboembolic events. Randomized trials have shown that low-dose aspirin significantly reduces fatal cardiovascular and embolic events for all patients with mechanical valves, particularly in patients with concomitant coronary or vascular disease.[229–232] There are increased bleeding events when higher doses of aspirin are used in patients formally anticoagulated with warfarin.[233,234] The linearized risk of a bleeding event is 0.1 to 3.5% per year, depending on how these events are defined, the range of anticoagulation used, and how often coagulation parameters are measured.[235–238]

The On-X valve (Medical Carbon Research Institute, Austin, TX) is purported to have lower thrombogenicity due to use of a purer form of carbon and enhanced contours over the pivot guides. This device is currently being investigated in a Food and Drug Administration–approved clinical trial for reduced anticoagulation with only clopidogrel and aspirin versus standard warfarin.

Bioprosthetic valves

Bioprosthetic valves are less thrombogenic than mechanical prostheses and do not require long-term anticoagulation with warfarin unless the patient is at high risk for thromboembolism or has had a thromboembolic event with their prosthesis.[252] Stented bioprostheses have a linearized risk for thromboembolism between 0.5 and 1% per year.[240–246] This risk appears to be lower in patients with stentless heterograft, allograft, or autograft valves.[247–252] Anticoagulant management of bioprostheses during the first 3 months after implantation remains variable between institutions. There is an increased hazard function for thromboembolism before the exposed surfaces of stented bioprostheses endothelialize.[253] The current ACC/AHA guidelines recommend anticoagulation with warfarin to an INR between 2.0 and 3.0 for the first

3 months for bioprosthetic valves as a class IIB recommendation.[28] This is discontinued at the end of the third month unless the patient is at high risk for thromboembolism. Low-dose aspirin is continued as monotherapy in low-risk patients, and in conjunction with warfarin in high-risk patients for the lifetime of the patient. Combined aspirin and warfarin have a survival benefit over warfarin alone in high-risk patients with bioprosthetic heart valves.[236] Aspirin significantly decreases the risk of thromboembolism in low-risk patients with bioprostheses versus no antiplatelet therapy.[254–257] If a patient has identified high-risk factors for thrombosis preoperatively, a mechanical prosthesis should be implanted unless the risk factor is amenable to correction since formal anticoagulation with warfarin will still be necessary. With aspirin, bioprosthetic valves have approximately the same risk of thromboembolism as fully anticoagulated mechanical valves, with fewer bleeding complications.[236]

Prosthesis Thrombosis

Prosthesis thrombosis is a rare but potentially devastating outcome after AVR. The incidence of prosthesis thrombosis is <0.2% per year and it occurs more often in mechanical prostheses.[258–260] Thrombolytic therapy may be used in some patients but it is often ineffective. Thrombolysis is recommended in patients with left-sided thrombosis who are experiencing significant heart failure (NYHA class III or higher) and are considered too high risk for surgery.[261,262] Cerebral or peripheral thromboembolism occurs in 12% of patients after thrombolytic therapy.[261] Surgical treatment includes replacement of the valve or open thrombectomy, and mortality from either procedure is similar at approximately 10 to 15%.[261] Recurrent thrombosis after de-clotting occurs in up to 40% of patients and we recommend valve replacement in virtually all patients who are managed operatively.

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis (PVE) is separated into two time frames: early (<60 days postimplantation) and late (>60 days postimplantation). Early PVE is usually a sequela of perioperative bacterial seeding of the valve, either during implantation or postoperatively from wound or intravascular catheter infections.[263] *Staphylococcus aureus*, *S. epidermidis*, gram-negative bacteria, and fungal infections are common in this period.[264–285] Although most cases of late PVE are caused by septicemia from noncardiac sources, a small proportion of late cases in the first year are attributable to less virulent organisms introduced in the perioperative period, particularly *S. epidermidis*.[269] Organisms responsible for late PVE include *Streptococcus* and *Staphylococcus* species and other organisms commonly found in native valve infectious endocarditis. All unexplained fevers should be meticulously investigated for PVE with serial blood cultures and TE and TTE. Transesophageal echocardiography provides more detailed anatomic information such as the presence of vegetations, abscesses, and fistulas, but often does not provide adequate views of the anterior portion of the valve.[270] Transthoracic views may be helpful in these cases. Mechanical valves are particularly difficult to visualize by echocardiography due to shadowing created by valve components.

The annual risk of PVE in the aortic position is 0.6 to 0.9% per patient year.[215,242,271–283] The 5-year freedom from PVE reported in many major series is >97%.[284–287] Mechanical valves may have a slightly higher early hazard for PVE than stented bioprostheses.[287] However, there is no difference in risk between patients with mechanical and stented bioprosthetic prostheses after the early phase. Stentless porcine heterografts and allografts are less likely to develop PVE since they have less prosthetic material that may serve as a nidus of infection.[288–295] These valves may be particularly helpful in valve rereplacement for PVE.

Outcome for patients with PVE is very poor. Invasive paravalvular infection occurs in up to 40% of cases of PVE.[296] Early PVE is associated with 30 to 80% mortality, while late PVE is associated with 20 to 40% mortality.[297,298]

Surgery is indicated for PVE in the following circumstances:

1. All cases of early (<60 days) of PVE.
2. Concomitant heart failure and valvular dysfunction.
3. Paravalvular leak or partial dehiscence, even in a stable patient, requires operative management, particularly if more than 40% of the valve's annular circumference is involved.
4. The presence of a new conduction defect, abscess, aneurysm, or fistula mandates operative management. All fungal, and most virulent strains of *Staphylococcus aureus*, *Serratia marcescens*, and *Pseudomonas aeruginosa* also require operation, as these organisms are highly invasive and antibiotic therapy is generally ineffective.
5. Any case of persistent bacteremia despite a maximum of 5 days of appropriate antibiotic therapy and no other source of infection.
6. Vegetations >10 mm are not penetrated well by antibiotics and usually need operative management.
7. Multiple systemic emboli.

Paravalvular Leak and Hemolysis

Paravalvular leak is uncommon outside of the setting of infective endocarditis when pledgeted sutures are routinely used. Technical errors may result in inappropriately large gaps between sutures, leaving a small portion of the prosthesis unattached to the annulus. If paravalvular leak is sufficient to cause significant hemolysis, surgical correction may be performed with a few interrupted pledgeted sutures. Hemolysis is uncommon with the currently available mechanical or stented bioprosthetic valves if they are functioning well. Pannus overgrowth and prosthetic structural degeneration interfering with normal valve opening and closure may cause hemolysis severe enough to warrant reoperation. Milder cases of hemolysis may be managed conservatively by dietary supplementation with iron and folic acid, and routine

measurement of hemoglobin, serum haptoglobin, and lactate dehydrogenase.

HEMODYNAMIC PERFORMANCE AND VENTRICULAR REMODELING

Left Ventricular Mass Regression

Pressure and volume overloading caused by aortic valve disease leads to increased intracavitary left ventricular pressures and compensatory LVH. In severe AS, concentric ventricular hypertrophy occurs without increasing end-diastolic dimension until late in the disease process, thus maintaining the ventricular wall thickness:cavity radius ratio. Severe AR causes volume overload with an increase in left ventricular end-diastolic volume and eccentric hypertrophy, but may not change the ratio of ventricular wall thickness to cavity radius.

Both pathologies result in an increase in left ventricular mass (LVM). Studies from the hypertension literature indicate that increased LVM has a strong negative prognostic effect. Several reports, including the Framingham Heart Study, indicate that increased LVM was a predictor of all cardiac events, including sudden cardiac death.[299–301] The overall goal of AVR is to alleviate the pressure and volume overload on the left ventricle, allowing myocardial remodeling and regression of left ventricular mass.

The clinical impact of LVM regression is not as well understood, despite its widespread acceptance as a measure of outcome after aortic valve surgery. Smaller studies have shown that in hypertensive patients undergoing medical treatment, patients with a reduction of left ventricular mass had fewer cardiac events than those whose left ventricular mass did not change or increased.[302] The prognostic implications of LVM regression after aortic valve surgery have not been rigorously studied, but logic would suggest that lack of LVM regression is associated with poor clinical outcome. There are no studies showing that there is incremental clinical benefit with greater degrees of ventricular mass regression.

Generally, LVM regresses significantly over the first 18 months and returns to within normal limits in many patients after AVR for isolated AS.[303–308] Ventricular mass regression may continue for up to 5 years after valve replacement.[309] However, some patients do not experience adequate ventricular mass regression and may experience poorer prognoses. Several authors have identified a situation, referred to as patient-prosthesis mismatch, in which the poor hemodynamic performance of a prosthesis results in poor regression of LVH and poor patient outcome.

Prosthesis-Patient Mismatch

Definitions

The term prosthesis-patient mismatch has been applied to several different clinical situations. It has been used to describe absolute small valve size (i.e., <21 mm), small valve size in a patient with a large body surface area, excessive transvalvular gradient postimplantation, increased transvalvular gradient with exercise, indexed effective orifice area, and various combinations of these variables.

Rahimtoola defined prosthesis-patient mismatch as a condition that occurs when the valve area of a prosthetic valve is less than the area of that patient's normal valve.[310] He described a clinical condition in which the patient experienced either no relief or worsening of symptoms due to the obstructive nature of the prosthesis, which creates a residual stenosis resulting in an elevated transvalvular gradient. To varying degrees, all mechanical and stented tissue prostheses and stentless tissue prostheses used in the subcoronary or inclusion root position are inherently stenotic.[311] The presence of rigid sewing rings, and in the case of stented bioprostheses, struts to hold the valve commissures, cause obstruction to outflow and will therefore cause a residual gradient despite normal prosthesis function. This was more true of first-generation prostheses used during the 1970s, when this condition was first described. The problem is exacerbated by annular fibrosis, annular calcification, and LVH, as seen in AS, that cause contraction of the native annulus, leading to the implantation of a smaller prosthesis. Two distinct terms are commonly used to describe the size of prosthetic valves: effective orifice area and geometric orifice area.

Effective orifice area

The most commonly cited definition of prosthesis-patient mismatch is a low indexed effective orifice area (IEOA). The IEOA is calculated by dividing the echocardiographically determined effective orifice area (EOA) by the body surface area. Effective orifice area is calculated by a reconfiguration of the continuity equation:

$$EOA = (CSA_{LVOT} \times TVI_{LVOT})/TVI_{AO}$$

where EOA is the effective orifice area in square centimeters, CSA_{LVOT} is the cross-sectional area of the left ventricular outflow tract(LVOT) in square centimeters as determined by two-dimensional measurement of the LVOT diameter, TVI_{LVOT} is the velocity time integral of forward blood flow in centimeters as derived from pulse-wave Doppler in the LVOT, and TVI_{AO} is the velocity time integral of forward blood flow in centimeters as derived from software integration of transvalvular continuous wave Doppler.[312] The EOA and mean systolic gradient of several commonly available bioprostheses are shown in Table 34-10.

Several authors suggest that prosthesis-patient mismatch occurs at an IEOA of <0.85 cm^2/m^2.[313,314] Dumesnil and Pibarot have redefined prosthesis-patient mismatch as follows, "prosthesis-patient mismatch occurs when the EOA of the prosthesis is too small in relation to the patient's body size, resulting in abnormally high postoperative gradients."[314] This definition is based on the assumption that transvalvular gradients begin to rise substantially at IEOAs below this value, and these elevated gradients potentially

cause increased left ventricular work that prevents adequate regression of LVH.[315]

EOA is an in vivo, functional estimate of the minimal cross-sectional area of the transvalvular flow jet downstream of a valve (Fig. 34-18). The EOA is dependent on several factors including the geometric area of the prosthesis, the shape and size of the LVOT and ascending aorta, blood pressure, and cardiac output. Mechanistic studies have shown that Doppler-derived EOA correlates best with catheter-derived EOA(as determined by the Gorlin formula) when the ascending aortic diameter is 4 cm, and tends to underestimate EOA in patients with smaller aortic diameters.[316] The EOA cannot be known for a specific valve in a specific patient until the valve has actually been implanted. Studies examining the effect of low IEOA on clinical outcomes have typically used published tables of EOA derived from historical controls instead of actually measuring true in vivo postoperative EOA. Moreover, these tables have been derived from relatively small numbers of valves in each size for each manufacturer with wide variability between studies. EOA has been shown to correlate with postoperative valve gradients.[317] Gradients and EOA are, in

Table 34–10.

The Effective Orifice Area (EOA) and Mean Systolic Gradient (MSG) of Commonly Available Bioprostheses

Prosthesis and references	19 mm		21 mm		23 mm		25 mm		27 mm	
	EOA (cm^2)	MSG (mm Hg)	EOA (cm^2)	MSG (mm Hg)	EOA (cm^2)	MSG (mm Hg)	EOA (cm^2)	MSG (mm Hg)	EOA (cm^2)	MSG (mm Hg)
Hancock Standard	1.0	25	1.0–1.3	18–30	1.3–1.5	7–24		13–17		
Hancock Modified Orifice	0.9	12–19	1.4	10–17	1.4	11–16	1.7	10–12		
Hancock II			1.2		1.3		1.5		1.6	
Medtronic Intact			1.5	17	1.6	19	17	1.9	15	
Medtronic Mosaic	1.2	16	1.3	14–15	1.5	12–13	1.8	11–12	2.0	9–10
CE Standard	0.85	26	1.3–1.4	18–21	1.3–1.6	15–30	1.2–2.1	13–21		
CE Supra-annular		17	1.2	11	1.4	12	2.1	16		9
CE Pericardial	0.95	18–19	1.1	13–14	1.5	11–14	1.4	10–11	1.6	10
Mitroflow Pericardial	1.3		1.4		1.7					
Toronto SPV				8	1.6–1.8	3–7	1.4–1.9	3.5–7	1.7–2.3	3–5
Medtronic Freestyle	1.0–1.4	18–22	1.3–1.4	7–13	1.4–1.5	7–14	1.7–2.0	5–9	2.0–2.3	5–7
Edwards Prima Valve	1.3–1.6	9	1.6	9	1.9	6	2.1	6	2.4	5

CE = Carpentier-Edwards; SPV = stentless porcine valve.

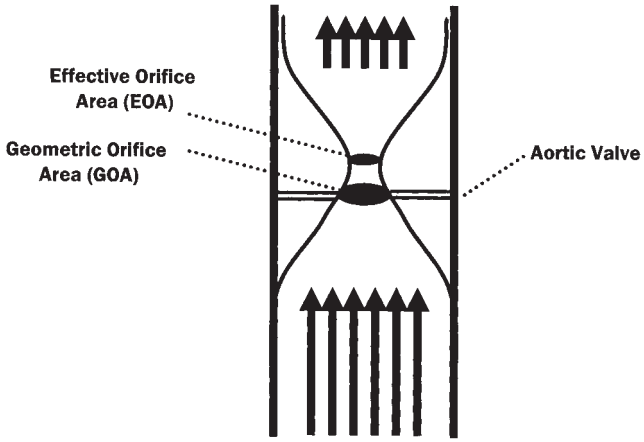

Figure 34-18. Diagrammatic representation of effective orifice area and geometric orifice area in relation to the left ventricular outflow tract and aortic root.

fact, mathematically related. Echocardiographic mean and peak gradients are calculated according to the Bernoulli equation:

$$\text{Peak gradient (mm Hg)} = 4 \times (V_{AVmax}{}^2 - V_{LVOTmax}{}^2)$$

$$\text{Mean gradient (mm Hg)} = 4 \times (V_{AVmean}{}^2 - V_{LVOTmean}{}^2)$$

Geometric orifice area

The geometric orifice area (GOA) (also known as the internal geometric area) of the valve is the maximal cross-sectional area of the valve opening that does not vary significantly between same-sized valves from the same manufacturer. It is a static measure that is known preoperatively for any given prosthesis based on manufacturer specifications or by measurement with calipers. As seen in Fig. 34-18, the GOA is always larger than the EOA for any given prosthesis.

Clinical significance

The significance of prosthesis-patient mismatch is controversial since there is conflicting evidence that lower IEOA causes diminished short or long-term clinical results.

Pibarot and Dumesnil studied 1266 patients undergoing AVR at a single institution. They defined moderate prosthesis-patient mismatch as IEOA <0.85 cm^2/m^2 and severe prosthesis-patient mismatch as IEOA <0.65 cm^2/m^2. They found that moderate or severe prosthesis-patient mismatch was present in 38% of patients. Multivariate analysis showed that moderate prosthesis-patient mismatch was associated with a doubling of perioperative mortality, and severe prosthesis-patient mismatch was associated with an 11-fold increase of perioperative mortality. Of note, the poor outcomes in the severe mismatch group were based on only 27 patients with 7 perioperative mortalities. These patients also had substantially longer intraoperative cardiopulmonary bypass times and concurrent coronary surgery. Rao and colleagues retrospectively studied prosthesis-patient mismatch in patients undergoing AVR at two large centers.[318] A total of 2154 patients were reviewed including 227 patients with prosthesis-patient mismatch, and 1927 patients without prosthesis-patient mismatch. Overall mortality was similar in both groups, but valve-related mortality was higher in the prosthesis-patient mismatch group at 10 years. Many valve-related mortalities included mechanisms of death that were unrelated to prosthesis-patient mismatch (embolic stroke, valve failure, endocarditis, bleeding, and reoperation) and supportive echocardiographic data were not provided. Effective orifice area was obtained from in vitro data supplied by the manufacturers according to the valve size implanted.

Ruel and colleagues performed a single-center analysis of 1563 mechanical and tissue aortic prostheses and found that IEOA <0.8 cm^2/m^2 was associated with increased prevalence of heart failure symptoms at a mean follow-up time of 4.3 years.[314] This relationship was not seen when prosthesis-patient mismatch was defined as IEOA <0.85 cm^2/m^2. Prosthesis-patient mismatch was not associated with early or late mortality in this series. Ruel and colleagues in a subsequent analysis showed that the effect of prosthesis-patient mismatch was confined to patients with preoperative LVD.[320] Using multivariate methods, they determined that overall survival and LVM regression was poorer in patients with prosthesis-patient mismatch and LVD than those who had LVD without prosthesis-patient mismatch. A confounding factor in this study was that patients with prosthesis-patient mismatch and LVD were 12 years older and had more significant comorbidities including concomitant coronary disease, which are independently associated with poorer survival and LVM regression.

Mohty-Echahidi and colleagues examined prosthesis-patient mismatch in patients receiving 19 mm and 21 mm mechanical valves and found that severe mismatch, defined as IEOA <0.60 cm^2/m^2, was associated with increased late mortality (hazard ratio 2.18) and increased CHF symptoms (hazard ratio 3.1) versus patients without mismatch. In a series of 1400 patients, Moon and colleagues reported that prosthesis-patient mismatch affected long-term survival in patients less than 60 years old but not in older patients.[321]

Several studies have also shown that prosthesis-patient mismatch does not influence clinical outcomes. Medalion and colleagues studied 892 AVRs and demonstrated that although 25% of patients received valves with an indexed internal orifice area less than two standard deviations below predicted normal aortic valve size, there were no differences in 15-year survival between patients with or without patient-prosthesis mismatch.[322]

Hanayama and colleagues recently reported a single institutional experience with patient-prosthesis mismatch in 1129 patients who were followed over a 10-year period.[323] They defined patient-prosthesis mismatch using two definitions: (1) IEOA less than the 90th percentile in the study population; and (2) valve gradient in the highest 90th percentile of the study population. The cut-off value for IEOA to define patient-prosthesis mismatch was 0.6 cm^2/m^2, which would be considered very severe by most groups. The cut-off

values for peak gradient and mean gradient were 38 mm Hg and 21 mm Hg. In this study, the average labeled size of valve in the low-IEOA and high-gradient groups were 22.4 mm and 23 mm, respectively. There were no differences in left ventricular mass index (LVMI) or survival at midterm follow-up between patients with normal and abnormal gradients. The only multivariate predictor of elevated postoperative gradient was valve size. Thus, although valve size is a predictor of abnormal postoperative gradient, no clinical significance could be correlated with this finding. Figure 34-19 shows that there were no differences in LVMI or survival at midterm follow-up between patients with or without patient-prosthesis mismatch defined as IEOA <0.6 cm^2/m^2.

More recently, Blackstone and colleagues have compiled the largest and most statistically sound examination of the role of prosthesis-patient mismatch in short- and long-term outcomes.[324] In a multi-institutional study of over 13,000 aortic prostheses, presence of an indexed GOA in the lowest 10th percentile was associated with a 1 to 2% increase in perioperative (30-day) mortality and had no effect on medium- or long-term survival (Fig. 34-20). An important finding in this study was that virtually no stented bioprostheses were in the group of patients in the lowest 10th percentile of indexed GOA, who predominantly received mechanical prostheses. In a subsequent study from the same group, Koch and colleagues prospectively examined functional status using the Duke Activity Status Index in 1108 patients undergoing AVR and found no relationship between indexed GOA and functional status at a mean follow-up of 8.3 months. Predictors of postoperative functional status are presented in Table 34-11.

Small aortic root

Many surgeons have expressed concern about postoperative outcomes in patients with small aortic roots in whom only very small (19 mm or smaller) valves can be implanted. Adams and colleagues reported significantly elevated perioperative, but not late, mortality among men, but not women, receiving 19 mm prostheses.[325] Conversely, Sawant and colleagues demonstrated that in patients with small aortic roots, body surface area and valve size were not determinants of long-term survival.[326] Studies by DePaulis and colleagues have shown that there was no difference in LVM regression between patients receiving 19 mm and 21 mm mechanical valves versus those with 23 mm or 25 mm valves.[327] Foster and colleagues showed that in patients with 17 mm and 19 mm prostheses who had resting transvalvular gradients >30 mm Hg, 93% were in NYHA class I at late follow-up.[328] Kratz and associates also reported that small valve size was not predictive of CHF or late death.[329] Khan and colleagues studied 19 mm to 23 mm Carpentier-Edwards pericardial valves and found that significant LVM regression occurred with each valve size, including 19 mm valves.[330]

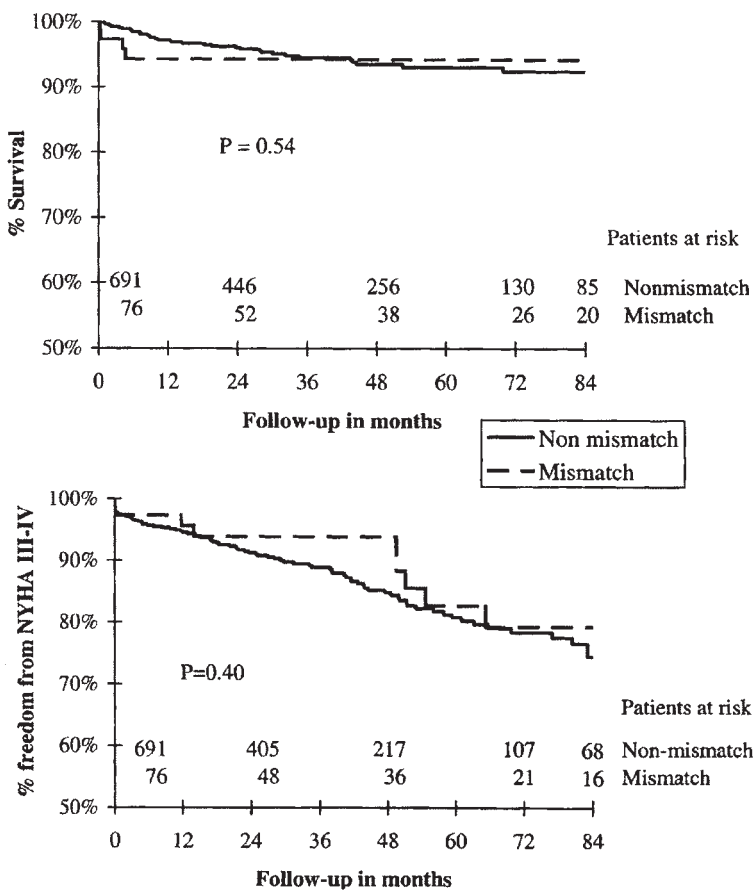

Figure 34-19. Actuarial survival and freedom from NYHA class III or IV in patients with and without prosthesis-patient mismatch. There were no significant differences in the two groups. (*Reproduced with permission from Hanayama et al.*[324])

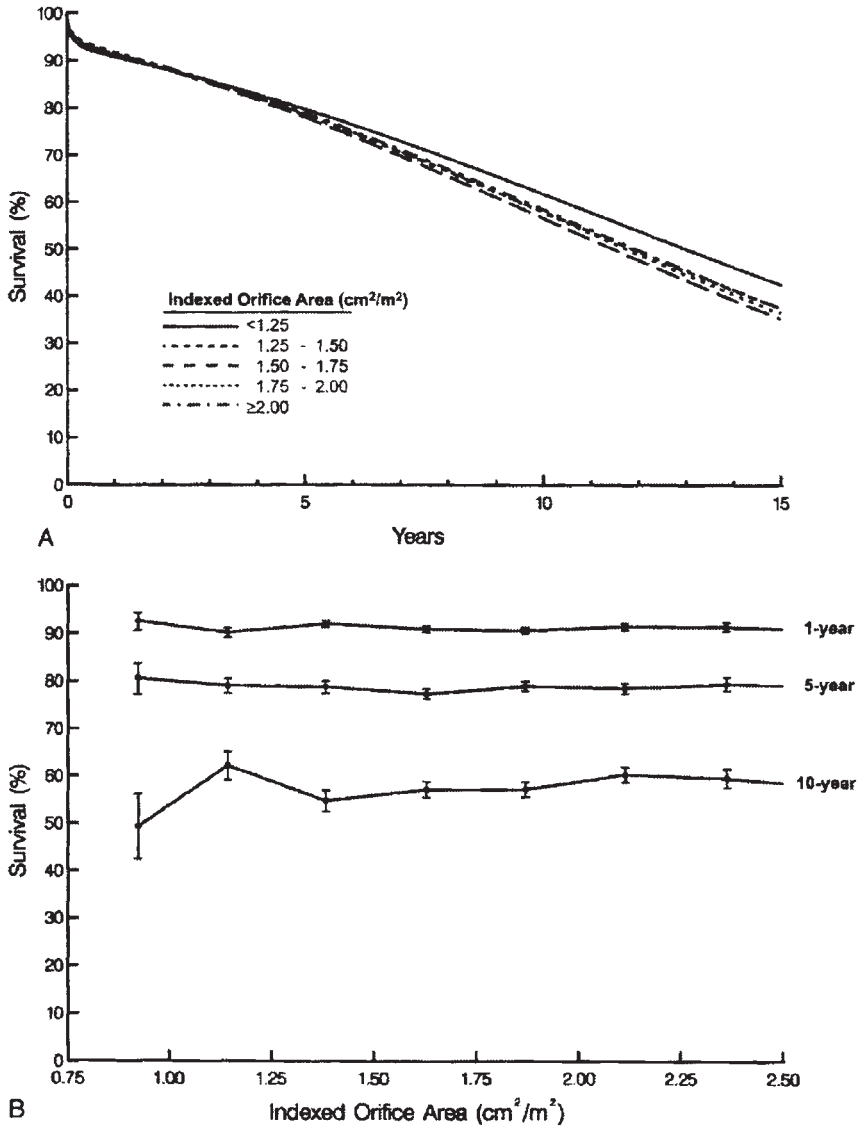

Figure 34-20. (A) Effect of indexed orifice area on non–risk-adjusted survival. (B) Time-related survival stratified by indexed orifice area. These are Kaplan-Meier estimates of 1-, 5-, and 10-year survivals in finely grouped strata of indexed orifice area. (*Reproduced with permission from Blackstone et al.*[344])

Data synthesis

While the literature regarding the clinical significance of prosthesis-patient mismatch remains divided, proponents of the concept advocate use of mechanical prostheses, which are presumably less obstructive than stented bioprostheses, aortic root enlargement, and stentless valves used in the subcoronary position and as full root replacement to achieve improved hemodynamics. Mechanical prostheses are not likely to alleviate prosthesis-patient mismatch versus the current generation of tissue valves. Mechanical valves may even be more often associated with prosthesis-patient mismatch.[331] Aortic root enlargement procedures require significant experience operating on the aortic root and may carry excessive mortality. Sommers and David reported a doubling of perioperative mortality among patients receiving annular enlargement procedures with AVR.[332] However, Castro and colleagues reported no increase in perioperative mortality among patients receiving annular enlargement procedures, implying that there is wide variability in surgical outcomes even among highly experienced centers.[333]

Use of a stentless prosthesis in the subcoronary position requires additional technical skill and cross-clamp time. Rao and colleagues compared hemodynamic data between stented Carpentier-Edwards pericardial valves and Toronto stentless porcine valves of equivalent diameter and found no hemodynamic differences in peak or mean gradient.[334] Additionally, concerns about durability discussed previously for patients with bicuspid pathology make subcoronary stentless bioprostheses a less viable option.

Aortic root replacement in patients without ascending aortic pathology, solely to diminish the potential long-term effects of prosthesis-patient mismatch is a potentially high-risk strategy. Recent data from the Society of Thoracic Surgeons' database on over 200,000 patients suggests that mortality for aortic root replacement for this indication was 9.5 versus 5.7% for isolated AVR.[138,335] This report strongly discouraged the use of aortic root replacement for this indication.

Table 34–11.

Multivariate Predictors of Functional Recovery After Aortic Valve Replacement

Follow-up DASI	Factor	Estimate ± standard error	Estimated odds ratio (95% upper and lower confidence intervals)	*p*	Reliability (%)
	Standardized orifice size (*z* score)	0.0040 ± 0.074	1.00 (0.87, 1.16)	0.96	1
	Balancing score	0.11 ± 0.11	1.11 (0.90, 1.37)	0.3	
Worse	Female sex	−0.50 ± 0.14	0.61 (0.46, 0.80)	<0.001	79
Worse	Age*	−0.39 ± 0.075	0.68 (0.58, 0.78)	<0.001	81
Better	Preoperative DASI	0.018 ± 0.0041	1.02 (1.01, 1.03)	<0.001	94
Worse	Preoperative creatinine (mg/dL)	−0.37 ± 0.094	0.69 (0.58, 0.83)	<0.001	41
Worse	Central venous pressure in the intensive care unit (mm Hg)	−0.037 ± 0.014	0.96 (0.94, 0.99)	0.01	46
Worse	Red blood cells transfused (units)	−0.45 ± 0.14	0.64 (0.49, 0.83)	0.001	82

**Age was transformed as exponent of age in years/50.*
DASI = Duke Activity Status Index.
Source: Adapted with permission from Koch CG, Khandwala F, Estafanous FG, Loop FD, et al: Impact of prosthesis-patient size on functional recovery after aortic valve replacement. Circulation 2005; 111:3221.

When faced with potential prosthesis-patient mismatch in the operating room, the decision to perform a more complex, higher-risk procedure must be balanced carefully with the potential benefits of implanting a larger prosthesis. Some reports have shown that transvalvular gradients in patients with lower IEOA often rise substantially with exercise.[336,337] Although the majority of patients undergoing AVR are elderly and unlikely to experience functional limitations from this situation, in younger, highly-active patients either root enlargement or stentless prostheses may provide better functional outcome with lower transvalvular gradients. In the rare circumstance of anticipated extreme mismatch (i.e., IEOA <0.6 cm^2/m^2) root enlargement is an acceptable approach in the hands of an experienced surgeon. Except in these circumstances, given the paucity of long-term data to support more complex procedures and well-documented increased risk, routine AVR with modern standard prostheses is acceptable and preferable.

PROSTHESIS SELECTION

An ideal aortic prosthesis would be simple to implant, widely available, possess long-term durability, would have no intrinsic thrombogenicity, would not have a predilection for endocarditis, and would have no residual transvalvular pressure gradient. Such a valve does not currently exist. Currently available options include mechanical valves, stented biologic heterograft valves, stentless biologic heterograft valves, allograft valves, and pulmonary autograft valves. Among these options pulmonary autograft valves and allograft valves are the most physiologic prostheses. They are less prone to thrombosis or endocarditis and have excellent hemodynamic characteristics.[338–346] The longevity of such valves is dependent on patient factors, the preparation of the valve, and the technical skill of the operating surgeon. Despite their potential benefits, these prostheses are not readily available and can be very technically demanding to implant compared to standard mechanical or stented bioprostheses. They are most beneficial in children and younger adults. Allograft valves may also improve the results of AVR in active endocarditis.[347] A further discussion of these valves is presented in subsequent chapters. As their use has remained confined to a few centers that perform such operations regularly, the remainder of this discussion will focus on issues regarding selection of mechanical or bioprosthetic valves.

Mechanical versus Biologic Valves

When selecting between mechanical and biologic heart valves, the surgeon and patient must balance the risks and

benefits of each choice. Mechanical valves are much less likely to undergo structural deterioration than bioprosthetic valves, and reoperation for structural valve deterioration is more common in patients with bioprosthetic valves. Mechanical valves are more thrombogenic than bioprosthetic valves and require formal anticoagulation with oral warfarin. Anticoagulated patients have a significantly increased risk of bleeding complications. Patients with mechanical valves and adequate anticoagulation do not have significantly greater risk of thromboembolic events than do those with bioprosthetic valves.[348] There is no difference in actuarial freedom from bacterial endocarditis between mechanical and bioprosthetic valves. In recent years a significant trend toward increasing use of bioprostheses has occurred in North America.

As stated earlier, the two randomized comparisons of mechanical and bioprosthetic aortic valves performed in the 1970s showed equivalent survival between valve types at 12 years of follow-up.[349,350] Long-term survival beyond 15 years was superior in the mechanical valve groups due to the risks of reoperation and structural failures of bioprostheses became more common.[351]

In these studies, the bleeding risk was significantly higher than the current standard in the anticoagulated group due to monitoring of the prothrombin time instead of the INR. Also, the rate of structural valve deterioration was higher than currently expected, since first-generation prostheses were used in these studies. It would not be practical or ethical to conduct a similar randomized study today with current prostheses. Analyses based on mathematical modeling of historic data currently suggest that at approximately 60 years of age, patients derive improved life expectancy and event-free life expectancy regardless of the need for concomitant coronary surgery.[352–354]

Special patient groups

Patients with an absolute requirement for long-term anticoagulation such as atrial fibrillation, previous thromboembolic events, hypercoagulable state, severe LVD, another mechanical heart valve in place, or intracardiac thrombus, should receive a mechanical valve regardless of age.

Patients in whom anticoagulation with warfarin is contraindicated, such as women of child-bearing age wishing to become pregnant, patients with other bleeding disorders, or those who refuse anticoagulation should receive a bioprosthesis. There is growing interest in using mechanical prostheses in women of child-bearing age and providing anticoagulation with subcutaneous low-molecular weight heparin injections.

Patients with end-stage renal failure were previously believed to have significantly elevated risk for early bioprosthetic structural valve deterioration. However, increased anticoagulation-related complications are also more likely in this group, and the current ACC/AHA guidelines do not recommend routine use of mechanical prostheses in these patients.

Age considerations

Currently available bioprostheses, such as the Medtronic Hancock II porcine and Carpentier-Edwards pericardial valve, have >90% freedom from structural valve dysfunction and >90% freedom from reoperation at 12-year follow-up.[355–357] The rate of structural deterioration is lower in patients over 65 to 70 years.

Hence, patients over 65 years at the time of surgery should receive a biologic valve. Patients under the age of 60 should have a mechanical prosthesis to minimize the risk of structural failure requiring repeat AVR in an octogenarian. Patients between 60 and 65 represent the group in whom there is still considerable debate regarding prosthesis selection. Those patients who have comorbidities such as severe CAD may be less likely to outlive their prosthesis and should receive a biologic valve. A detailed discussion of these risks and benefits of prosthesis selection should occur with all patients and their families prior to entering the operating room.

Stented versus Stentless Biologic Valves

Stentless porcine valves have gained popularity in cardiac surgery due to pioneering work by Dr. Tirone David at the Toronto General Hospital in 1988.[358] Since they lack obstructive stents and strut posts, stentless valves provide residual gradients that are similar to those of freehand allografts. Stentless valves, however, are more difficult to implant and require a longer cross-clamp time such that the risks of a more complex operation must be matched to a specific benefit the patient may receive with a stentless valve. Cohen and colleagues randomized patients to receive Carpentier-Edwards pericardial valves and Toronto stentless porcine valves and compared clinical outcomes.[359] There were no differences in the measured size of the aortic root between the two groups. Postoperative echocardiography showed that there was no difference in indexed EOA or LVM regression between groups (Fig. 34-21). They also found no difference in functional outcome between valves at 1-year follow-up (Fig. 34-22). These findings challenge the notion that stentless

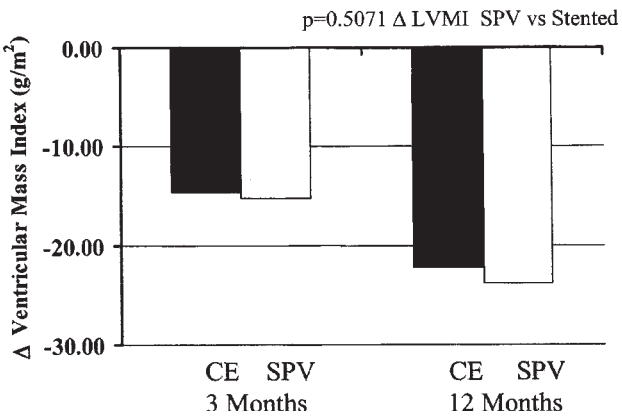

Figure 34-21. Indexed ventricular mass regression in stentless and stented valve patients over time. There were no significant differences in the two groups. CE = Carpentier-Edwards stented valve; LVMI = left ventricular mass index; SPV = Toronto stentless porcine valve. (*Reproduced with permission from Cohen et al.*[359])

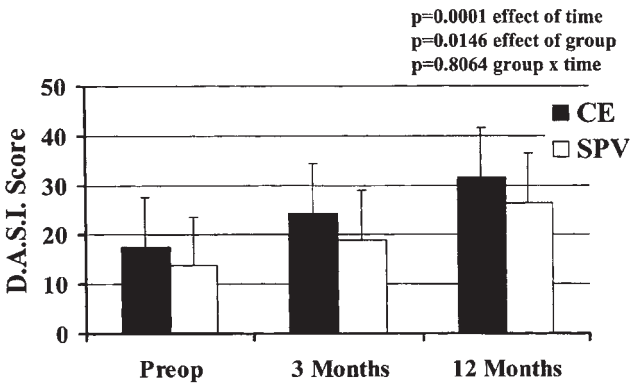

Figure 34-22. Change in Duke Activity Status Index (D.A.S.I.) scores in stentless and stented valve patients over time. There were no significant differences in the two groups. CE = Carpentier-Edwards stented valve; SPV = Toronto stentless porcine valve; Preop = preoperative. (*Reproduced with permission from Cohen et al.*[359])

porcine valves provide increased IEOA or hemodynamic or clinically significant benefit. In a randomized trial comparing Sr. Jude Toronto stentless porcine valves to Carpentier-Edwards pericardial valves, Chambers and colleagues found no difference in hemodynamic function including gradients or IEOA, LVM regression, or mortality between groups. Arenaza and colleagues also performed a multicenter randomized trial comparing the Medtronic Freestyle valve to the Medtonic Mosaic valve and found increased IEOA in the stentless group, but no differences in LVM regression or clinical outcomes at 1-year.

Walther and colleagues performed a small randomized trial comparing the ability of stented porcine and stentless porcine valves to cause regression of LVH.[360] They showed that despite equivalent annular dimensions in the stented and stentless groups, larger valves (by labeled size) were implanted in the stentless group. The patients receiving stentless valves had a slightly higher degree of LVM regression than those receiving stented valves. No clinical follow-up was provided. Borger and colleagues showed modestly lower mean gradients in stentless prostheses versus stented prostheses (9 mm Hg versus 15 mm Hg) and LVMI (100 g/m^2 versus 107 g/m^2) in their nonrandomized study.[361] However, there was no difference in risk-adjusted midterm survival between groups.

Hence, there is conflicting evidence that the use of stentless valves results in improved LVM regression or clinical outcomes over stented bioprostheses. Several studies have shown adequate LVM regression in patients receiving even small stented bioprostheses. There is also little evidence that incremental improvements in LVM provide additional clinical benefit. Thus, the routine use of stentless bioprostheses cannot be recommended for most patients with small aortic roots based on currently available data. At this time, stentless porcine valves are most useful in a relatively younger patient with a small aortic root who is active and likely to be limited by the elevated residual gradient a small stented bioprosthesis may create. There are reports of decreased thromboembolic events in stentless valves.[362]

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CHAPTER 35

Stentless Aortic Valve Replacement: Autograft/Homograft

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The number of heart valve procedures performed annually in the United States continues to increase and surpassed 93,000 in 2003. Despite this increasing experience, the search for an ideal replacement for a diseased aortic valve continues. Currently, there are essentially five choices for replacement of the aortic valve including a mechanical valve prosthesis (e.g., St. Jude bileaflet), a stented bioprosthetic valve (e.g., xenograft), a stentless bioprosthetic valve (e.g., Medtronic Freestyle), an aortic homograft, and a pulmonary autograft (i.e., the Ross procedure). Since there is not an ideal valve choice, the selection of a suitable valve for aortic valve replacement (AVR) must be individualized through consideration of the relative advantages and disadvantages of these five options. To this end, we believe there are seven valve-related issues to be considered when selecting a valve replacement option. These include durability, flow characteristics, risk of thromboembolism and need for anticoagulation, technical ease of insertion, infectibility, availability, and valve-related noise. Consideration of these issues in the context of an individual patient will allow prudent selection of a suitable valve, all having their relative advantages and disadvantages. This chapter will provide an overview of aortic allografts and pulmonary autografts, and provide a basis for their consideration, relative to other AVR choices currently available. See Table 35-1 for a listing of the advantages and disadvantages of currently available valves.

HISTORICAL PERSPECTIVE

Gordon Murray was the first to utilize an aortic homograft for treatment of aortic valvular disease.[1] After successful attempts in the animal laboratory, Murray placed valve-bearing aortic homograft segments in the descending aorta for treatment of severe aortic insufficiency (AI) with good results up to 4 years postoperatively.[2] Subsequently, the hemodynamic benefits of heterotopic placement of an aortic homograft in the descending aorta for AI were confirmed by Beall and associates, also in the animal laboratory.[3] Kerwin and colleagues of Toronto extended the clinical experience of heterotopic homograft to nine patients, with good results in six patients up to 6 years postoperatively.[4] At nearly the same time, Bigelow and coworkers of Toronto reported placing an aortic homograft in the orthotopic position, but the patient died of a coronary thrombosis within a day.[5] Successful orthotopic placement of an aortic homograft was soon performed independently and nearly simultaneously[6] by Donald Ross of Guy's Hospital in London,[7] Barratt-Boyes of Green Lane Hospital in Auckland,[8] followed a few months later by Paneth and O'Brien of The Brompton Hospital. In 1964, Barratt-Boyes reported his early experience with aortic homografts in 44 patients, with good to fair results in all but three patients.[8]

Since these initial efforts to utilize homografts in the aortic position, the procurement and preservation of these biologic valves have changed significantly. Initially, aortic valves were implanted shortly after collection.[9] This technique fell out of favor and was rapidly supplanted by techniques to sterilize and preserve the valve for later use—a fundamental strategy of contemporary tissue banking. Valves were collected cleanly or sterilely and then were sterilized with beta-propiolactone[8,10] or 0.02% chlorhexidine,[11] followed by ethylene oxide[11] or radiation exposure.[12] After chemical sterilization, valves were placed in Hanks balanced salt solution at 4°C for up to 4 weeks, followed by freeze-drying.[8,13] Recognizing that the incidence of valve rupture was high in chemically treated valves, Barratt-Boyes introduced antibiotic sterilization of homografts in 1968.[14] Cryopreservation of allografts was introduced in 1975 by O'Brien in an attempt to increase the cell viability of preserved allografts.[15] Cryopreservation continues to be the most commonly used method for aortic allografts.

Table 35–1.

Advantages and Disadvantages of Different Types of Aortic Valve Replacements

	Durability	Hemodynamics	Thromboembolic risk	Difficulty of insertion	Availability	Infectibility	Noise
Mechanical	Excellent	Good	Low with anticoagulation	Easy	Yes	?Increased	Increased
Stented bioprosthetic	Limited	Good	Low	Moderate	Yes	?Increased	Minimal
Stentless bioprosthetic	Limited	Excellent	Low	Moderate-difficult	Yes	?Lower	Minimal
Allograft	Limited	Excellent	Low	Moderate-difficult	Limited	?Lower	Minimal
Autograft	Limited	Excellent	Low	Moderate-difficult	Yes	?Lower	Minimal

Recognizing that homografts may incite alloreactivity, it was suggested that autologous biologic valves would diminish this risk while maintaining the superior hemodynamic profile. In accord, use of the pulmonic valve to replace another valve was first reported in 1961 when Lower and colleagues of Stanford transposed the pulmonic valve to the mitral position in dogs.[16] Shortly thereafter, Pillsbury and Shumway, also of Stanford, experimentally transposed the autologous pulmonic valve to replace a diseased aortic valve.[17] Donald Ross extended this work to humans, reporting in 1967 a series of 14 patients in whom he replaced a diseased aortic valve (AV) with an autologous pulmonic valve.[18] Since that time, this procedure has come to bear his name—the Ross procedure—also described as a pulmonary autograft. Widespread early fervor about this procedure was quickly tempered when surgeons appreciated its technical demands as well as considering it to be a "double valve" replacement for a "single valve" problem. While there was a surge of renewed interest in the Ross procedure in the 1990s, this has diminished in recent years. Currently, over 240 surgeons worldwide have performed the Ross procedure, as reported in The Ross Procedure International Registry, which was established in the early 1990s to catalogue these procedures and follow the outcomes.

ALLOGRAFTS

Procurement and Preservation

In the United States, the majority of allograft valves are obtained from heart-beating organ donors whose hearts are not suitable for transplantation. Allografts obtained from fresh cadavers less than 24 hours old comprise the second main source of valves. The processing of cadaveric tissue is increasingly performed by regional tissue centers that specialize in the procurement and preservation of human tissues for ultimate allotransplantation. The increasing prevalence of cardiac allotransplantation has allowed the use of fresh "homovital" allografts,[19] which may have enhanced preservation of cellular viability. Ideally, fresh valves would be implanted within 24 hours, but even at centers with significant experience, the interval between harvesting and implantation is up to 60 days, with an average interval of 3.9 days.[19] Accordingly, cryopreservation is the most common technique used, which optimizes cellular viability[15] and prolongs shelf life, which is an obvious advantage given the shortage of organ donors.

For cryopreservation, the heart is procured under sterile (multi-organ donor) or clean (cadaveric donor) conditions and gently rinsed with cold isotonic salt solution (e.g., Ringer lactate) to remove the blood and its elements from the cardiac chambers. The heart is then placed in a bag containing ice-slush solution and kept cold until further processing. Warm ischemia time does not exceed 12 hours, unless the donor is in an environment with temperature $\leq$8°C within 6 hours of death, which can extend the "warm" ischemia time to 24 hours. Donor blood is obtained for culture and serologic testing for common infectious agents (e.g., hepatitis B and C, human immunodeficiency virus, human T-cell lymphoma virus, and *Treponema pallidum*). The following details are based on procedural protocols of The Northwest Tissue Center, Seattle, WA,[20] and are similar to those of other institutions.[21] Once at the tissue center, an aortic block is dissected in a controlled environment (a class 100 clean room environment). Donor tissue and the transport solution are cultured for aerobic and anaerobic organisms, fungi, and acid-fast bacilli. Proximally the dissection includes the aortic ring and the anterior leaflet of the mitral valve with a variable amount of ventricular muscle, and extends distally to the left subclavian

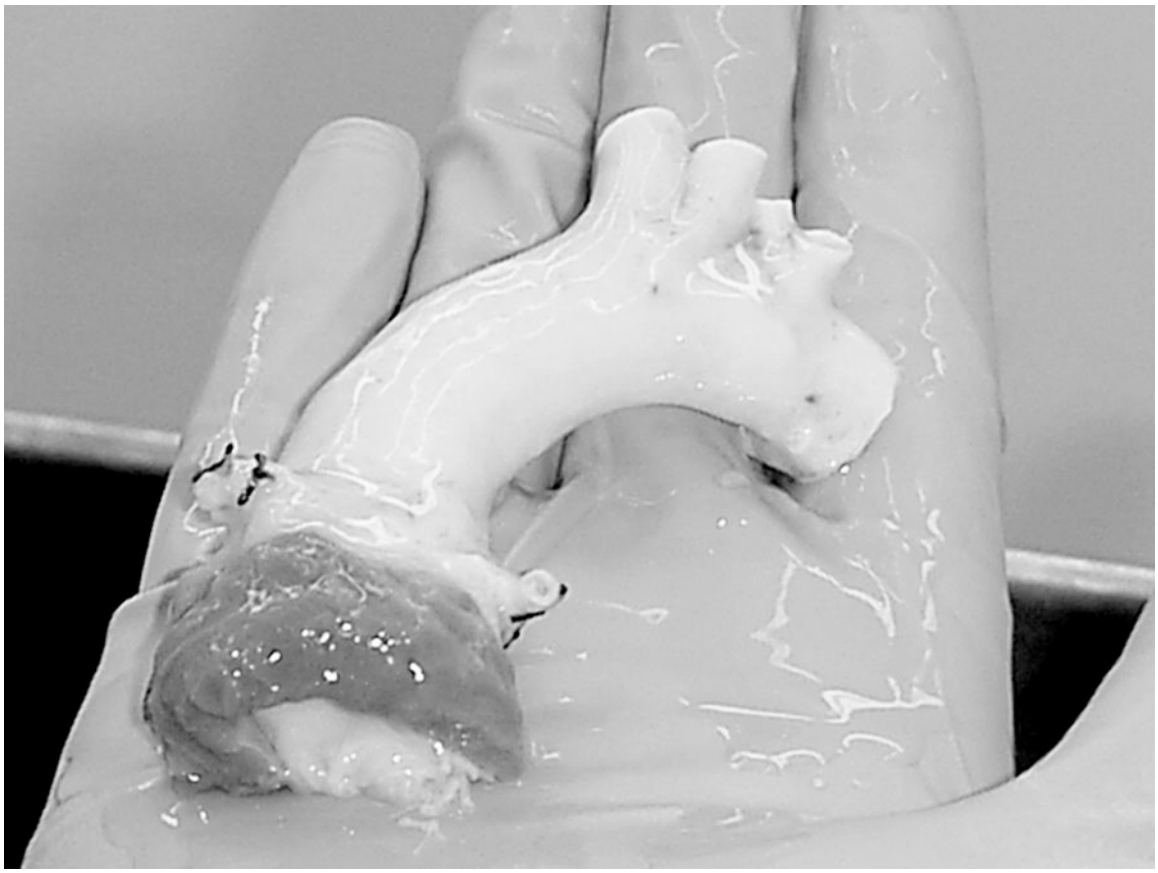

Figure 35-1. Aortic valve allograft after harvesting from the donor. The block includes a variable amount of ventricular muscle and the anterior leaflet of the mitral valve. Additional trimming for replacement is performed at the time of implantation. (*Reproduced with permission from The Northwest Tissue Center, Puget Sound Blood Center.*)

artery, including the branches of the thoracic aorta. The coronary ostia are ligated, allowing a subsequent interposition "free-root" allograft if needed. The base of the graft contains a variable amount of ventricular muscle that may be trimmed at the time of graft implantation. The valve is inspected for leaflet fenestrations, atheroma, or damage that may make it unsuitable for implantation. Of these, leaflet atheroma absolutely contraindicates use of the allograft, while fenestrations or other damage are relative contraindications, and depend on their severity and magnitude. Obturators are then used to size both the valve and the aorta (Fig. 35-1).

After harvesting, the allograft block undergoes a series of rinses and is then placed in a nutrient medium (e.g., RPMI-1640) with low levels of antibiotics (polymyxin B sulfate 250,000 units, cefoxitin sodium 60 mg, vancomycin HCl 12.5 mg, and lincomycin HCl 30 mg)[22] for sterilization. Although this regimen originally included amphotericin B, it is often omitted to optimize cellular viability.[23] The allograft can then either be used as a fresh homovital allograft, or prepared for cryopreservation. Throughout this process, cultures are serially obtained to rule out contamination that may preclude use of the graft.

The sine qua non of cryopreservation is controlled rate freezing, as introduced by O'Brien and colleagues in 1975.[15] Prior to packaging, the air in the packaging room is sampled for viable particles, as are the gloves of the technologist, and three designated locations in the sterile packaging field. The allograft is transferred from the antibiotics to a sterile storage pouch containing culture medium (e.g., RPMI-1640), 10% fetal calf serum, and 7.5% dimethyl sulfoxide DMSO (a cryoprotectant). These substrates are designed to provide nutritive support to the allograft and minimize crystal formation and tissue damage during the freezing process. A final sample is taken of the packaging solution for aerobic and anaerobic organisms. Within 2 hours of exposure to DMSO, the allograft is frozen at −1°C per minute down to −40°C and then placed in vapor-phase liquid nitrogen storage (about −195°C) until it is used. After tissue cultures and serology results are available (about 4 to 6 weeks) and negative, the valve may be used for implantation; if there are any positive culture or serology results, the valve is discarded.

After release of the allograft from the tissue center, it is shipped in a container validated to maintain temperatures below −100°C for 10 days. Two temperature-sensitive indicators, which turn red if temperatures exceed −100°C, are included with each shipment to ensure maintenance of shipping temperatures. Upon arrival at the institution where it will be used, the storage pouch is removed from the liquid nitrogen and placed in warm saline (37° to 42°). The allograft size and

number are confirmed. After removal from the storage pouch, the allograft then undergoes a series of gentle rinses and thawing, in solutions that have increasingly dilute DMSO, followed by a final rinse in pure nutrient media prior to use. The allograft is then ready for final trimming and implantation.

Cellular and Immunologic Aspects of Allografts

Normal valves are ultrastructurally comprised of viable cellular components, including endothelium, fibroblasts, and smooth muscle cells, and an amorphous and fibrillar extracellular matrix, derived primarily from fibroblasts and smooth muscle cells.[24] In nonpathologic states, there is a steady state between destruction of these elements and remodeling, which underlies an overall structure and function. In accordance with the paradigm that structural integrity, and thus function, depends on cellular viability of an allograft, preservation techniques have attempted to optimize the preservation of viable cellular elements to improve function and durability.

As mentioned, earlier methods of chemical sterilization and irradiation had a prohibitive incidence of cusp rupture[14] and histologic analysis of these allograft valves reveals nonviable cellular elements.[25] Antibiotic sterilization of allografts and storage in a balanced salt solution or nutrient medium at 4°C does not maintain cellular viability beyond a few days.[26,27] The durability of these valves is improved over chemically sterilized valves with a freedom from reoperation for valve degeneration at 10 years of 89%.[15] Gentle procurement and cryopreservation of allografts has been shown to maintain donor fibroblast viability up to $9^{1}/_{2}$ years after implantation in one patient, and viable fibroblasts have been consistently demonstrated in a small number of other patients.[15] More recently, persistence of viable, functional donor fibroblasts in allografts harvested up to 70 months earlier has been reported.[29] Also, using in situ hybridization technology, the viable fibroblasts in the explanted allografts were demonstrated to be of both recipient and donor origin. Other investigators have demonstrated no cellular viability of allograft valves after antibiotic treatment[26] or after explantation.[28] Of note, however, the methods of valvular preservation in the latter investigation[28] were not reported, and these valves were explanted primarily for deterioration, contributing to significant selection bias. In the end, the extent to which viable cellular elements persist in allografts after cryopreservation is not clear. Given the occasional findings of viable cells, particularly fibroblasts, up to 9 years after implantation,[15] it is likely that some viable cells persist in allografts, at least some of the time. Moreover, when viable cells are present, they are likely to be of both donor and recipient origin.[15,29] The discrepant findings with respect to the persistence of viable cells in the allograft may relate to warm ischemia times or differences in procurement and preservation techniques. More importantly, when present, the extent to which these viable fibroblasts remain functional and contribute to the structural integrity of the allograft components is not known.

While modifications of valve preservation have attempted to maintain cellular viability of the allograft[15] to improve long-term structural integrity and function,[30] the presence of viable donor cells may be detrimental by inciting an allograft rejection reaction.[31] Multiple studies have demonstrated the generation of donor-specific alloantibodies directed against human leukocyte antigens (HLA) class I (A and B antigens) and II (DR antigens) in allograft valve recipients.[32,33] The development of panel reactive antibodies seems to increase with time,[33] approximating 82% at 6 years postgraft implantation,[34] occurs in both adults and children, and is irrespective of the method of cryopreservation.[35] Despite consistent evidence of antibody formation directed against the HLA antigens of the allograft, the clinical significance is not clear.

Dignan and associates reported a significant association between HLA class II antigen mismatch and postoperative fever and homograft dysfunction in recipients of cryopreserved allografts.[36] In recipients of homovital allografts, Smith and colleagues reported no significant association between HLA class I or II antigens and long-term (6 years) valve function,[34] although there was an increased prevalence of valve degeneration in those patients with HLA antibodies: in HLA antibody–negative patients the actuarial freedom from valve degeneration at 1, 5, and 10 years was 100%. In patients with panel reactive antibodies <50% freedom from valve degeneration at 1, 5, and 10 years was 100, 97, and 92%, and 98, 94, and 88% in those patients who were highly sensitized.[34] Taken together, these data suggest that antibody-mediated alloreactivity may play a causal role in allograft valve dysfunction over time, but larger studies are certainly needed with adequate power to detect small (i.e., 5% at 10 years) differences between allograft recipients who are HLA matched and mismatched. In the meantime, until such data are available, it has been suggested that prospective matching of HLA antigens may be warranted.[34] Recognizing that investigation of allografts in humans is limited to preimplanation analysis (i.e., during procurement or preservation) or valves that require explantation due to valve failure, heart transplantation of the recipient, or recipient death, investigators have developed alternative models for this inquiry.

Accordingly, to better understand the immunologic aspects of allograft valve dysfunction, numerous investigators have used animal models of allograft implantation. Multiple studies of allograft implantation across major histocompatibility complex barriers in rats demonstrate significant cellular infiltration into thickened valve leaflets over the first 28 days, which is temporally followed by valve degeneration and failure.[37–40] The cellular infiltration may be phasic, characterized by early monocyte infiltration,[37] followed by progressive monocyte/macrophage and T-lymphocyte infiltration, which is maximal by 7 days postimplantation.[37,40] There is a coincidental decline in allograft donor cell viability over this time that is paralleled by declining valve structure and function.[37] Importantly, in T-cell–deficient rats, these cellular events do not occur and allograft function is preserved, providing additional support for immune-mediated valvular destruction.[38] Moreover, immune modulation with cyclosporine and antiadhesion molecule (anti-α4/β2 integrin) therapy attenuates leaflet cellular

infiltration and prevents allograft structural failure.[41] Taken together, these data strongly support a donor-specific, cell-mediated (primarily T lymphocytes) immune reaction directed against the donor alloantigens that is followed by structural valve failure—a cellular cascade typical of solid organ rejection.

In summary, despite intensive investigation over the past three decades, the relative contribution of the immune response, preservation techniques, and warm ischemia time to ultimate valve degeneration (i.e., sclerosis or calcification) is not clear. More importantly, after consideration of the structural benefits and the immune-reaction risks, the net advantage of maintaining cellular (particularly fibroblasts) viability in the allograft is not well defined.[31] Future investigations should endeavor to further clarify the relative contributions of these factors to allograft valve antigenicity, immunogenicity, and durability. Furthermore, the impact of immune modulation on long-term allograft function warrants further study.

Indications

Aortic valve replacement with an allograft has a number of advantages including excellent hemodynamic profile with low transvalvular gradients and possibly enhanced regression of left ventricular mass (LVM),[42] low risk of thromboembolism without the need for systemic anticoagulation, and low risk of prosthetic valve infection. Allograft durability is limited, however, with a freedom from reoperation at 20 years of 38 to 50% and a freedom from structural valve failure at 20 years of 18 to 32%.[43,44] The incidence of structural failure is dependent on the ages of the recipient and the donor. Allograft failure increases with decreasing recipient age, and durability is improved in older recipients. Also, allograft failure increases as the donor age increases. Considering these data underscoring poor allograft durability, we believe the current indications for an aortic allograft are limited. The primary indication in adults is for treatment of active AV endocarditis. However, we are not aware of any data indicating the superiority of allografts compared to other valve options in this setting, and the ideal valve choice for replacement of an infected AV has not been defined. Aortic allografts can also be considered for patients requiring composite valve/root aortic replacement who cannot be anticoagulated.

Preoperative Evaluation

Preoperative preparation for placement of an aortic allograft is similar to that for other AV operations. Transthoracic echocardiography (TTE) is an invaluable diagnostic tool for evaluation of the AV and associated anatomic structures, including the leaflets, the annulus, the sinuses, the sinotubular junction, the subvalvular left ventricular outflow tract (LVOT), and the ascending aorta. In this regard, the preoperative TTE can accurately predict aortic annulus diameter within a few millimeters, and thus the size of the homograft required.[45–47] Transesophageal echocardiography (TEE) should routinely be used for intraoperative confirmation of the anatomy and to assist with sizing of the homograft, and to assess postrepair function. The accuracy of TEE in assessing annular dimensions has been demonstrated.[48,49] While TTE and TEE can accurately approximate the annular dimensions and homograft size, direct surgical measurement is imperative.

Operative Technique

General preparation

A full median sternotomy is used with standard techniques of cardiopulmonary bypass (CPB). Aortic cannulation is obtained as far distally as possible, near the innominate artery, and a two-stage cannula is placed into the right atrial appendage. A ventricular vent can be placed into the right superior pulmonary vein. Both antegrade and retrograde blood cardioplegia are delivered. The aortotomy incision can be transverse or an obliquely oriented reverse "lazy-S" that begins above the right coronary ostia (Fig. 35-2). After

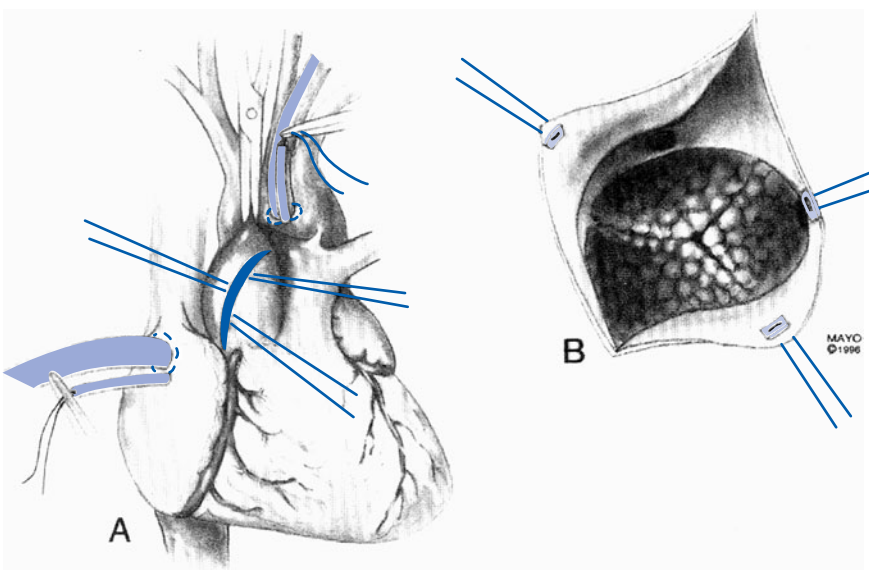

Figure 35-2. Standard cardiopulmonary bypass is performed. A "lazy-S" or oblique aortotomy is performed beginning above the right coronary cusp with the transverse portion just cephalad to the noncoronary cusp. This incision provides excellent exposure for all techniques when replacing the aortic valve and root. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

retraction of the aorta, facilitated with silk stay sutures, the valve is excised. The aortic root and annulus are then closely examined for geometric morphology and symmetry, indicating feasibility of a good result with a homograft. Next, the aortic ring is sized with standardized obturators or Hagar dilators. Since this represents an external diameter of the recipient, and allografts are sized based on internal diameters, an allograft 2 to 4 mm smaller than the recipient measurement is obtained. The appropriately sized allograft can then be thawed. If the allograft was selected based on accurate TTE or TEE measurements, it should already have been thawed. The allograft is then trimmed.

Because the allograft block contains a variable amount of ventricular muscle, mitral leaflet, and the arch, the goal of trimming is to remove excess tissue and tailor the allograft for placement depending on the planned insertion technique. To this end, the mitral leaflet is shaved and trimmed, and the ventricular septum is debulked. A straight lower margin, which will contain the lower suture line, is created 2 to 3 mm below the nadir of each aortic cusp. If the freehand scalloped techniques (i.e., scalloped or intact noncoronary sinus) are to be used, the sinuses are removed from the ascending aorta, leaving three pillars of aorta supporting each commissure of the cusps. For the intact noncoronary sinus technique, the noncoronary sinus is spared (Fig. 35-3). Finally, in cases of active endocarditis with annular abscess, the excess allograft tissue may be used to reconstruct the annulus following adequate débridement.

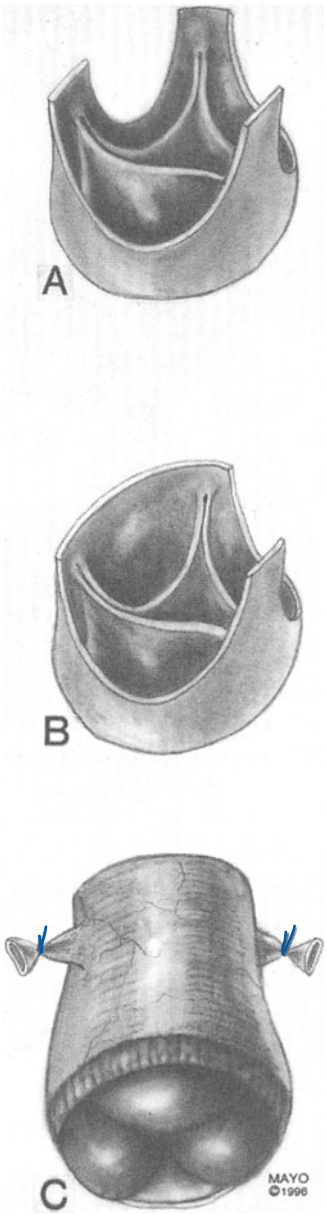

Figure 35-3. Preparation of an aortic homograft from the aortic block. The ventricular muscle and mitral leaflet are removed. (A) The freehand subcoronary insertion technique involves removal of sinus aorta within 5 mm of the cusp attachments down to within 3 mm of the cusp bases, thus removing all three sinuses. (B) The intact noncoronary sinus technique involves preservation of the noncoronary sinus. (C) For aortic root replacement, the entire aortic wall can be retained, and then be implanted as an "inclusion cylinder" or "mini-root" insertion. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

Techniques of allograft placement

There are multiple techniques for placing the allograft in the aortic position, and the strategies have continued to evolve over time. Ross[7] and Barratt-Boyes[50] originally described the 120° rotation scalloped freehand technique. Numerous groups later modified this technique, whereby the right and left coronary sinuses were scalloped, but the noncoronary sinus was left intact—the intact noncoronary sinus technique. Later this technique was further altered to preserve all the sinuses on the donor and insert the allograft as a cylinder within the recipient aortic root, with reimplantation of the coronary ostia as needed. More recently, the allograft has been implanted as a mini-root interposition graft when the severely diseased aortic root must be excised. Thus, there are essentially four techniques for placing an aortic allograft: (1) 120° rotation scalloped implant, (2) intact noncoronary sinus scalloped technique, (3) aortic root inclusion cylinder technique, with reimplantation of the coronary ostia as needed, and (4) aortic mini-root replacement with interposition allograft.

SCALLOPED 120° ROTATION FREEHAND TECHNIQUE: For the scalloped 120° freehand rotation technique, the sinus aorta is trimmed within 5 mm of the cusp attachments down to within 3 mm of the cusp bases, effectively removing all three sinuses.[50] The valve is then rotated 120° in the counterclockwise direction, so that the donor right sinus lies below the recipient left coronary sinus (Fig. 35-4). This critical maneuver brings the weaker muscular portion of the allograft posteriorly adjacent to the fibrous trigone and anterior leaflet of the mitral valve.[50,51] Two suture lines are required for this technique. The lower suture line can either be a continuous running suture or simple interrupted sutures can be used, usually of 4-0 or 5-0 polypropylene (Figs. 35-5 through 35-7). For the running suture, the homograft can be turned

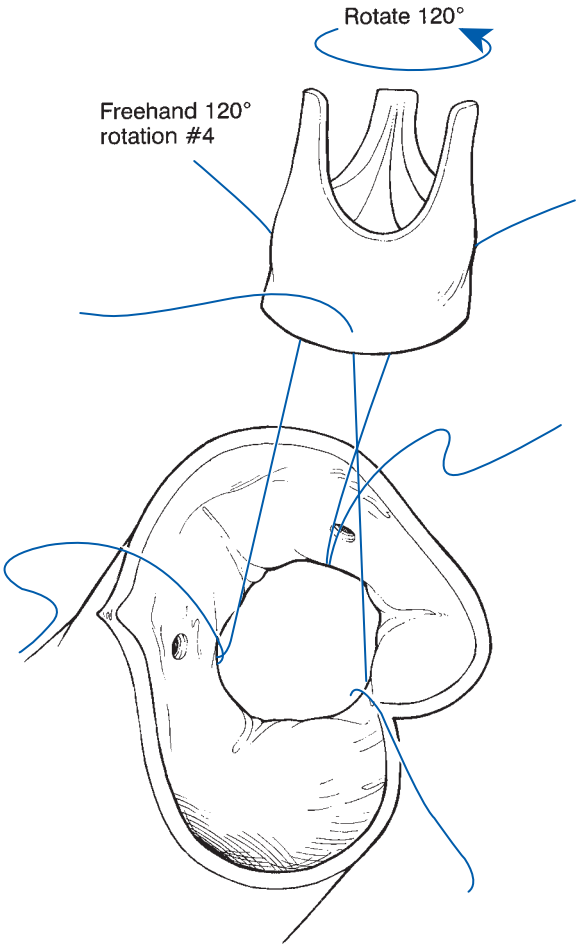

Figure 35-4. For the scalloped 120° rotation freehand technique, the allograft is rotated 120° counterclockwise so that the donor right sinus lies below the recipient left coronary sinus. Three orientation stay sutures are placed below the nadir of each cusp.

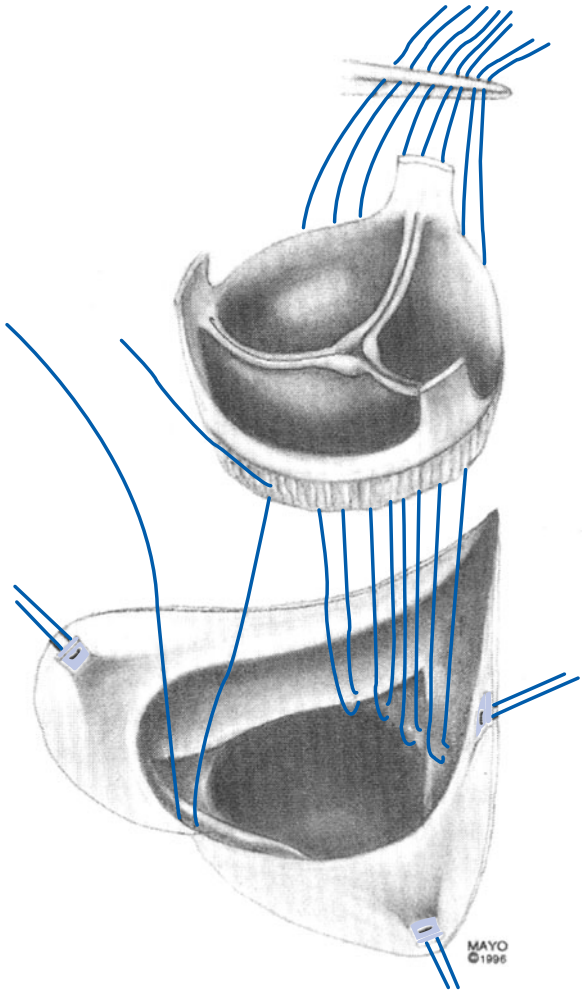

Figure 35-5. The inferior suture line with simple interrupted sutures. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

inside out to facilitate the lower suture line. In the area of the membranous septum, sutures are placed more superficially to avoid the conduction system.

As Dearani,[51] McGiffin,[52] and others[53,54] have emphasized, proper alignment of the commissures in the aortic root is absolutely critical for proper coaptation of the AV leaflets to ensure good long-term graft function. Accordingly, if the commissures are malaligned or kinked, the leaflets will not coapt properly and a regurgitant valve ensues. Moreover, if there is only slight malalignment initially with a competent valve, the free cusp edges may be subjected to increased stresses over time, leading to premature structural deterioration and aortic regurgitation (AR).[51] Similarly, size discrepancy between the donor allograft and the recipient sinotubular junction is likely to result in aortic insufficiency.[55] For these reasons, the scalloped 120° freehand rotation technique is considered more demanding than the other allograft placement techniques and may have poorer long-term results than the other methods of allograft placement.[44,51–54] Recognizing these technical and physiologic aspects of the scalloped subcoronary implant, it is a good technique for patients with small, symmetric aortic roots and sinotubular junctions, while it is a poor choice for those with dilated, asymmetric, or severely diseased roots or sinotubular junctions.

FREEHAND INTACT NONCORONARY SINUS TECHNIQUE: Scalloping of the right and left coronary sinuses while preserving the noncoronary sinus is a technical extension of the scalloped 120° subcoronary implant technique (Fig. 35-8). This modification increases stability of the homograft and maintains symmetry more easily. Furthermore, the risk for noncoronary cusp prolapse is reduced in patients with a dilated or abnormal sinotubular junction.[56] Accordingly, it is a reasonable choice for patients with mildly dilated or asymmetric aortic roots and those with AI. For the intact noncoronary sinus technique, the allograft is prepared as above, except the noncoronary sinus is preserved. The allograft is then inserted into the aortic root maintaining anatomic alignment without any rotation and is sutured as described above. Additionally, mattress sutures are placed through

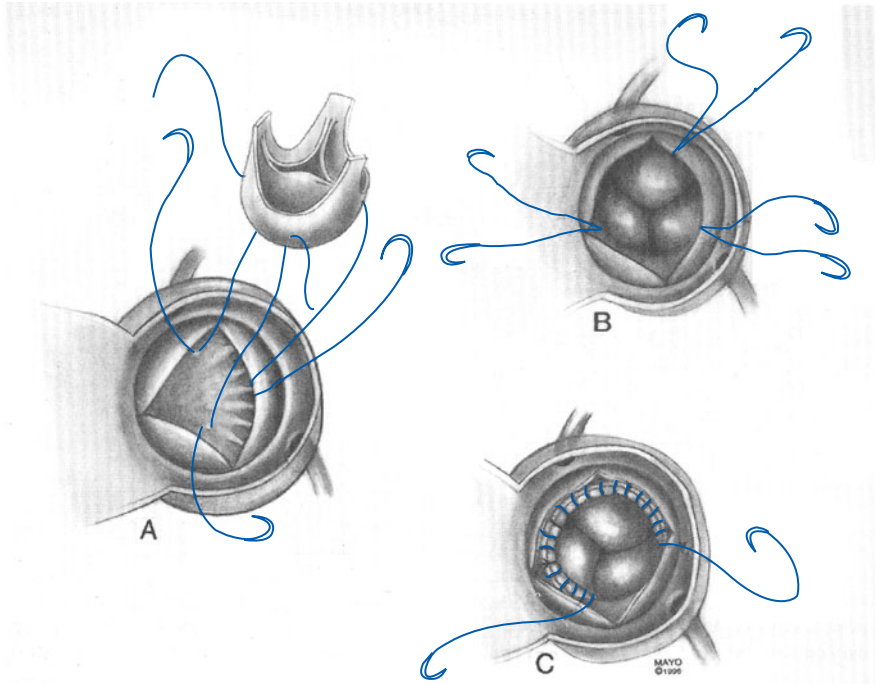

Figure 35-6. The inferior suture line with continuous suture. (A) The double-arm orientation stay sutures facilitate placement. (B) The allograft is inverted into the ventricle and the stay sutures are tied. (C) The stay sutures are then "run" in a clockwise manner to complete the lower suture line. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

the native aorta and the noncoronary sinus of the allograft to obliterate the space between the noncoronary sinus and the native aorta.

AORTIC ROOT REPLACEMENT: In patients who have dilated or geometrically distorted aortic roots, root replacement techniques are a good alternative. In many ways these techniques are technically easier to perform than the freehand techniques described above. Furthermore, a 2 to 3 mm disparity in donor-recipient root size is tolerated reasonably well, which increases the effective donor pool and reduces the probability of not having an allograft available. Despite earlier concerns about increased perioperative morbidity with root replacement techniques, recent reports from experienced surgeons do not support this.[51,57] Root replacement has become the most commonly used technique for placement of a homograft in the aortic position.

AORTIC ROOT REPLACEMENT WITH INCLUSION CYLINDER TECHNIQUE: Ross and others modified the aforementioned techniques to place the allograft as a sleeve or cylinder within the aortic root. The technique of implantation is very similar to that outlined above. For the inclusion cylinder technique, the sinuses are retained, and the cusp-sinus relationships are preserved (Fig. 35-9). Depending on the length of the cylinder, the recipient coronary ostia may need reimplantation into a buttonhole in the side of the allograft or directly into the donor coronary ostia. Conversely, if the distal aspect of the allograft is caudal to, or near the recipient coronary ostia, then minimal scalloping of the allograft wall will suffice to ensure coronary flow. We create the

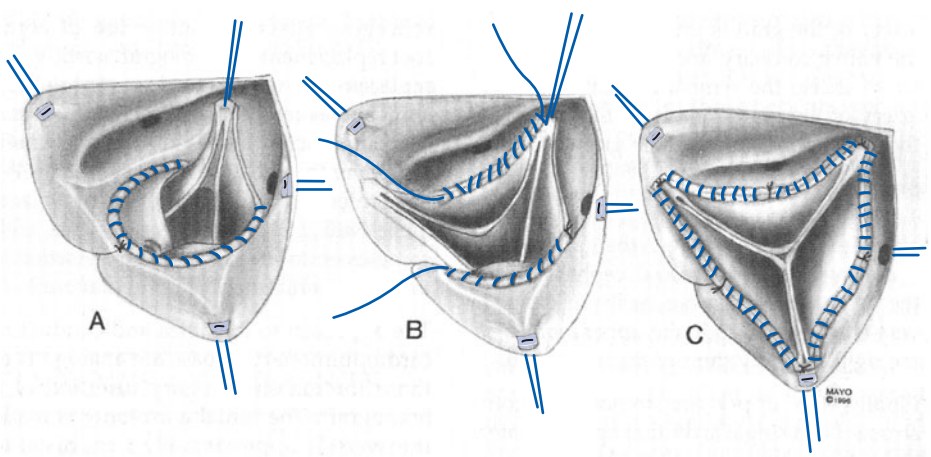

Figure 35-7. The downstream continuous suture line. (A) The allograft is everted after completion of the inferior suture line, by applying traction to the commissural posts. (B) A continuous suture completes the implantation. (C) Completed suture line. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

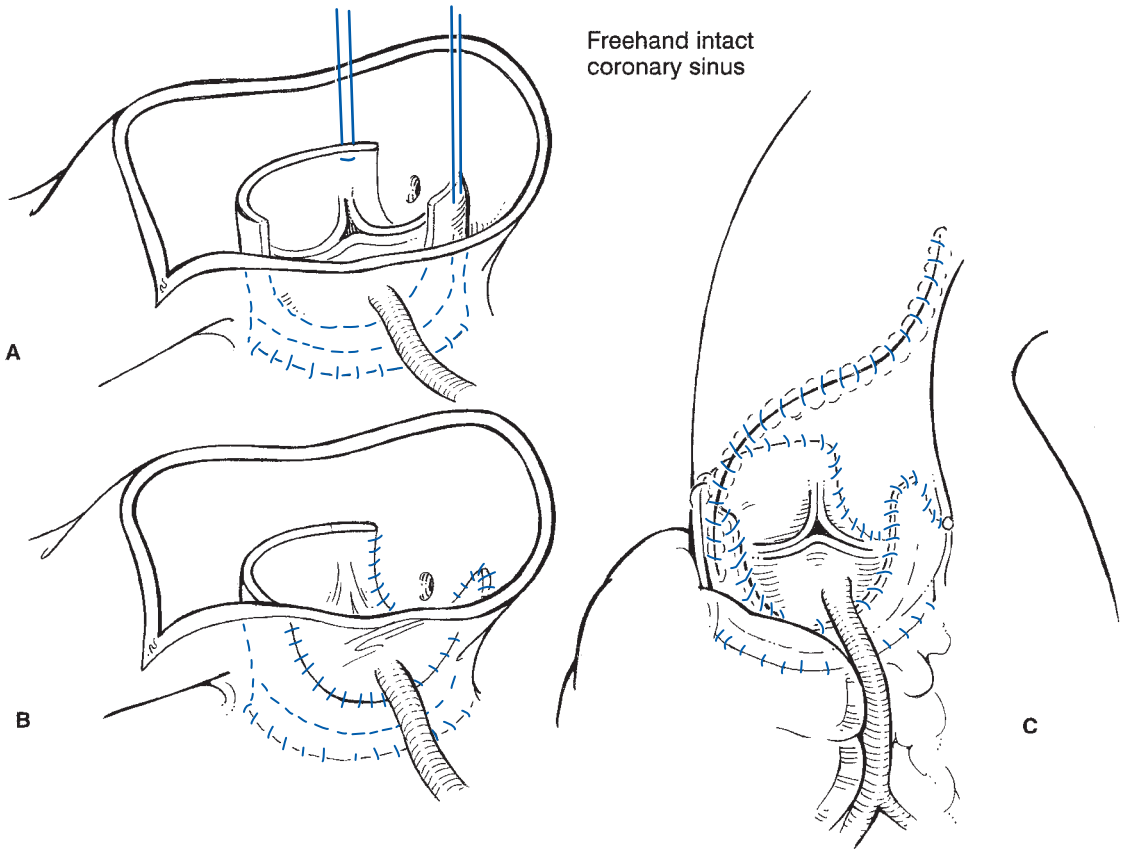

Figure 35-8. The intact noncoronary sinus technique. (A) This technique is nearly identical to the scalloped freehand technique, except the anatomic alignment of the donor allograft is maintained. (B) The noncoronary sinus is sutured to the corresponding aortic wall after partial closure of the aortotomy. This ensures minimal tension on this suture line. (C) The space behind the noncoronary sinus is obliterated with a U-stitch and the aortotomy is closed.

proximal suture line with everting, pledgeted horizontal mattress 2-0 Ticron sutures, and use a running 4-0 polypropylene suture for the distal suture line. The coronary buttons are reimplanted with a running 5-0 polypropylene suture.

AORTIC ROOT REPLACEMENT WITH FREESTANDING (INTERPOSITION) ROOT REPLACEMENT: The aforementioned techniques have been further modified to allow complete, or freestanding, replacement of the aortic root, now the most commonly used technique for allograft placement. To this end, the aortic root is completely excised and the homograft is interposed as a cylinder between the LVOT and the ascending aorta. Again, we use everting, pledgeted 2-0 Ticron horizontal mattress sutures for the proximal suture line, and a running 4-0 polypropylene suture for the distal suture line. The coronary arteries are reimplanted into the side of the allograft using a running 5-0 polypropylene suture. In all the aforementioned techniques, the aortotomy is closed with a running 4-0 polypropylene suture.

Postreplacement assessment

Intraoperative TEE with Doppler color-flow measurement is the most valuable postreplacement assessment tool, after the patient has been separated from CPB. The accuracy of the TEE assessment can be further enhanced with volume loading and administration of phenylephrine to effect vasoconstriction. Moreover, the transvalvular gradient, orifice area, subvalvular structures, and presence of regurgitation may all be accurately determined with TEE. With appropriate loading conditions, moderate to severe AI warrants reinstitution of CPB with inspection and revision of the allograft as needed. Mild AI is usually tolerated well and does not warrant re-exploration.

Postoperative management

Postoperative management following allograft placement is similar to that of other aortic valve replacements, and is dictated by the antecedent physiology that resulted from the aortic stenosis (AS) or regurgitation that required surgery. Aortic stenosis produces a hypertrophied, noncompliant ventricle that requires adequate preload and maintenance of sinus rhythm for adequate cardiac output.

In contrast, AI results in a dilated left ventricle that may be coincidentally hypertrophied. Again, ensuring adequate preload and aggressively treating arrhythmias is imperative. Since patients with AI are chronically vasodilated to maintain systemic perfusion, vasoconstricting agents may

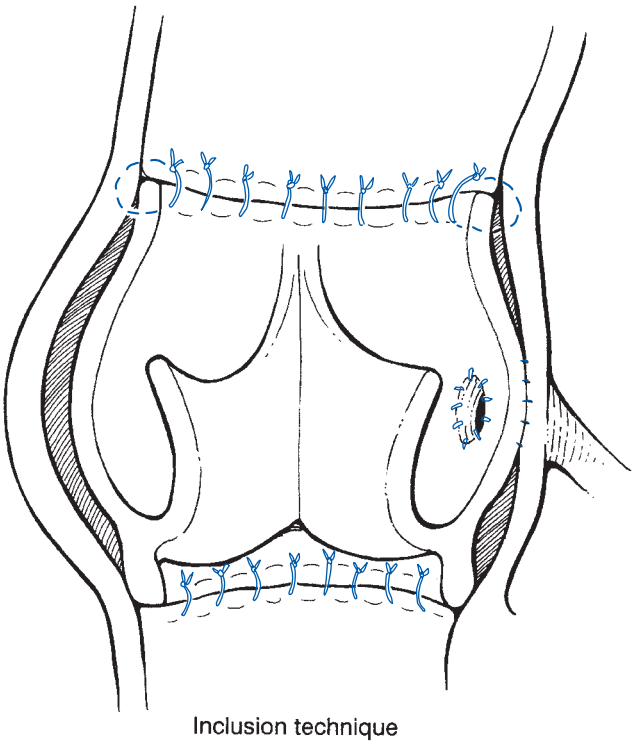

Figure 35-9. The inclusion cylinder technique for aortic root replacement. The cylinder retains the aortic allograft anatomic relationship. Depending on the length of the cylinder, the recipient coronary ostia may require reimplantation.

be required after the patient is normothermic in the intensive care unit.

In both of these groups, systolic hypertension should be treated aggressively to protect the aortic suture line. Other than atrial arrhythmias, which are treated aggressively to restore atrial-ventricular synchrony, these patients are also susceptible to heart block, since the atrioventricular node and left bundle lie in the membranous septum underneath the right coronary annulus. When this occurs, epicardial pacing is employed as needed, and when persistent beyond a few days, a permanent pacer may be placed.

Long-term anticoagulation is not required and once-daily aspirin suffices.

Results

Perioperative complications

In patients without endocarditis at the time of allograft placement, operative mortality is 1 to 5%.[43,44,57] Notably, numerous experienced and talented groups have reported that the root replacement technique does not impact early mortality.[44,57] In contrast, patients with endocarditis at the time of allograft valve placement have a much higher early mortality, from 8 to 16%.[19,44,59–61] In these patients, early mortality was higher in patients with cardiogenic shock,[61] or prosthetic valve endocarditis (18.8%) compared to native valve endocarditis (10%).[59]

Early postoperative AI occurs infrequently and most often results from technical factors, like inaccurate sizing of the allograft, or valve distortion during placement, particularly with the scalloped subcoronary implant technique. This complication should be appreciated intraoperatively with loading maneuvers and intraoperative TEE, as previously mentioned.

Hemorrhage, heart block, stroke, myocardial infarction, and infectious complications occur with similar frequency to those of other AVRs, and are not unique to homografts.

Long-term outcomes

As mentioned, 30-day mortality following homograft placement is less than 5% in patients without endocarditis. Crude survival at 10 and 20 years is reported to be 67 and 35%, respectively,[44] while in other studies actuarial survival at 10, 20, and 25 years is 81,[43] 58,[43] and 19%[57] (Table 35-2).

The durability of allografts is limited. Structural valve failure (aka, primary valve failure or deterioration) of allografts increases with time, and approximates 19 to 38% at 10 years and 69 to 82% at 20 years.[43,44] Structural deterioration appears to be age related, with earlier failure in younger recipients,[57] while Lund and associates have found that recipient age >65 and increasing donor age may increase structural failure.[44] Freedom from repeat AVR, for any reason, parallels structural valve failure and is 86.5% and 38.8% at 10 and 20 years, respectively.[43]

Importantly, when structural valve deterioration occurs, we have found reoperation and allograft valve/root excision to be technically quite demanding. Grossly, the allografts become severely calcified, which makes circumferential dissection very challenging, particularly at the coronary button ostia. While the coronary arteries themselves are usually normal-quality tissue, the proximal rim of the button is often calcified, making removal and reimplantation more challenging. Furthermore, because the base of the allograft also becomes heavily calcified, we have often found the annulus to be heavily scarred and calcified, and subsequently narrowed. Bearing in mind the concept of patient-prosthesis mismatch, and the goal of providing an effective orifice area index (>0.75 cm^2/m^2), we have had a low threshold for performing an annular enlargement procedure (both posterior and anterior). Taken together with the limited durability, relative to other currently available options with comparable versatility, we almost never use allografts for replacement of diseased AVs.

Hemodynamic characteristics of allografts are excellent at short- and medium-term follow-up, both at rest and during exercise.[62,63] However, progressive allograft dysfunction develops over time that coincides with deteriorating hemodynamic performance of a progressively abnormal valve.

Table 35–2.

Long-Term Follow-Up of Homograft Valves: Summary of Large Experiences

Reference	Patients (no.)	Follow-up (y)		Overall survival			Freedom from: Structural valve failure			Freedom from: Reoperation AVR			Freedom from: Thromboembolism		
		Max	Mean	10 y	15 y	20 y	10 y	15 y	20 y	10 y	15 y	20 y	10 y	15 y	20 y
Lund et al[44]	618	27.1	10.1	67%	48%	35%	62%	34%	18%	81%	55%	35%	89%	85%	80%
Langley et al[43]	200		15.6	81%	68%	58%	81%	62%	32%	87%	70%	39%	Overall,	99%	Freedom
O'Brien et al[57]	1022	29	7.3	77%	60%	42%				Overall, 87%			94%	92%	83%

AVR = aortic valve replacement.

Infectibility of allografts is low, with freedom from endocarditis at 10 years of 93 to 98%,[43,44] and at 20 years of 89 to 95%.[43,44,57] Similarly, freedom from thromboembolism at 15 and 20 years in patients undergoing AVR plus coronary artery bypass graft (CABG) is 92 and 83%, respectively.[57] O'Brien and colleagues found that neither preservation methods or implantation techniques affected overall 20-year rates of thromboembolism, endocarditis, or structural valve deterioration.[57]

In patients with active endocarditis requiring AVR, results are much poorer. Operative mortality is nearly twice that of patients without endocarditis, from 8 to 17%,[59–61] and is higher in patients with prosthetic valve endocarditis.[60] Late survival ranges from 58% at 5 years[59] to 91% at 10 years,[61] and is significantly lower in patients with prosthetic valve endocarditis (PVE).[60] Importantly, the risk of recurrent endocarditis is <4% up to 4 years postoperatively.[51,60,61] As a result of these acceptable outcomes in a high-risk group of patients, many consider allografts the preferred valve for aortic replacement in patients with active endocarditis.

Conclusions

Allograft replacement of an aortic valve has become less common with the increased availability of bioprosthetic valve alternatives. The aortic allograft is a versatile valve allowing placement as a valve or as an aortic root replacement, which is the most common insertion technique. Aortic allografts have many favorable attributes including low operative mortality rate, excellent early and midterm hemodynamics across the allograft, low valve-related noise, low thrombogenicity, and low infectibility. The primary, and significant, shortcoming of aortic allografts is progressive deterioration of valve structure and function over time, which limits its use in younger patients with long life expectancy. Limited availability and technical expertise for insertion are also limiting factors for more widespread utilization of aortic allografts. For patients with active endocarditis of either the native or prosthetic AV, allograft replacement is a reasonable option. Furthermore, with respect to biologic replacement of the aortic root, longer follow-up is needed for the currently available xenografts to determine the relative durabilities between aortic allograft root replacement and xenograft root replacement.

PULMONARY AUTOGRAFT

Theoretical Considerations

Replacement of a diseased aortic valve with a pulmonary autograft has a number of advantages including: (1) freedom from thromboembolism without the need for anticoagulation; (2) improved hemodynamics through the valve orifice without obstruction or turbulence; (3) growth of the autograft with time, particularly beneficial for young patients who continue to grow after receiving the aortic autograft;[64] and (4) the assumption that replacement of the AV with living autologous tissue is preferential to prosthetic or xenogeneic materials.

Patient Selection

In addition to individual surgeon experience, a number of patient factors influence consideration of the Ross procedure for replacement of a diseased AV. Table 35-3 summarizes the important patient factors to bear in mind when considering the Ross procedure. The only absolute contraindications are significant pulmonary valve disease, congenitally abnormal pulmonary valves (e.g., bicuspid or quadricuspid), Marfan syndrome, unusual coronary artery anatomy, and probably severe coexisting autoimmune disease, particularly if it is the cause of the aortic valve disease. Of note, bacterial endocarditis is not a contraindication for the Ross procedure, though when present, it

Table 35–3.

Patient Factors Influencing Ross Operation Selection

Favorable	Unfavorable
Young	Age <1 or >70 years
Anticoagulation contraindicated	No contraindications to anticoagulation
Good left ventricular function	Severe left ventricular dysfunction
Aortic stenosis	Aortic insufficiency
Small–normal aorta and aortic annulus	Larger than normal or dilated aorta or annulus
No pulmonic valve pathology	Pulmonic valve pathology
>20 Years life expectancy	Limited life expectancy
No other valvular disease	Other valvular disease present (e.g., mitral)
No systemic autoimmune disease present	Autoimmune disease

usually dictates that the root replacement technique be used. Additional minor considerations often come into play including patient age, associated medical conditions, physiologic reserve, suitability for anticoagulation, and underlying ventricular function, as the time on CPB is potentially long.

After 1988, there was a steady increase in the number of Ross procedures performed until the peak frequency in 1996, then a steady and small decline until 2000 (Fig. 35-10). The recent decline in the number of Ross procedures performed temporally coincides with the increased appreciation of abnormal flow dynamics across the components of the Ross repair, particularly the right ventricle to pulmonary artery conduit.

Technique

Since the initial description by Ross of the scalloped subcoronary implant, a number of modifications have been described, including the inclusion cylinder technique and the root replacement technique. These techniques are performed identically to those outlined above for aortic homografts. According to the Ross Procedure International Registry, the root replacement technique is the most

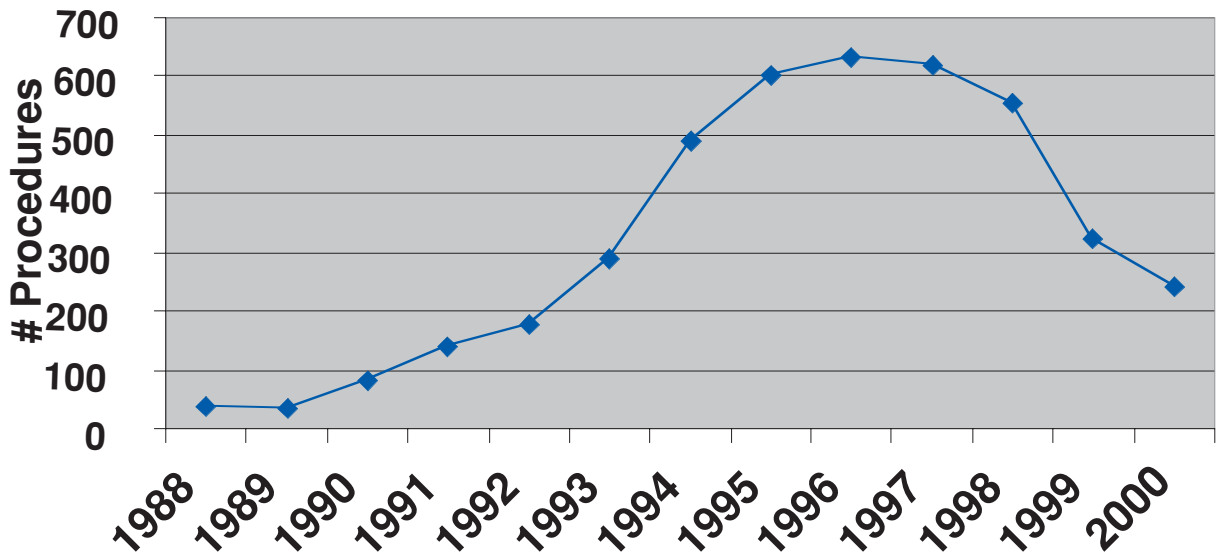

Figure 35-10. Ross procedures performed according to the Ross Registry 1988–2000. (*Adapted from the Ross Procedure International Registry; http://www.rossregistry.com.*)

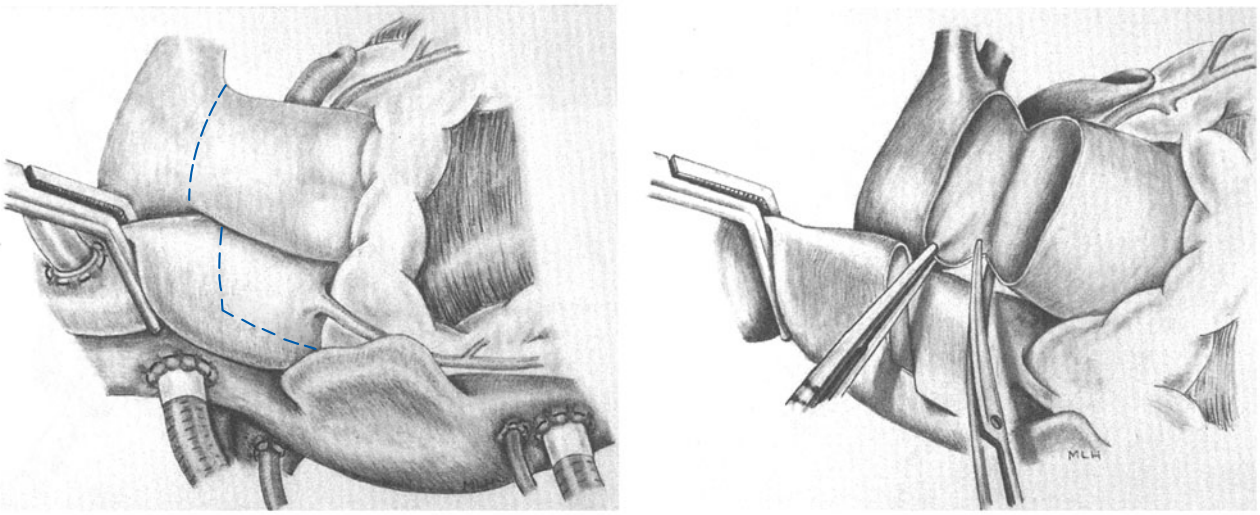

Figure 35-11. The distal pulmonary artery is incised at the origin of the right pulmonary artery. A transverse arteriotomy is made to allow careful inspection of the pulmonary artery. Shown from the surgeon's perspective, as though standing on the patient's right side. (*Reproduced with permission from Elkins RC: Aortic valve: Ross procedure, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

commonly performed variation owing to its superior versatility and possible decreased incidence of early and late graft failure.[65]

The conduct of the operation is similar to placement of an aortic homograft. Full CPB is utilized with arterial cannulation of the distal aorta. Again, the ventricular vent is placed through the right superior pulmonary vein. Cardioplegia is delivered antegrade and retrograde, via the coronary sinus catheter. A transverse or oblique reverse "lazy-S" aortotomy is performed similarly to placing an allograft. After retraction of the aorta, facilitated with stay sutures, the AV and root are inspected and the suitability of the pulmonary autograft for repair is confirmed. The AV is then excised, along with the coronary ostia as buttons. When the root replacement technique is used, the aortic root is excised as previously described for the allograft. Attention is then turned to the pulmonary artery (PA) and pulmonic valve.

The PA is mobilized to its bifurcation. The PA is then sharply divided transversely just proximal to the bifurcation (Fig. 35-11). This allows visual inspection of the pulmonic valve endoluminally, which is normally tricuspid, without fenestrations or atheroma (Fig. 35-12). The discovery of a bicuspid or quadricuspid valve, or the presence of large fenestrations or atheroma precludes use of the valve as an autograft. The mobilization of the PA then begins distally, near the transverse arteriotomy, and continues proximally toward the valve. The dissection is initiated posteriorly staying very close to the PA, taking care not to buttonhole the wall (Fig. 35-13). The left main

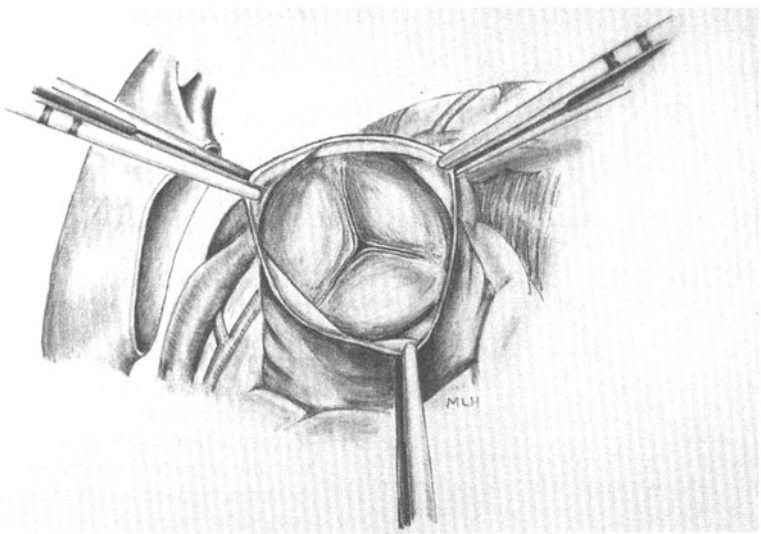

Figure 35-12. The normal trileaflet pulmonic valve with three equal sinuses and no fenestrations or other abnormalities. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

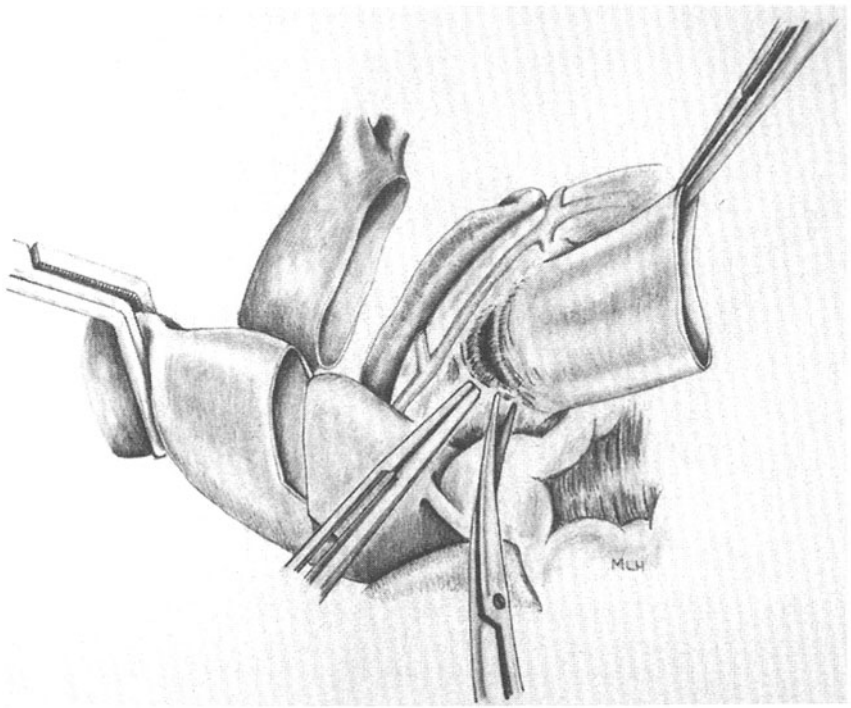

Figure 35-13. Dissection of the pulmonary autograft is initiated on the posterior aspect of the proximal pulmonary artery. Dissection is continued in this plane, adjacent to the pulmonary artery, until the septal myocardium is encountered. The left main coronary artery and left anterior descending artery are protected. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

coronary artery and its bifurcation into the left anterior descending (LAD) artery with the septal perforators, and circumflex arteries should be identified and avoided. When these are not easily appreciated, a probe may be placed into the left coronary os, through the aortotomy, to facilitate identification of the left main coronary artery and its branches. The dissection continues proximally until septal musculature is reached, taking care to avoid injury to the conal branch of the right coronary artery. A point 3 to 4 mm below the pulmonic annulus is identified, often facilitated by passing a probe through the pulmonic valve, and the right ventricular outflow tract (RVOT) is divided (Fig. 35-14). Where the RVOT meets the septum, the dissection must be kept superficial (i.e., on the right ventricular side) to avoid injury to the septal perforators of the LAD artery. The adventitia of the autograft is preserved. After complete

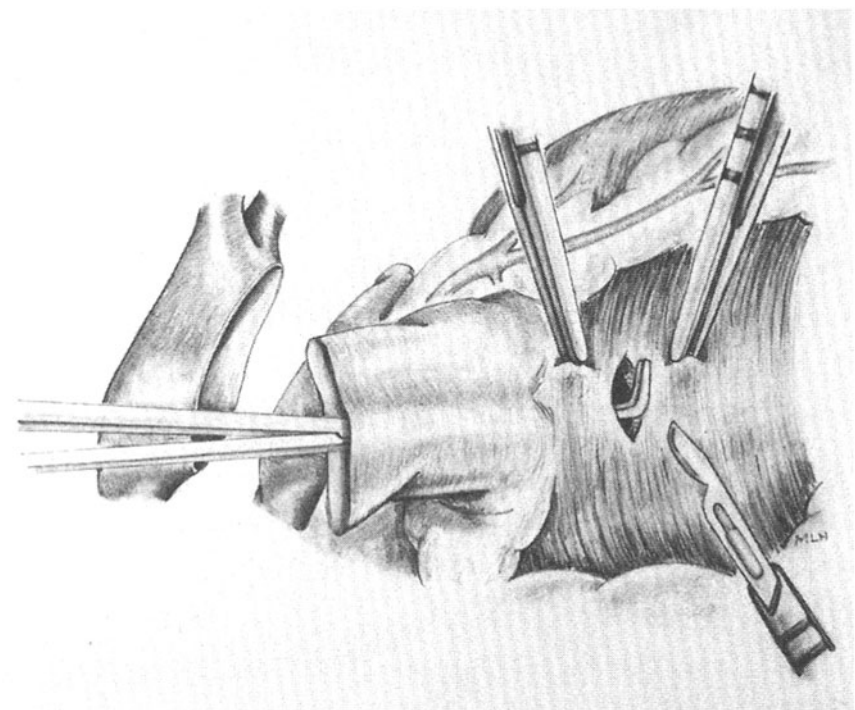

Figure 35-14. Identification of the anterior right ventriculotomy is facilitated by placement of a right-angled clamp through the pulmonary valve and indenting the myocardium 3 to 4 mm below the pulmonary valve annulus. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

division, the autograft is then accurately sized at its base, as well as the RVOT, and an appropriately sized allograft is obtained.

Root replacement technique

The autograft is oriented so that the posterior pulmonary sinus becomes the noncoronary sinus. The proximal suture line is performed first. In adults, this is performed with either everting pledgeted horizontal mattress 2-0 Ticron or a running 4-0 or 5-0 polypropylene. In children and adolescents, an absorbable monofilament suture (e.g., Maxon, Davis & Geck, Manati, Puerto Rico) is used, recognizing future growth of the autograft with the patient.[64] The left coronary artery is then implanted at the midpoint of the left coronary sinus, as previously described. Again, 5-0 polypropylene is used in adults and 6-0 Maxon is used in children. The distal suture line is then performed, after the autograft is trimmed 4 to 5 mm beyond the sinotubular junction of the autograft. A running 4-0 or 5-0 polypropylene suture is used in adults, while Maxon is used in children. The importance of similarly sized aortic and pulmonary valves has recently been suggested.[66] If a size or geometric mismatch between valves occurs, the diameter of the aortic annulus and/or sinotubular junction may be surgically reduced, with a reduction aortoplasty, as performed by Elkins.[67] Also, if the ascending aorta is aneurysmal, it may be replaced with an interposition Dacron graft bridging between the distal autograft and the ascending aorta just proximal to the innominate artery. This is followed by reimplantation of the right coronary artery, similar to that described for the left coronary artery. After the suture lines are inspected, the cross-clamp is removed and the operation is completed during rewarming.

A pulmonary homograft, oversized by 4 to 6 mm, is then obtained. The homograft is trimmed, and the proximal anastomosis is performed to the RVOT with running 4-0 polypropylene. Again, the left coronary artery and its branches lie close to the posterior aspect of the anastomosis, and sutures must be precisely placed in the endocardium to avoid kinking or injuring these structures. The distal suture line is then completed with a running 4-0 or 5-0 polypropylene suture. De-airing and weaning of CPB is performed in a standard fashion.

Inclusion cylinder technique

The inclusion cylinder technique is nearly identical to that previously described for the allograft (Figs. 35-15 and 35-16).

Results

Ross initially reported his results in 1991, setting the standard for outcomes after the Ross procedure.[68] He reported follow-up in 339 patients up to 24 years with an 80% survival and an 85% freedom from reoperation. More recently, a longer follow-up report from this initial series included 131 patients (long-term survivors) with a mean follow-up of 20 years (range 9 to 26 years).[69] In this report, freedom from reoperation was 76 and 62% at 10 and 20 years, respectively. Freedom from autograft replacement was 88 and 75% at 10 and 20 years, respectively. The main indication prompting autograft replacement was severe regurgitation in 28/30 patients. At 25 years, the pulmonary homograft was free of replacement in 69% of patients. Indeed, these outcome results have set the benchmark for AV repairs using autologous pulmonic valve. It is worth noting that most of the patients in Ross' series were repaired by the scalloped subcoronary implant technique, whereas the root replacement technique is the most commonly performed technique today.

Current data from the Ross Registry resemble Ross' initial results with a 68% survival, 84% freedom from RVOT repair/replacement, and an 82% freedom from autograft explant over 25 years.

Operative risk

With increasing experience and improved perioperative care, operative risk has declined since Ross first described this procedure. According to the International Ross Registry, overall perioperative mortality (i.e., <30 days) is now 4.1% (129 deaths in 3922 patients). Although 4.1% perioperative mortality is acceptable for some cardiac operations, many believe it is unacceptably high for the younger patients who are most often subjected to the Ross procedure. This controversial point highlights the need for individualized therapy with respect to valve replacement through consideration of all the risks and benefits associated with the available options. We do not believe that the risks of the Ross procedure are prohibitive in appropriately selected patients. Furthermore, as more experience is gained with this procedure, a volume-outcome relationship may be apparent, supporting regional specialization and referrals to "centers of excellence."

Pulmonary autograft dysfunction

Early autograft dysfunction occurs infrequently. Elkins reported early autograft dysfunction (<6 months) in 3/195 patients (1.5%).[64]

Late autograft dysfunction is an increasingly recognized phenomenon following the Ross procedure, although few studies have followed patients longitudinally with routine evaluations. A recent report of midterm follow-up (mean 2.47 years) in 132 consecutive patients who underwent routine echocardiographic evaluations of the pulmonary autograft revealed mild aortic insufficiency (graded 1/4) in 39.2 to 53.6% of patients, depending on follow-up interval.[70] Three percent of patients had moderate insufficiency early after surgery, increasing to 14.3% at 5 years. The mean transvalvular gradient across the AV was minimal (3 mm Hg) early and remained stable during follow-up.

In Elkins' series of 289 patients, 6% of the patients (16 patients) required autograft reoperation.[64] In the patients who received root replacement implants, 97% had no change in autograft function during follow-up, while only 1% had severe insufficiency (3+). In contrast, of those who received scalloped subcoronary or inclusion cylinder implants, 86% had no change in autograft function, while 8% had progressed to severe insufficiency (3+).

David and associates have provided additional insight into late autograft dysfunction following the Ross procedure,

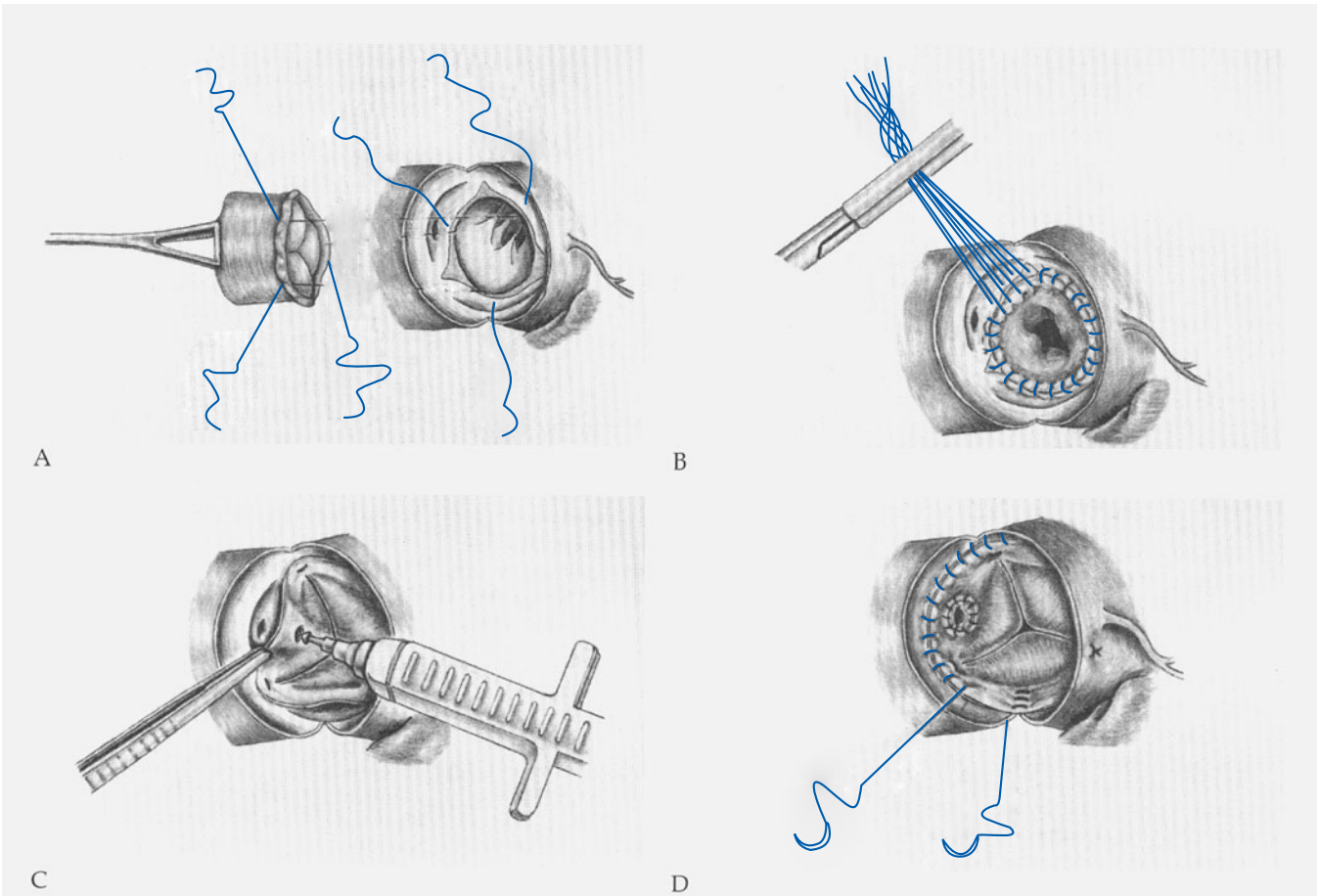

Figure 35-15. Inclusion cylinder technique. (A) Placement of three polypropylene sutures to orient the pulmonary autograft. The posterior sinus of the pulmonary autograft becomes the new left coronary sinus. (B) The autograft is inverted into the left ventricle and the proximal sutures are tied and divided. (C) The pulmonary autograft is reinverted. Horizontal mattress sutures are placed to secure the height and position of the autograft (but not tied until the right and left coronary arteries are implanted). An aortic punch (4 or 5 mm) is used to create an opening in the autograft to allow attachment of the coronary artery ostia. (D) Completion of coronary artery anastomosis. Commissural stay sutures are tied and divided, and the distal suture line is initiated at the commissure between the left and right coronary artery. This is continued to the aortotomy extension into the noncoronary sinus. This portion of the aortotomy is closed with a running suture line with the suture including a full-thickness bite of the noncoronary sinus of the pulmonary autograft. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

by assessing dilatation of the pulmonary autograft after the Ross procedure.[71] From 1990 to 1997, 118 patients with a mean age of 34 (17 to 57) underwent the Ross procedure. Of note, if there was ≥2 mm size mismatch between the aortic and pulmonic sinotubular junction or annuli, they were surgically reduced prior to implantation. The root replacement technique was most commonly used (71/118, 60%), followed by the root inclusion technique (45/118, 38%), and the subcoronary implant least commonly (2/118, 1.7%). Follow-up was 12 to 96 months (mean 44 months) including annual echocardiography. Over the observation period the diameter of the sinuses of Valsalva significantly increased from 31.4 to 33.7 mm. Furthermore, with respect to operative techniques, aortic root replacement was significantly positively correlated with increased risk of dilatation. No interpretable changes were seen in the aortic annulus over time. However, the diameter of the sinotubular junction increased in patients who had aortic root replacement and decreased in those subjected to root inclusion technique. During the observation period, only 5.9% (7/118) of patients developed moderate AI. However, all the patients with AI had dilatation of the aortic annulus and/or the sinotubular junction.

Taken together, these data indicate that the autologous pulmonic valve in the aortic position is quite durable and able to withstand the increased stresses at this position. Furthermore, although the valve effective orifice area (EOA) does not seem to change, up to 50% of patients may develop mild AI, which seems to increase with time, likely resulting from dilatation of the pulmonary autograft sinotubular junction and/or sinuses of Valsalva. Although it is suggested that this may be affected by surgical technique, it is unclear whether the use of the root replacement technique or root inclusion

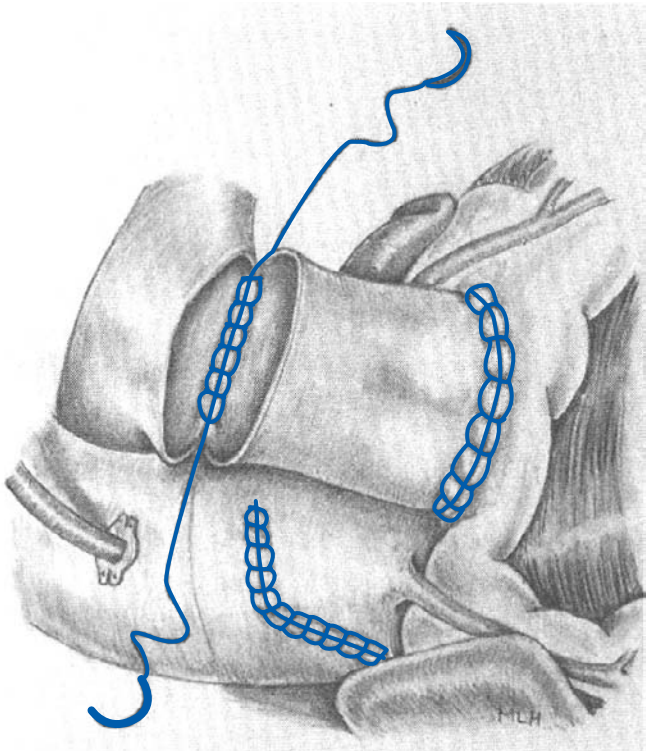

Figure 35-16. Completion of the closure of the aortotomy for the inclusion cylinder technique. The aortic cross-clamp is removed. The pulmonary homograft reconstruction of the outflow tract is accomplished with two continuous sutures of polypropylene. The proximal suture line is completed first. (*Reproduced with permission from Schaff HV, Cable DG: Aortic valve replacement with homograft, in Kaiser LR, Kron IL, Spray TL (eds): Mastery of Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1998.*)

technique impacts the development of late pulmonary autograft dysfunction. Additional investigation is needed to elucidate risk factors for this complication and surgical interventions that may attenuate the frequency (e.g., reduction aortoplasty or Dacron banding of the aortic annulus and sinotubular junction).

Homograft dysfunction

Although the cryopreserved homograft has many advantages for a right ventricle to pulmonary artery conduit, it has become increasingly clear that it is susceptible to stenosis, degeneration, and calcification. Since current cryopreservation techniques result in varying degrees of donor cell viability, these effects may be immunologically mediated, although this remains controversial.[72] Again, the precise incidence of this phenomenon is likely underappreciated due to lack of routine echocardiographic screening.

Midterm echocardiographic follow-up results of 132 patients (mean follow-up 2.47 years) after the Ross procedure demonstrated early minimal transvalvular gradients (3 $\pm$ 4 mm Hg) with significant worsening (+6 $\pm$ 8 mm Hg) over time.[70] Furthermore, there was decreasing valve EOA (-0.74 ± 0.82 cm^2), mostly within the first 6 months. This resulted in 19.3% of patients having an EOA index of <0.85 cm^2/m^2 at 1-year follow-up. Put another way, after 2 years the pulmonary valve EOAs were, on average, 31% less than immediately following surgery. Through multivariate analysis, only small homograft size and hypertension were found to be significant negative predictors of EOA at 1 year follow-up.

Raanani and colleagues followed 109 consecutive patients after the Ross procedure to identify the incidence and risk factors for homograft stenosis.[73] Echocardiographic follow-up (mean 39 $\pm$ 20 months) was available in 105 (97%) patients. The primary abnormality identified was homograft stenosis. In support, they identified a peak systolic transvalvular gradient of $>$20 mm Hg in 28.5% (30/105) of patients and $>$40 mm Hg peak gradient in 3.8% (4/105) of patients. This obstruction occurred at all levels of the homograft, as opposed to just at anastomotic sites, and was associated with homograft thickening. Moderate or severe homograft insufficiency was identified in 9.5% (10/105) of patients. Through multivariate analysis, the only independent significant predictors of homograft stenosis were cryopreservation duration $<$20 months, donor age $<$30 years, and small homograft size, which approached statistical significance.

Taken together, these data indicate that pulmonary homograft stenosis may develop in up to 30% of patients following the Ross operation. More importantly, the clinical significance of these data is not clear. For example, in the context of congenital pulmonary stenosis, it appears that peak transvalvular gradients of $<$50 mm Hg are usually well tolerated.[74] However, it would be erroneous to extrapolate these data to the demographic of the Ross procedure, as many of these patients are into adulthood when they undergo this procedure. Furthermore, similar to the pulmonic autograft in the aortic position, the incidence and severity of pulmonic insufficiency appears to increase with time. Clearly, these data suggest that future endeavors to improve the Ross procedure should be directed to elucidating the mechanisms underlying the pulmonary homograft stenosis and toward therapy to minimize these untoward effects.

SUMMARY

The search for the ideal valve to replace the diseased AV is ongoing and available techniques are imperfect. Nonetheless, the Ross operation, whereby the pulmonic valve is transposed to the aortic position and the RVOT is replaced with cryopreserved allograft (most commonly), has proven to be a durable solution for complex congenital abnormalities and disease isolated to the AV, particularly in children and young adults.

Observations of the long-term durability of the pulmonic autograft in the aortic position affirm its ability to withstand the increased physical stresses at this location and maintain near normal hemodynamics over time, making it an excellent choice for replacement of a diseased AV. The incidence of AI is low and increases with time, likely resulting from dilatation of the pulmonary autograft sinotubular junction and/or the sinuses of Valsalva. Further

studies are needed to discern the risk factors for this occurrence, but utilizing the root replacement technique compared to the root inclusion technique may affect it.

The allograft in the pulmonic position is more susceptible to complications, namely stenosis, which occurs primarily within the first year. Up to 30% of patients may have a hemodynamically significant stenosis at this location that is likely immunologically mediated, though the clinical significance of these findings remains unclear. Small homograft size is consistently a risk factor for stenosis, thereby supporting the current practice of oversizing the homograft by 2 to 3 mm. Future attempts to improve outcome after the Ross procedure should be directed toward reducing homograft stenosis.

The Ross procedure remains a reasonable option for replacement of the diseased AV, particularly in children and young adults. For adults, given the alternatives for AV and root replacement, the utility of the pulmonary autograft is more limited. As longer follow-up continues to accumulate, the risks and benefits of this procedure relative to other treatment options for replacement of a diseased AV will be better characterized.

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CHAPTER 36

Stentless Aortic Valve Replacement: Porcine and Pericardial

Paul Stelzer

HISTORY AND CONCEPT

The concept of replacing the aortic valve with a stentless device is not new. The very first replacement of the aortic valve ever done in the anatomic position was done with a stentless device, namely the aortic homograft.[1] However, because of the lack of availability and the logistics of preservation and distribution, homograft (human donor) valves and conduits were not a practical option for the majority of patients requiring aortic valve replacement. Initial attempts to expand the possibilities by using xenograft valves were fashioned on the freehand subcoronary homograft model.[2] Subsequent replacement devices that incorporated a support structure for mechanical or tissue valves were easier to implant but intrinsically obstructive by taking up space in the aortic annulus. With this history in mind, Tirone David first proposed and helped develop a modern-day heterograft equivalent which ultimately became the Toronto SPV (stentless porcine valve) (St. Jude Medical, Inc., St. Paul, MN).[3] From the beginning, it was appreciated that eliminating the stented support frame and sewing ring would eliminate some problems and create new ones. Not the least of these would be the need for different surgical techniques for implantation and the need to deal with the unpredictable changes in aortic root geometry on which the competency of these valves would often depend over time.

The logical place to begin was with a glutaraldehyde-preserved porcine aortic root simply extracting the valve in one piece from the root. Scalloping out the porcine sinuses of Valsalva and thinning down the porcine septal muscle left a structure that was friable in places, leading to the external polyester fabric covering which extends from the annulus to the top of each commissure of the Toronto SPV. The factory-prepared porcine tissue removed the need for muscle trimming by the surgeon and proved to be much less "floppy" and easier to handle than the homograft valve. However, it shared issues of sizing and the influence of more than just the annulus to support its function. So important was the influence of the native sinotubular junction (STJ) to the competence of the stentless valve that sizing was felt more appropriately based on this dimension than on the annulus itself. The patient with marked discrepancy between annulus and STJ became a challenge for this type of valve, requiring tailoring of the STJ or use of an alternative device.

Recognizing the range of aortic root variability and disease of the root itself, the concept of stentless valve replacement was expanded to replacement of the entire aortic root, paralleling the homograft experience.[4] This required development of entirely new technology to prepare and test porcine aortic roots to be used as total aortic root replacement. The Medtronic Freestyle Aortic Root Bioprosthesis (Medtronic Inc., Minneapolis, MN) and the Edwards Prima (Edwards Lifesciences LLC, Irvine, CA) provided alternatives that allowed the surgeon to use the entire root, modify it for intra-aortic use as an inclusion cylinder (root inclusion), or scallop it for a subcoronary implant. The subcoronary technique could be modified to leave the noncoronary sinus wall of the porcine root intact, which gave more predictable support to two of the three commissures.

The flexibility of these devices made them more broadly useful, but with flexibility inevitably comes complexity and initial enthusiasm was dampened by the perception of increased risk and technical difficulty. Early adopters became facile with experience while skeptics lauded the improvements in the simpler stented devices as equivalent to the advantages of stentless valves. With the advent of full root replacement with a bioprosthesis came the challenges of hemostasis and coronary reimplantation inherent in all aortic root surgery. The hemodynamic and potential durability advantages already proven for the aortic homograft root[5] were envisioned for the stentless porcine roots, but acceptance was slowed by risk/benefit ratio concerns. An early comparison of full root aortic homografts and the porcine stentless equivalent showed very favorable results for the

much more available bioprosthesis.[6] Surgeons experienced in root replacement found the stentless porcine root a logical extension of the scarce homograft and a welcome alternative to mechanical valved conduits or the more cumbersome proposition of sewing a stented or stentless tissue valve into a vascular graft.

DURABILITY ISSUES

General Considerations

One of the foremost concerns of any tissue valve is that of durability. From the very first experience with porcine valves, the Achilles heel of heterograft tissue has been structural degeneration, usually from calcification. This proved to be particularly true in the very young, for reasons which remain elusive. Improvements in tissue preservation technology were applied to both stented and stentless valves as they became available. Stentless porcine valves have the additional consideration of the porcine aortic wall which is an integral part of the device in addition to the leaflets themselves. This tissue does not respond in the same way as do the leaflets because of inherently different cellular and stromal structure. Devices made partially or wholly from bovine pericardium share many of the same constraints as porcine leaflets but not all to the same extent.

Impact of Fixation Pressure

Porcine valves were initially fixed in low concentrations of glutaraldehyde at high pressure (60 to 80 mm Hg) but later at low pressure (2 to 5 mm Hg). Attempts to demonstrate durability benefits of the lower pressure fixation have been inconclusive. The concept of zero-pressure fixation was first introduced in the Medtronic Freestyle, the total root design of which allowed instillation of glutaraldehyde solution from either end of the root at 40 mm Hg (diastolic pressure of the pig), which led to the term "physiologic pressure fixation," while the aortic leaflets were suspended in the middle with pressure on either side of the leaflet balanced out to zero.[7] The goal of this method was to preserve more normal morphology of the leaflets, which would allow more natural bending patterns through the cardiac cycle. Using a combination of accelerated wear testing in a pulse duplicator and biaxial mechanical testing of the tissue, Christie and colleagues demonstrated better preservation of both circumferential and radial stretch in the Freestyle leaflets compared to leaflets fixed even at low pressure, which flattens the native collagen crimp.[8]

Antimineralization

Antimineralization techniques were also introduced about the same time as the stentless valves. XenoLogiX (Edwards Lifesciences, Irvine, CA), No-React (Shelhigh, Inc., Union, NJ), AOA (two-alpha-amino oleic acid) (Biomedical Design, Inc., Atlanta, GA), and BiLinx (St. Jude Medical, Inc., St. Paul, MN) are among the agents used to mitigate the calcium deposition so often seen to hasten tissue valve degeneration. The juvenile sheep model and the rat subcutaneous implant model are the typical proving grounds for these methods before clinical application. An excellent review of ongoing efforts to solve the calcification problem was done by Schoen and Levy, the highlights of which follow.[9]

Surfactants such as sodium dodecyl sulfate act as detergents which largely remove acidic phospholipids from the cell membranes where calcium ions are known to react and form calcium phosphates. AOA binds in a covalent fashion through its amino linkage to residual aldehyde moieties in the tissue to inhibit calcium flux through the tissue. This agent has proven very effective at mitigating calcium deposition in porcine leaflets, but not aortic wall in rat subdermal implants.[10] Clinically, it seems to have positive effects on both, though less so on the aortic wall.

The proprietary No-React treatment was developed by Gabbay and colleagues.[11] It is reportedly a combination of aldehyde-based cross-linkage followed by a detoxification process and use of a surfactant. Despite good performance in the subdermal rat implants, extensive fibrous sheathing leading to cusp retraction was seen as well as failure to prevent calcification in the sheep model.[12]

Trivalent metal ions represented by iron (FeCl3) and aluminum (AlCl3) inhibit calcification of both pericardium and porcine cusps in the subdermal implant model. Part of this action may be due to complex formation with phosphates, decreasing their availability for calcium phosphate formation. They also inhibit the activity of alkaline phosphatase, which may be involved in the initial calcification process. Additional benefit from aluminum may come from its demonstrated ability to prevent calcification of elastin, a major molecule in porcine aortic wall whose structure is permanently altered by the trivalent aluminum ion. Aluminum is an essential part of the BiLinx treatment. The safety of using aluminum in this way has been demonstrated clinically in the new Toronto Root Bioprosthesis (St. Jude Medical, Inc., St. Paul, MN) with no change in serum aluminum levels at 6 months.[13]

Ethanol (80%) can be used to remove cell wall phospholipids and cholesterol from tissues treated with glutaraldehyde.[14] Ethanol is an active component of St. Jude's BiLinx and Edwards' XenologiX treatment, which has been shown experimentally to remove over 90% of phospholipids in both bovine pericardium and porcine leaflet tissue as a way of reducing sites for calcium attachment in vivo.[15]

Novel techniques such as dye-mediated photooxidation have been developed to provide alternative fixation methods which avoid glutaraldehyde altogether.[16] This method has been shown to prevent calcification in both leaflets and aortic wall in a bovine implant model at 3 and 6 months.[17] Clinical use of this method has not been pursued.

Combination treatments may hold the key to addressing the issue of differential behavior of the aortic wall and aortic leaflets in response to these calcium mitigants. A combination of AOA followed by ethylcarbodiimide treatment

takes advantage of both the amino and the carboxyl groups of the AOA for cross-linking and decreases calcification in both leaflets and aortic wall in the rat subdermal implant model.[18]

Development and clinical application of new methods of increasing tissue durability is an ongoing process. Animal models have proven helpful, but careful pathologic examination of explanted devices is essential, as only the human body provides the ultimate test of bioprosthetic durability.

Intrinsic Durability Advantage of Stentless Design

In addition to the fixation and calcium-mitigating treatments, the stentless valves have an additional theoretical durability advantage over stented valves. The intrinsically obstructive nature of the stented valves creates turbulent flow patterns through the left ventricular outflow tract into the proximal aorta which are not seen in the normal aortic root. Normal laminar flow patterns with reverse flow eddy currents in the sinuses of Valsalva are seen in stentless valve replacements. The lack of turbulent flow and presence of the eddy patterns which enhance gentle leaflet closure decrease the opening and closing stresses on both the commissures and the body of the leaflets. Any decrease in mechanical stress to these areas has a positive impact on durability. The best way to avoid mechanical stresses on the leaflets as well as optimizing their function may well be to use the full root replacement technique which has been shown to have durability and competency advantages over the long term with aortic homografts by O'Brien and colleagues in Brisbane, Australia.[19]

The Test of Time

Always in the minds of advocates and critics alike is the paradox of potential harm that may offset any potential long-term benefit. Most valves of either stentless or stented variety will last 7 years or longer. The real test of time does not come into the equation until 10 to 15 years. Therein lies the dilemma of adopting new techniques or devices long before data are available for the long term. Fully 13 years after the first modern stentless porcine valve was implanted, Jamieson predicted "The long-term performance advantages or disadvantages of stentless bioprostheses compared to stented bioprostheses will require at least another 5 to 7 years of cumulative stentless bioprostheses experience."[20]

Risk of Reoperation

Durability is important in tissue valves of any kind, primarily to avoid the undesirable event of reoperation. This must be taken into the perspective of other undesirable events with alternative (mechanical) valves, namely the double-edged sword of thromboembolic phenomena and anticoagulant-related hemorrhage. This is particularly important in the younger age group most likely to require reoperation if a tissue valve is implanted and most likely to participate in contact sports with greater injury potential. In a review of experience with 332 patients between the ages of 45 and 65 the group at Laval Hospital in Quebec City showed excellent survival and freedom from adverse events at 7 years across the tissue spectrum including 140 Freestyle, 54 aortic homografts, 76 Ross procedures, and 62 stented xenografts.[21] Freedom from bleeding, stroke, and endocarditis were >95% in all groups. Advances in reoperative techniques including anesthesia, perfusion, and myocardial protection strategies have made the prospect of a second valve replacement much less onerous than it was 20 years ago. In addition, simple maneuvers such as closing the pericardium at the first operation make sternal re-entry much safer for a second. With this in mind, there has been decreased use of the Ross procedure in the 40 to 60 age group in favor of stentless valves which are simpler. The perfect Ross may last for 40 years, but two operations with stentless valves may accomplish the same thing. (A home run has no scoring advantage over two doubles as long as the latter are both hit in the same inning.)

CLINICAL RESULTS

Hemodynamics, Survival, and Left Ventricular Mass Regression

Durability aside, the major potential advantage of the stentless valve is to more closely approximate the optimal hemodynamics of the normal human valve. A 10-year experience with 321 patients compared subcoronary stentless porcine with subcoronary aortic homograft valves. There were no differences detected at a mean of 4.9 years in survival, reoperation, endocarditis, or structural degeneration.[22] Coupled with those outcome measures are the dependent effects on left ventricular hypertrophy and mass regression and subsequent survival advantage. It is well known that virtually all the alternatives for replacing a highly stenotic aortic valve result in regression of left ventricular mass (LVM).[23] In a case-match study comparing the earliest years of the Toronto SPV to the Hancock II stented valve, David found a survival advantage at 8 years for the stentless device: 91 versus 69% ($p < 0.006$).[24] He felt this was due to superior hemodynamics of the stentless valve.

Westaby and colleagues with the independent statistical help of Grunkemeier compared survival in a group of 160 consecutive patients with subcoronary Freestyle valve implants with 247 contemporaneously matched patients with stented Carpentier-Edwards porcine valves. They found at 5 years a significant advantage in the stentless Freestyle group with 84% survival versus 69% in the stented group.[25]

In a 10-year retrospective review of 145 Toronto stentless patients and 106 Carpentier-Edwards stented patients, Van Nooten and colleagues in Belgium showed similar mass regression in the two groups, but there was a significant midterm survival advantage in the stentless group (84 versus 74% at 4 years and 78 versus 68% at 6 years; $p < 0.001$).[26] In a related publication this group explained

that the mass regression had a nadir at 3 years and an interesting slow increase which began at 5 years correlated with systemic hypertension in this age group.[27]

In Leipzig a slightly smaller study (but prospectively randomized) between 106 stentless and 74 stented aortic valves for aortic stenosis, the regression of LVM index at 6 months was significantly greater for the stentless group ($p < 0.05$).[28] The authors postulated the difference was due to better transvalvular hemodynamics.

An early study done in London showed the stentless porcine valve (Toronto SPV) to be equivalent to the aortic homograft and both to be superior to either stented or mechanical valves in measures of left ventricular recovery. These included mass regression, wall thickening, fractional shortening, and even diastolic relaxation by greater peak velocity of dimension lengthening.[29] Significant improvement occurred in all patients, but that improvement was greater and faster in the stentless/homograft group.

Cardiac magnetic resonance imaging (MRI) is more precise in measuring LVM than echocardiography, but is more difficult and costly to obtain. A small but prospectively randomized study of 39 patients found the expected significant LVM reduction at 6 months after aortic valve replacement (AVR) for aortic stenosis, with the degree of regression independent of prosthesis choices including stentless, stented, and mechanical valves.[30]

Carefully documented comparisons of stented and stentless valves is sparse in terms of exercise hemodynamics and quality-of-life measurements. A small study at St. Thomas' Hospital in London compared 21 patients with Toronto stentless valves to 29 patients with Perimount (Edwards Lifesciences LLP, Irvine, CA) stented valves using bicycle ergometry. They could detect no statistically significant differences between the two valve types in peak velocity, mean pressure difference, or effective orifice area at rest or on peak exercise.[31]

Operative Risk and Long-Term Complications

In order to take advantage of any potential hemodynamic and survival advantage of a stentless device, the operative risk must be low and the risk of adverse valve-related events also low, such as thromboembolism (TE), endocarditis, structural degeneration, and reoperation. In a large experience (404 patients) in Leicester, England, with 11 types of stentless valves (221 Medtronic Freestyle, 55 Shelhigh, 33 Shelhigh Composite conduits, 25 Sorin, 25 CryoLife O'Brien, 17 Aortec-Elan, and 5 others) by a single surgeon (A. W. Sosnowski) over 5 years showed an overall early mortality of only 4.2%.[32] The risk of isolated AVR was only 2.4%, that with concomitant coronary artery bypass graft (CABG) only 3.6%, and rates were higher for multiple valve surgery or Bentall procedures. Regression analysis revealed the usual predictors of operative death—ejection fraction (EF) <30%, active endocarditis, redo surgery, and cardiogenic shock. The only procedure-related risk was the Bentall operation. Five-year freedom from endocarditis, TE, hemorrhage, and reoperation ranged from 96 to 99%, with actuarial survival of 88%. These authors considered the stentless aortic valve to be the operation of choice for patients over 60 years of age.

The outcome bar has been set very high by O'Brien, who reported a remarkably low 30-day mortality rate of only 0.99% in a consecutive series of 402 patients over 10 years.[33] This was done in a typically older population (average age 73.5 years) with nearly one-half (46%) requiring concomitant CABG. Actuarial survival at 8 years was 70.8 ± 7.1%. The incidence of thromboembolic complications was rigidly documented (56 episodes in 40 patients), which led to permanent neurologic damage in only 18 patients. Of nine patients who developed endocarditis, five maintained complete competence of the replacement valve and three were cured of infection without surgery. Freedom from reoperation at 8 years was 96.7 ± 2.1%. A fascinating magnetic resonance study of 10 patients several years after surgery showed another potential benefit of this particular valve. Physiologic systolic stretching of the aortic annulus was restored.

Use of the full root replacement technique has been tempered by documented higher operative mortality rates in early series.[34] However, under the leadership of the superb aortic surgeon Hans Joachim Schafers, the team at Homburg-Saar, Germany, had excellent results despite a spectrum of serious aortic and associated problems. Overall mortality was 6.7% in a group of 149 that required replacement not only of the root, but of the ascending aorta in 22% and the arch in 13% with 32% requiring coronary bypass. The isolated aortic valve disease patients had only 1.8% mortality risk.[35]

IMPLANT TECHNIQUES

Subcoronary and Modified Subcoronary

It may seem too obviously simple, but the use of a transverse aortotomy as opposed to an oblique one is a distinct advantage in using the stentless valves. Early experience in South Africa with the Biocor stentless valve showed crowding of the two commissures on either side of an oblique aortotomy carried down into the noncoronary sinus.[36] Closure of the aortotomy caused a decrease in the effective size of the noncoronary sinus, pushing the two adjacent porcine commissures toward each other. Since the three-dimensional geometry of the native aortic root becomes a part of the functional geometry of the stentless valve, it makes sense to leave this structure as intact as possible.

Even a transverse aortotomy can be a problem if made too close to the sinotubular junction. At least 1 to 1.5 cm of clearance is needed to place the stentless device within the root and still close it above the tips of the commissures of the new valve. Complete transsection of the aorta is often helpful in gaining full exposure for implantation.

The proximal suture line is usually done with simple interrupted technique using 2-0 to 4-0 braided sutures. Approximately 20 to 30 sutures are used depending on the

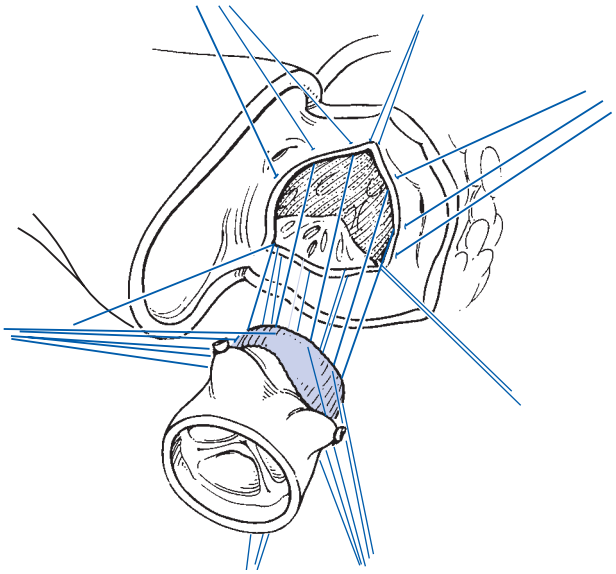

Figure 36-1. Modified subcoronary technique—proximal suture line. Interrupted sutures are placed in a circular plane coursing through the annulus itself at the lowest point of each sinus, but well below the commissures except anteriorly where the conduction system must be avoided. These are best organized on suture guides alternating colors, then divided in thirds and passed through the inflow end of the stentless valve. (*Modified and reproduced with permission from Kon ND, Westaby S, Amarasena N, et al: Comparison of implantation techniques using Freestyle stentless porcine aortic valve. Ann Thorac Surg 1995; 59:857.*)

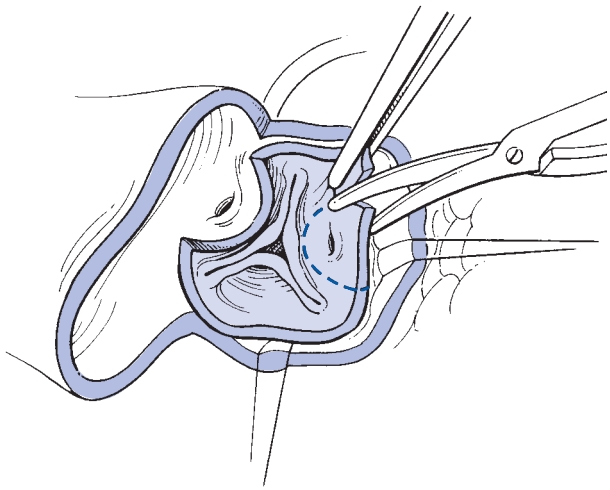

Figure 36-2. Modified subcoronary technique—preparing the sinuses. Either before or after the device is slid down and the proximal sutures tied, the sinuses facing the native left and right coronary ostia are scalloped out below the level of those recipient coronaries. Care is taken to avoid cutting into any cloth covering or getting too close to the leaflets of the new valve. (*Modified and reproduced with permission from Kon ND, Westaby S, Amarasena N, et al: Comparison of implantation techniques using Freestyle stentless porcine aortic valve. Ann Thorac Surg 1995; 59:857.*)

size of the annulus (Fig. 36-1). Suture guides are very helpful in keeping these many sutures organized. The device is parachuted down into the root and the sutures tied and cut. The right and left sinuses are scalloped out either before or after this step (Fig. 36-2). A distal suture line of continuous small (4-0) caliber polypropylene suture is then constructed coursing below the coronary ostia, taking care not to buckle the stentless tissue or distort the positions of the commissural posts. Stay sutures can be placed at the top of each commissure to help maintain orientation. One suture is begun at the bottom of the left and another at the bottom of the right sinus and run up to the top of each commissure (Fig. 36-3). The porcine tissue and especially the cloth-covered portion of some devices must not encroach on the ostium of either coronary, as obstructive granulation tissue may form in this location. The top of the device is trimmed down to the level of the native aorta, taking care to stay above the top of each commissure. If the noncoronary sinus of the stentless valve is kept intact, the distal suture line can be completed by running along the top to join the two sutures. The aortotomy is closed with continuous suture incorporating the tops of the commissures and the retained noncoronary sinus edge. The completed concept of the complete and modified subcoronary implant technique is shown in Figs. 36-4 and 36-5.

Alternative methods of attaching the proximal end of a subcoronary implant were examined in Hungary using 102 Sorin Pericarbon stentless pericardial valves. It took

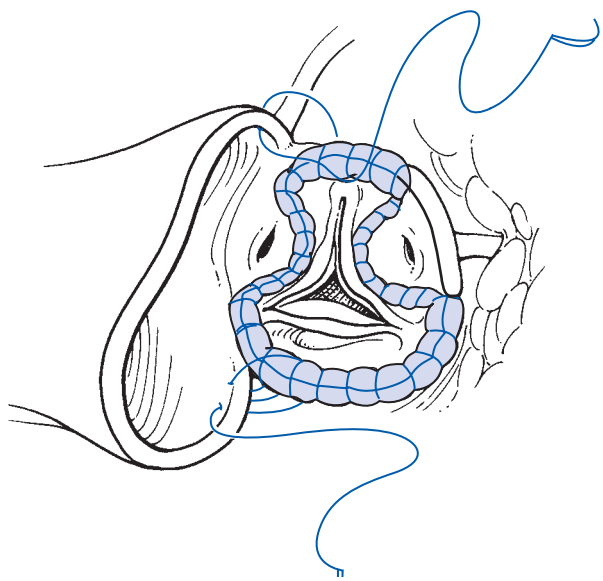

Figure 36-3. Modified subcoronary technique—distal suture line. A continuous 4-0 polypropylene suture is begun in the bottom of each sinus below the coronary ostium. This is brought around and up to the top of the adjacent commissures, where the top of the device is trimmed down to the level of the native aorta to allow completion of the suture line. This demonstrates the completed distal suture line and beginning of the aortic closure which incorporates the tops of the commissures again as well as the top of the retained noncoronary sinus. (*Modified and reproduced with permission from Kon ND, Westaby S, Amarasena N, et al: Comparison of implantation techniques using Freestyle stentless porcine aortic valve. Ann Thorac Surg 1995; 59:857.*)

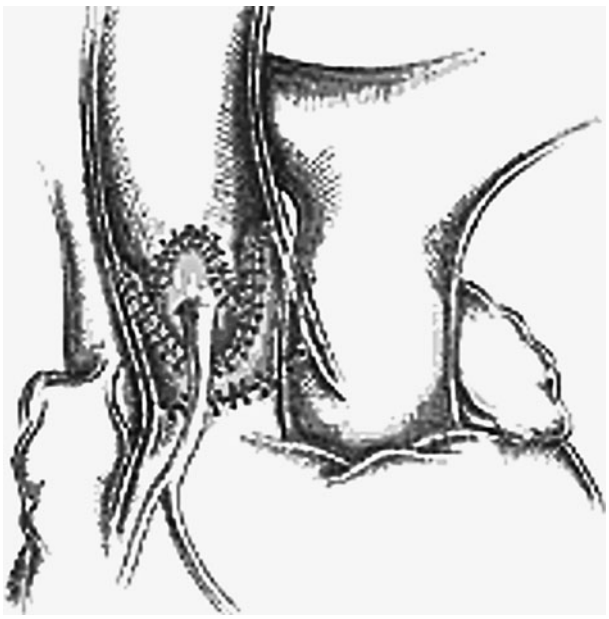

Figure 36-4. Subcoronary technique—final appearance. (*Used with permission of Medtronic Inc., Minneapolis, MN.*)

longer to use interrupted simple sutures than either interrupted mattress or continuous sutures, but there was no difference in operative mortality or transvalvular gradients in follow-up.[37]

An expanding hematoma in the space between the native and the porcine noncoronary sinus walls is undesirable, but a small fixed collection in this area usually resorbs over time. One technique to minimize this problem is to rotate the Freestyle root 120° to put the porcine right coronary stump in the patient's noncoronary sinus. A small cut in the sinus allows the porcine stump to be extruded to the outside of the native sinus where it is secured with a pledgeted mattress suture of 4-0 polypropylene.

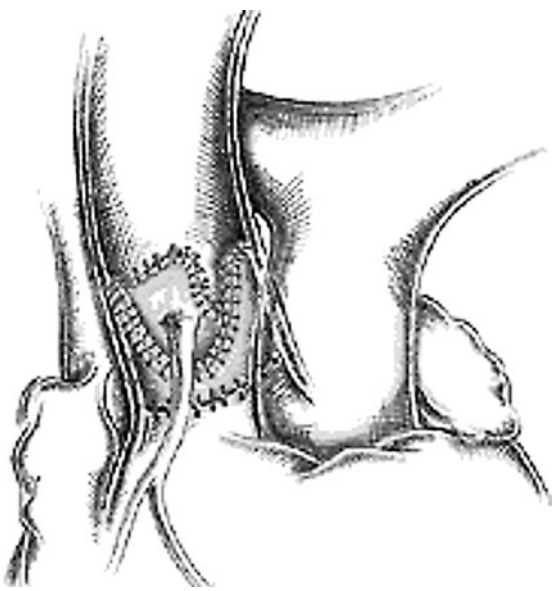

Figure 36-5. Modified subcoronary technique—final appearance. (*Used with permission of Medtronic Inc., Minneapolis, MN.*)

The subcoronary method has been preferred by most early adopters of the stentless valve since the first available, the Toronto SPV, was a completely scalloped device which required this method of implantation. Various technical observations have been made with experience to deal with the issue of sizing, which is very important with these valves. If the size chosen is too small, the inflow end becomes needlessly obstructive and the outflow end is stretched out to reach the native commissures with decreased leaflet coaptation and more regurgitation as a result. Oversizing to fit a larger sinotubular junction leads to buckling of the inflow end which can produce both relative stenosis and regurgitation as well as harmful turbulent flow. In short, how the device is sized and implanted can dramatically influence both its function and its durability. One attempt to standardize some of these variables was the development of a rigid template-style sizing instrument that could be placed in the root to precisely demonstrate how each size Toronto valve would fit.[38] This has not been widely adopted. The commercially available cylindrical sizers from each manufacturer have proven more practical in this regard as long as both the annulus and the sinotubular junction are measured. For minor discrepancies, the sinotubular junction should dominate. If there is a major difference (>3 mm), an alternative technique (root replacement) or device (stented valve) should be considered.

Root Inclusion

In an effort to completely preserve the three-dimensional geometry of the bioprosthetic root devices without completely replacing the native root, a minority of users have chosen to employ the root inclusion method. This involves a proximal suture line (continuous or interrupted) like the subcoronary technique in a circular plane coursing below the commissures. Generous openings are made by excising the sinuses facing the right and left main coronary ostia (Fig. 36-6). These are then tacked around the ostia much as a root inclusion Bentall procedure with continuous 4-0 polypropylene suture. The aortotomy is then closed in standard fashion after trimming the device top down as necessary to incorporate in the closure, making sure that the complete circle of the sinotubular junction is left intact. The only difference between the root inclusion method and the subcoronary technique is that the complete sinotubular ring of the stentless device is preserved, thus preventing any chance of dilatation at that level in the future. The top of the device is incorporated in the closure of the aortotomy (Fig. 36-7). Practically, this method is the most difficult and should not be used unless the root is large enough to place a 23-mm or larger device. It may, however, be the most desirable in a younger patient with a larger aortic root. The bioprosthetic sinotubular junction will not dilate over time, and at a subsequent operation, after gently removing this device, the entire native aortic root will be available for a complete range of replacement choices.

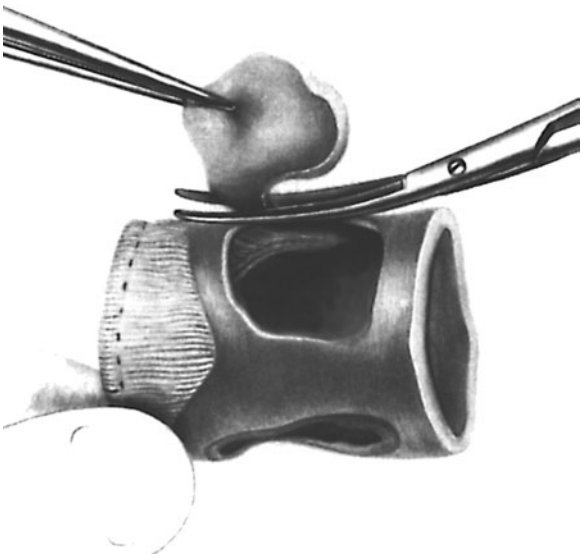

Figure 36-6. Root inclusion technique—trimming out sinuses. Very generous openings are made in the two appropriate sinuses facing the native coronaries without violating the sinotubular junction of the stentless valve. (*Modified and reproduced with permission from Krause AH: Technique for complete subcoronary implantation of the Medtronic Freestyle porcine bioprosthesis. Ann Thorac Surg 1997; 64:1495.*)

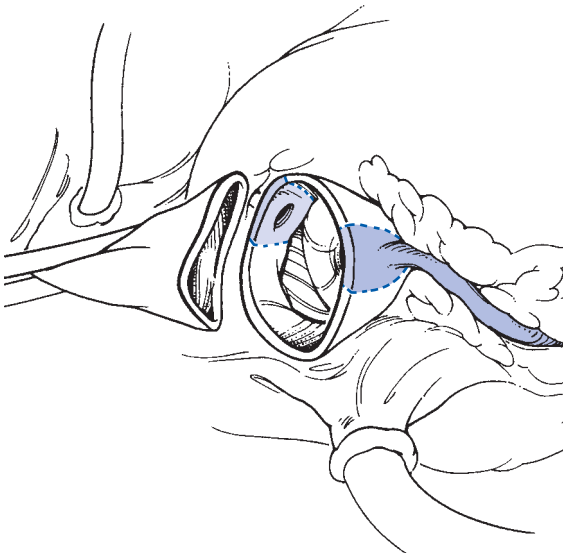

Figure 36-8. Full root technique—initial incisions. The aorta is transsected 1 to 1.5 cm distal to the coronary ostia, which are then mobilized from the root with "buttons" of aortic wall as indicated by the dashed lines. (*Modified and reproduced with permission from Kon ND, Westaby S, Amarasena N, et al: Comparison of implantation techniques using Freestyle stentless porcine aortic valve. Ann Thorac Surg 1995; 59:857.*)

Full Root Replacement

In many ways, complete replacement of the native aortic root is the simplest method for those devices that can be used in this way. Since the tubular three-dimensional geometry of the device is not altered, its factory-tested performance is not affected by the implantation. The operation is done in exactly the same manner as the root replacement technique used to implant an aortic homograft or a valved conduit. The valve is excised and the root thoroughly débrided. If a cylindrical sizer of 23 mm fits through the annulus, a 25-mm bioprosthesis can always be used and usually a 27-mm bioprosthesis is easily placed. While the valve is being rinsed, the coronary arteries are separated from the root with generous "buttons" of aortic wall and mobilized with gentle cautery technique (Fig. 36-8). It is helpful to preserve a little extra aortic tissue at the top of each button to use for stay suture retraction and to maintain axial orientation.

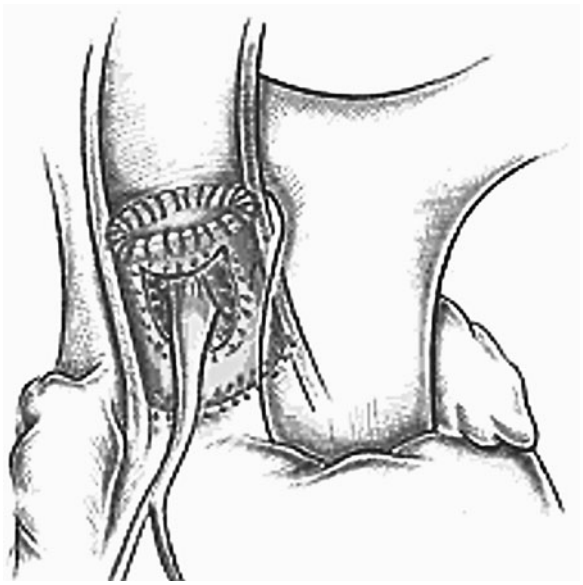

Figure 36-7. Root inclusion technique—final appearance. (*Used with permission of Medtronic Inc., Minneapolis, MN.*)

Depending on the height and position of the native right coronary artery, the device may be implanted anatomically or rotated to put the porcine left in the patient's right sinus. The proximal suture line is constructed with continuous polypropylene (3-0 or 4-0) suture beginning beneath the right-left commissure to assure proper alignment of the coronaries. Alternatively, interrupted sutures can be placed and organized on suture guides for precise distribution of sutures around the root. A strip of autologous pericardium or felt material can be incorporated into this suture line for hemostatic support if desired (Fig. 36-9). The continuous suture line is tightened with nerve hooks and tied securely if this method is used.

The coronary "buttons" are then reimplanted into the appropriate sinuses of the stentless root, cutting an orifice in the root slightly smaller than the button since the fixed tissue will not stretch. Continuous small (5-0) caliber polypropylene suture is used for these anastomoses. Extreme care must be taken to keep the right coronary high and to the patient's right to avoid kinking when the right ventricle fills up. Small conus or atrial branches may require sacrifice to protect the course of this vessel. Ironically, greater care must be taken if the right is a nondominant vessel, as it is more easily kinked.

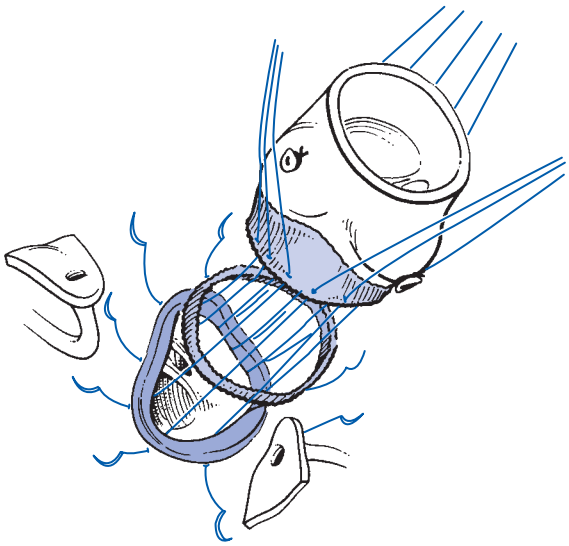

Figure 36-9. Full root technique—proximal suture line. This is the interrupted technique with a reinforcing "collar" of fabric or pericardium. (*Modified and reproduced with permission from Kon ND, Westaby S, Amarasena N, et al: Comparison of implantation techniques using Freestyle stentless porcine aortic valve. Ann Thorac Surg 1995; 59:857.*)

The fat at the base of the right coronary should be fully mobilized prior to implantation to let this ride up freely.

The distal end of the bioprosthesis is usually smaller than the distal aorta but this difference can be gathered together and also helped by trimming the distal end of the device on a bevel with more trimmed posteriorly than anteriorly. The distal suture line is constructed with continuous polypropylene (Fig. 36-10). Some surgeons have found a thin layer of biological glue to be helpful in avoiding bleeding problems at these important suture lines exposed to aortic pressures. Strict avoidance of episodic hypertension after surgery is also important.

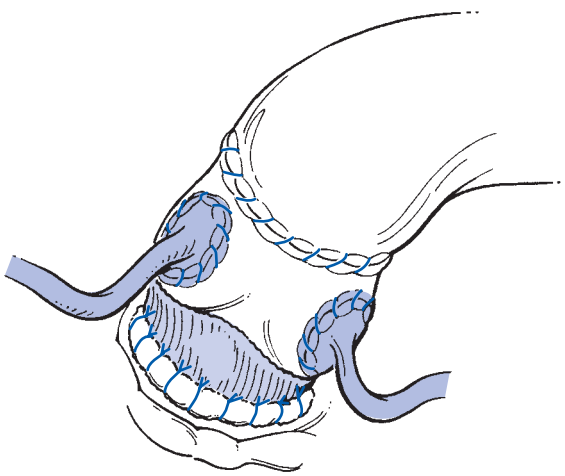

Figure 36-10. Full root technique—final appearance. The coronary "buttons" have been reimplanted and the distal end of the device attached to the native aorta. (*Modified and reproduced with permission from Kon ND, Westaby S, Amarasena N, et al: Comparison of implantation techniques using Freestyle stentless porcine aortic valve. Ann Thorac Surg 1995; 59:857.*)

Single Suture Line

The appeal of a single suture line (common to the stented devices) has led to two separate approaches to allow this. The Shelhigh Superstentless and the 3F Therapeutics valve can be implanted with a proximal suture line that resembles a stented valve implant. The top of each commissure is equipped with a small patch that is then attached to the aortic wall at an appropriate location with the sutures tied on the outside. The Sorin Freedom Solo and the CryoLife O'Brien valves are placed with a more sophisticated supra-annular running suture line that places the stentless annulus securely above and along the scalloped course of the native annulus up and around each commissure (Fig. 36-11). Three sutures are begun (one at the nadir of each sinus) and brought progressively up to each commissural tip with the ends brought outside the aorta for tying (Fig. 36-12). (The use of a 3-0 polypropylene suture with a small taper cut half circle V5 needle facilitates secure attachment.) Sewing part of the way with each limb and then completing each allows better visualization of the native aortic wall in the deeper parts of the sinuses.

Choice of Technique

The very small root is difficult for intra-aortic techniques whether one uses a stentless or a stented valve. Petrachek describes a small root algorithm based on indexed effective orifice area (IEOA) expected for a given size. The expected superior hemodynamics (as opposed to stented valves) leads him to recommend a stentless subcoronary valve for most patients over 65 years of age. If this is hindered by anatomic constraints, a stented valve is acceptable if the IEOA is >0.85 cm^2/m^2. Root replacement is his next choice, but there is a

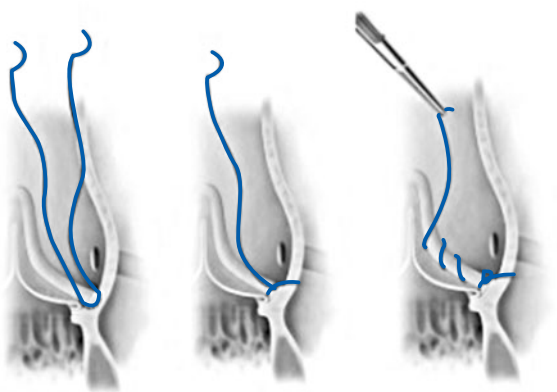

Figure 36-11. Single suture line technique—supra-annular stitches. Deep bites of aortic wall just above the annulus are joined to the entire depth of the aortic wall of the device beginning in the depths of each sinus. (*Modified and used with permission of Sorin Biomedica Cardio S.pA., Saluggia, Italy.*)

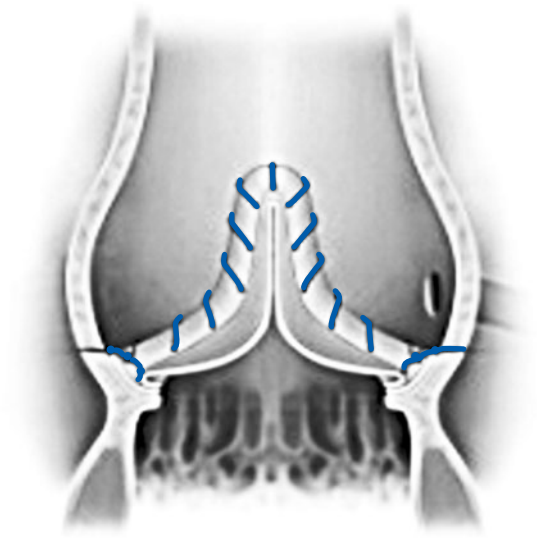

Figure 36-12. Single suture line technique—final appearance.The commissures of the replacement valve are superimposed over the native commissures and the attachment sutures are brought to the outside of the aorta to tie. (*Modified and used with permission of Sorin Biomedica Cardio S.pA., Saluggia, Italy.*)

perceived increase in operative risk.[39] He also points out the need to address subvalvular obstruction in the small root patient.

Several clinical scenarios make other techniques advisable. A large root in a young patient likely to outlive his valve is ideal for the root inclusion technique, which by preserving the native root should make reoperation easier. However, a severely diseased or aneurysmal root needs replacement. A very large root with distal dilatation is certainly a poor place for modified subcoronary technique and is better served by root replacement with a large stentless device. If complete root replacement is required in a very young patient, keeping the coronary buttons large will allow repeat root replacement with greater safety.

Calcification around the coronary ostia is a warning flag. Extensive calcification may interfere with suturing either of a button for full root or even the distal suture line of a subcoronary implant. This may be the place for a stented valve or a stentless valve that can be implanted with a single suture line just above the annulus.

Low lying coronary ostia make stentless porcine (but not necessarily pericardial) intra-aortic implant techniques difficult. If just the right ostium is low, rotating the device moves the higher porcine right sinus to the native noncoronary sinus, leaving the lower porcine left coronary to use for the right. The full root technique allows both to be moved up higher. Truly bicuspid valves with only two sinuses usually present with coronary ostia directly opposed. These are most difficult for intra-aortic techniques but can be handled quite easily with full root replacement and mobilization.

Anomalies of coronary origin present unique challenges and great care must be taken to avoid injury to the anomalous vessel, as it may run in the aortic wall for some distance. If concomitant coronary bypass grafting is done, the proximal anastomoses are best placed in the native aortic wall whenever possible. In the face of severe left main disease or ostial occlusion of either coronary, reimplantation can be ignored, the ostia sutured closed or ligated, and the coronary circulation supplied by appropriate grafts.

There is no need to compromise the outflow tract with a tiny valve or resort to root-enlarging procedures. Small roots (<23 mm) can be upsized at least one size (2 mm) and usually two by using the root replacement method. The distal aorta is almost always larger in these situations and will still be larger than the bioprosthetic root.

The issue of patient-prosthesis mismatch was studied in a group of 303 patients with small aortic roots in Lahr, Germany, with focus on quality of life as well as survival. IEOA <0.75 cm^2/m^2 was predictive of impaired quality of life ($p = 0.016$) and in patients with aortic regurgitation it negatively impacted survival ($p = 0.017$).[40] This certainly makes sense. Trading aortic regurgitation for relative aortic stenosis is not well tolerated since many of these ventricles have limited contractile reserve. The authors point out that use of the root replacement technique in these patients is preferable since mismatch is extremely rare with this technique.

ECHOCARDIOGRAPHY OF STENTLESS VALVES

Gradients and Their Time Course

Consistently found with subcoronary implantation of stentless porcine valves is an early drop in transvalvular gradients with a corresponding increase in effective valve orifice area. This is felt to be due to left ventricular outflow tract remodeling. The drop in gradient is most dramatic in the first 3 to 6 months after surgery, but some further drop may be seen up to 3 years later. Interestingly, this fall in gradient is less predictably seen in the fully pericardial stentless valves.[41] Perhaps this reflects the inherently thinner profile of the pericardial tissue in the aortic root. With the full root replacement valves, the gradients are very low from the outset and remain that way. Mean gradients in single digits are typical in all but the smallest sizes of these valves.

Echocardiographic Appearance of Stentless Valves

Intraoperative transesophageal echocardiography has become a widely accepted standard of valvular heart surgery both to document valve function and to assess ventricular function. With subcoronary implantation of stentless valves using interrupted braided sutures at the inflow end and continuous polypropylene at the outflow, small paravalvular jets of regurgitation are commonly seen. The prolific group led by Bach and Deeb at the University of Michigan looked at the echocardiographic consequences of these paravalvular leaks.

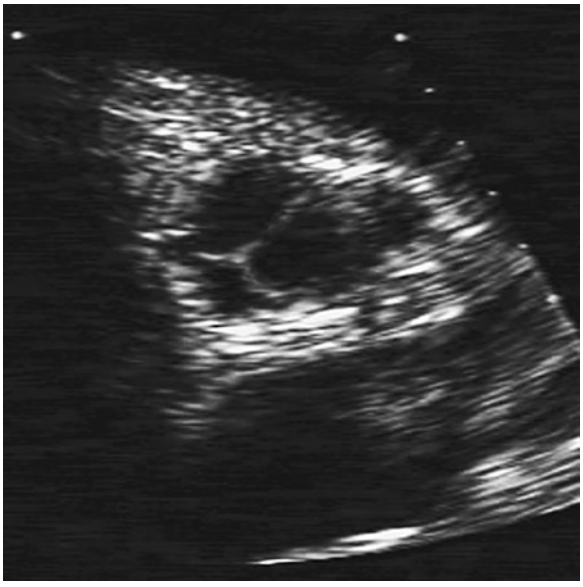

Figure 36-13. Short-axis echocardiogram of full root Freestyle valve. The aortic wall is slightly thicker than a native aorta.

As long as they are less than 2 mm wide, they resolve completely in the early postoperative period.[42] There is frequently an echo-free space between the porcine aortic wall and the native wall in the noncoronary sinus when the modified subcoronary technique is used. This should not have color flow within it and will resolve with time. Full root replacement technique produces such a natural flow pattern and gross appearance that the only clue to its bioprosthetic nature is the thicker wall of the aortic root (Figs. 36-13 and 36-14). The early drop in transvalvular gradients seen with subcoronary implants of porcine valves is not seen in full root replacements. A normal velocity envelope is the rule (Fig. 36-15).

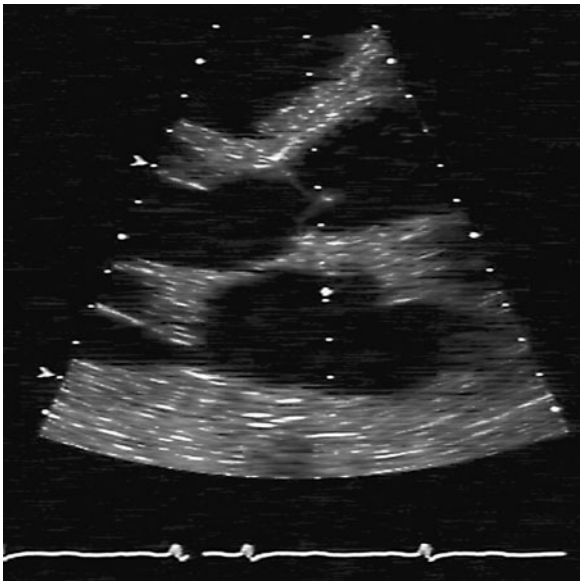

Figure 36-14. Long-axis echocardiogram of full root Freestyle valve. Note the nearly normal appearance of the root and leaflets with full opening of the outflow tract.

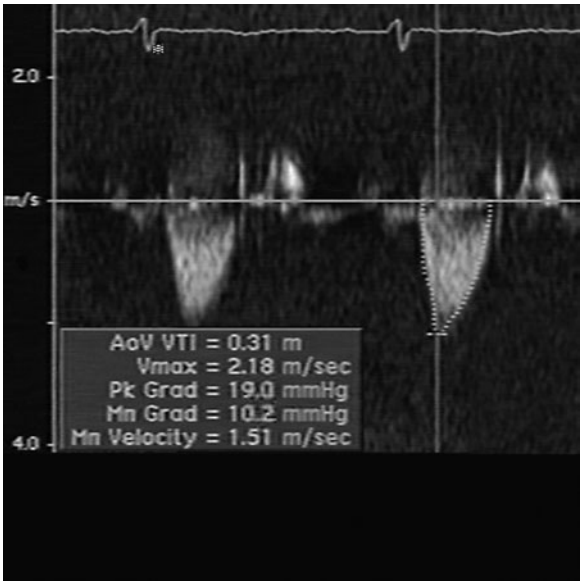

Figure 36-15. Continuous wave Doppler velocity envelope of full root Freestyle valve.

SPECIFIC VALVES

Toronto SPV and Toronto Root

The Toronto SPV (St. Jude Medical, Inc., St. Paul, MN) was the first modern stentless valve available and has set the standards for its successors. It is a fully scalloped glutaraldehyde-fixed porcine valve with the entire external aspect covered with cloth (Fig. 36-16). It must be implanted with the full subcoronary technique. Given its early development, it has no antimineralization treatment, so its clinical advantages could be explained only by its stentless design. Follow-up for an early group of 200 Toronto SPV patients beginning in

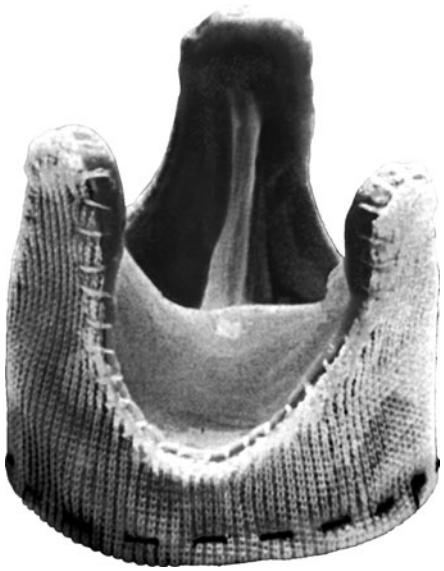

Figure 36-16. The Toronto SPV (*Used with permission of St. Jude Medical, Inc., St. Paul, MN.*)

1992 was reported by David and colleagues in 2004.[43] Operative mortality was only 2.5% in this group averaging 64.6 years of age with 34.5% requiring CABG. Actuarial survival at 5 and 10 years was 89.2 and 62%, respectively. Freedom from structural valve deterioration was 98.5% at 5 years, but turned sharply down at 10 years to only 77.9% with poorer results in patients with preoperative bicuspid aortic valves or primary aortic regurgitation. The behavior follows that of first-generation porcine tissue, which in fact this valve really is, but also reinforces the important role of the sinotubular junction which, when dilated over time, adversely affects both the competence and the durability of the subcoronary stentless valves. Reoperation was required in 12 patients (8 from structural deterioration) but the total incidence of adverse valve-related events was low. Six patients suffered thromboembolic episodes, five developed endocarditis, and one valve thrombosis occurred. The real message from this data is that porcine tissue may be less obstructive in the stentless form, but just like its stented cousin, it must be treated differently to gain a durability advantage.

The latest iteration of this device (currently in clinical investigation) is the Toronto Root Bioprosthesis. This takes advantage of modern anticalcification methods (BiLinx) and presents the surgeon with the complete range of implant flexibility from subcoronary to full root replacement (Fig. 36-17). With this development, the original SPV design will probably fade quickly from the clinical arena.

Edwards Prima and Prima Plus

The Edwards Prima and its successor the Prima Plus (Edwards Lifesciences LLC, Irvine, CA) is a porcine root with a thin cloth reinforcement over the muscle bar. The porcine coronaries were excised in the earlier version but preserved in the later version without ligation. A fine suture marks the limits of safe sinus excision to avoid injuring

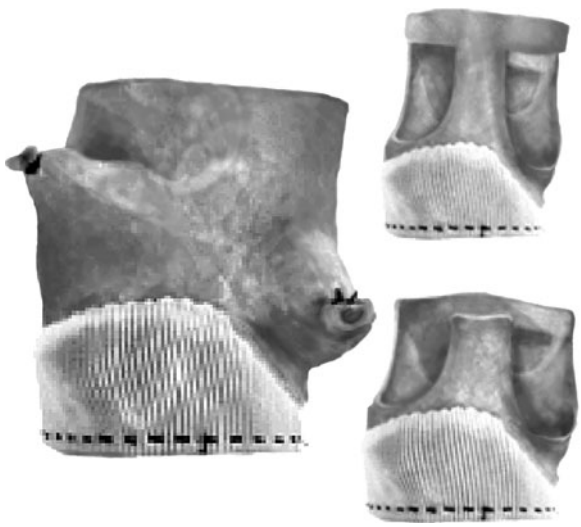

Figure 36-17. The Toronto Root. This can be used as a full root, inclusion root, or either subcoronary implant. (*Used with permission of St. Jude Medical, Inc., St. Paul, MN.*)

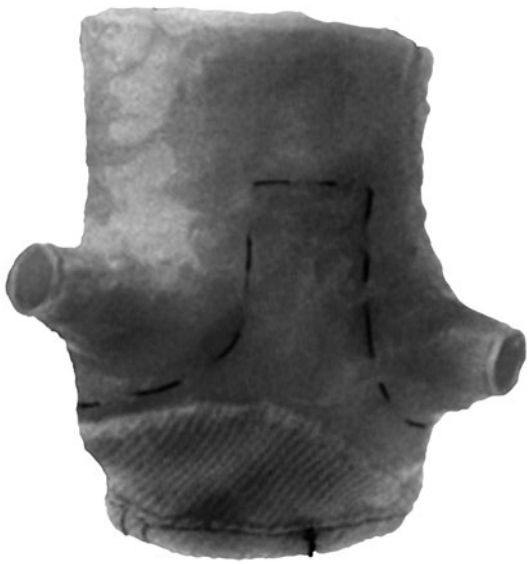

Figure 36-18. The Edwards Prima Plus. The dashed line is a marking suture delineating the safe extent of sinus excision so this can be used as a full root, inclusion root, or either subcoronary implant. (*Used with permission of Edwards Lifesciences LCC, Irvine, CA.*)

leaflets (Fig. 36-18). The Prima Plus is a low-pressure fixed valve with proprietary XenoLogiX treatment for calcium mitigation. Eight-year follow-up of these devices was reported by the Oxford Heart Centre in England.[44] Patients averaging 72 years of age at the time of surgery had survival rates of 82 ± 5% at 5 years and 72 ± 6% at 8 years. Freedom from structural valve failure was 97 ± 2 % at both 5 and 8 years. Valve gradients dropped early and showed no change after the third year. Mean discharge gradients of 9.7 ± 6.2 mm Hg dropped to 6.8 ± 4.4 mm Hg with a corresponding increase in effective valve orifice areas from 1.63 ± 0.71 to 1.91 ± 0.54 cm^2. Mild aortic regurgitation was seen in 17% but showed no progression over time, consistent with documented stability of normal aortic root geometry over that time in these patients.

Medtronic Freestyle

Clinical investigation of the Freestyle Aortic Root Bioprosthesis (Medtronic, Inc., Minneapolis, MN) began in 1992. It is a complete porcine root with ligated coronaries and a thin fabric "skirt" over the porcine septal muscle bar (Figs. 36-19 and 36-20). The cloth is extended around the inflow end with marking sutures for commissural orientation. The device is fixed with physiologic (40 mm Hg) pressure applied to the aortic wall but a net zero pressure across the leaflets. It is treated with alpha-amino-oleic acid as a calcium mitigant. This device was the first stentless xenograft that was intended to be implanted with the full spectrum of techniques from a fully-scalloped subcoronary valve implant to a total free-standing root replacement.

The original group of Freestyle investigators reported the 10-year results of 725 patients (668 >60 years of age). Of

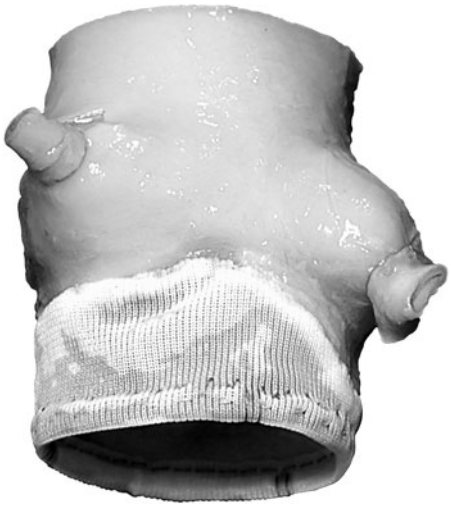

Figure 36-19. The Medtronic Freestyle Aortic Root Bioprosthesis. The longitudinal view shows the fabric covering of the porcine septal muscle and the associated higher position of the right coronary stump. (*Photographed by Stelzer, P and used with permission of Medtronic, Inc., Minneapolis, MN.*)

these, 509 had subcoronary, 178 full root replacement, and 38 root inclusion operations. Mean gradients were 10 mm Hg or less for all three implant methods, and were lowest in the full root group. Freedom from significant aortic regurgitation was better in the full root (97.7 ± 1.6%) than the subcoronary (87.2 ± 2.8%) patients at 10 years ($p < 0.005$).[45] Actuarial survival at 10 years was 94.5 ± 2.9%, 92.9 ± 5.8%, and 97.8 ± 12.5% for subcoronary, full root, and root inclusion patients, respectively, with none of these differences statistically significant. There were no significant differences in the small adverse event rates either. A total of 33 patients required reoperation including 10 for endocarditis and 10 for structural deterioration (only 3 with leaflet calcification). These are encouraging data in support of the tissue treatment conveying a durability advantage to these valves over the untreated stentless design.

In an important companion report, Kon and his Wake Forest team showed that exclusive use of the full root replacement method could be used safely (3.9% operative mortality) with superb results out to 8 years with 59.8% survival at that point.[46] There were no reoperations and no significant regurgitation developed in these valves with mean gradients only 6 to 7 mm Hg.

CryoLife-O'Brien

The CryoLife-O'Brien Model 300 (CryoLife International Inc., Kennesaw, GA) is a unique stentless device made by combining three carefully matched noncoronary sinuses with their leaflets into a single three-leaflet valve without any additional biologic or cloth support (Fig. 36-21). The tissue is fixed in glutaraldehyde but there is no specific antimineralization treatment of this valve. The design allows for supraannular implantation with a single suture line. Oversizing by 1 to 2 mm is possible, but excessive oversizing can cause buckling of tissue with resultant obstruction or regurgitation or both. The precise technical details of implanting this valve have been delineated by O'Brien himself.[47] The device must be placed above the native annulus with deep bites in the native aortic wall and extremely broad bites of the aortic wall of the prosthesis as close to the base of the leaflet as possible to avoid leaving space under the device.

A series of 206 patients averaging just under 73 years of age was studied over 8 years (mean 56 months) at the Klinikum Krefeld in Germany. The 30-day operative mortality of 4.8% is realistic for this age group with 35% undergoing concomitant coronary surgery. Of note, most patients received 25 mm or larger valves, but severe regurgitation resulted from too much oversizing, leading to early reoperation in three patients. The early decrease in

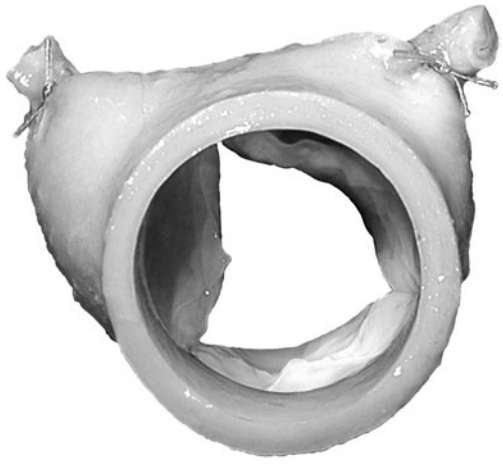

Figure 36-20. Top view of Medtronic Freestyle. The bulging porcine sinuses are visible and thickness of the tissue is apparent. (*Photographed by Stelzer, P and used with permission of Medtronic, Inc., Minneapolis, MN.*)

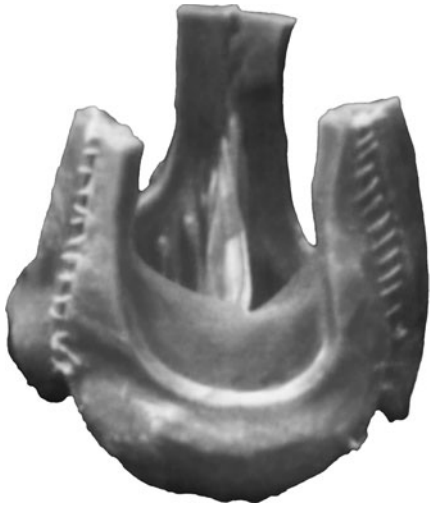

Figure 36-21. The CryoLife-O'Brien valve. This device has no cloth covering and no muscle because of its composite design. Sutures joining the three segments are obvious at each commissure. (*Used with permission of CryoLife Inc., Kennesaw, GA.)*

transvalvular gradients typical of stentless valves placed inside the native aortic root was observed with a significant increase in effective valve orifice areas in the first 6 months. Actuarial survival at 8 years was 82% ± 3% with none of the 12 late deaths being valve-related. There was no endocarditis and freedom from thromboembolic events was 93%.[48]

The progressive improvement in effective orifice area holds true even for the smaller sizes. Gelsomino and colleagues in Udine, Italy, followed 62 patients receiving 21- to 23-mm CryoLife O'Brien valves over a 7-year period. Nearly 80% of these were female. At discharge, 12 patients had IEOA $<0.85\ cm^2/m^2$, but only two persisted at 6 months and none at late follow-up. Patients with higher IEOAs demonstrated earlier concentric remodeling but after 1 year there was no difference. This is consistent with the improvement in gradient and increase in valve area over time and its favorable impact on regression of ventricular hypertrophy.[49]

It should be noted that the CryoLife-O'Brien 300 valve was originally called the Bravo Model 300 (Bravo Cardiovascular Inc., Irvine, CA) before the rights were obtained by CryoLife. This is not to be confused with the Bravo 400, which was a complete porcine root equipped with outflow reinforcement using equine pericardium.[50] The rights to this device were also obtained by CryoLife, but its production was discontinued.

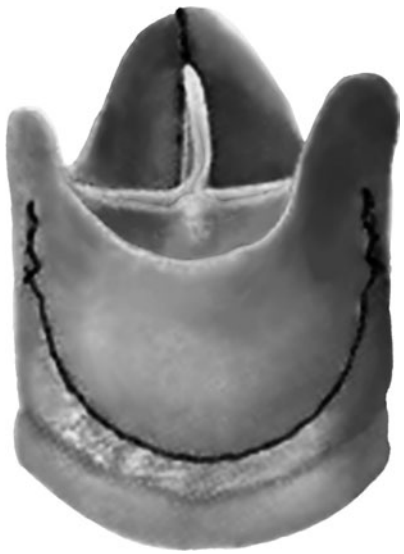

Figure 36-22. The Sorin Pericarbon Freedom Valve. This is a completely pericardial construction designed for subcoronary implantation with a double suture line, but it can also be trimmed to allow a single suture line technique. The newer Freedom Solo is designed specifically for use with a single suture line. (*Modified and used by permission from Huysmans HA, David TE, Westaby S: Stentless Bioprostheses, 2nd ed. Oxford, UK, Isis Medical Media Ltd, 1999.*)

Sorin Pericarbon Freedom and Freedom Solo

The Sorin Pericarbon Freedom valve (Sorin Biomedica Cardio S.p.A., Saluggia, Italy) is a completely pericardial stentless valve constructed by sewing two sheets of bovine pericardium together and then making a tube out of the combination (Fig. 36-22). The inner sheet is shaped to provide "leaflets" and the outer sheet provides support for attachment. They are sewn together with a special tension-relieving cross-stitch at the commissures using pyrolite carbon-based impregnation of the suture material (Fig. 36-23). It was originally designed for implantation with a double suture line like the full subcoronary porcine devices.

In Hungary, a group of 102 Pericarbon stentless valves were implanted over the 3-year period of 2000 to 2002 and followed for a mean of 26 months. Early mortality was 6.8% with none of these valve-related. Similarly to porcine stentless valves implanted within the native aorta, these valves demonstrated a drop in transvalvular gradient over time. The mean gradient dropped from 12.8 ± 8.5 to 9.1 ± 2.3 mm Hg and peak gradient fell from 22.5 ± 13.9 to 16.1 ± 4.3 mm Hg. There was no more than trivial regurgitation in any patient but one developed early endocarditis and required reoperation.[51]

The question of implant suture technique with this valve was addressed at the Charité in Berlin with a prospective matched trial (not randomized) of 139 patients to compare continuous and interrupted suturing of the inflow end of the Sorin Pericarbon Freedom stentless valve. There was no difference in outcome but a slightly shorter clamp time for the continuous technique.[52]

The Sorin valve can also be implanted with a single suture line technique like the one used for the CryoLife O'Brien valve. The excess tissue is trimmed from the inflow end of the device and the sinuses are fully scalloped. Using this technique in Bergamo, Italy, Repossini and colleagues reported 65 consecutive patients operated on between 2002 and 2004.[53] They had a mean age of 69 and nearly one-half had concomitant procedures with only one early mortality. Clamp times averaged 76 minutes. Regurgitation was trivial in only four at operation and remained detectable in only one 6 months later. Gradients were respectable with mean 10.2 ± 7.1 and peak 18.1 ± 12.3 mm Hg. These were for 25 to 29 size valves with 25 and 27 being the most frequently implanted sizes. Experience like this led to the production of the Sorin Freedom Solo valve which is specifically designed for the single suture line implantation method.

Biocor Stentless

The Biocor Stentless aortic valve (Biocor Industria e Pesquisas LTDA, Belo Horizonte, Brazil) is a porcine aortic valve

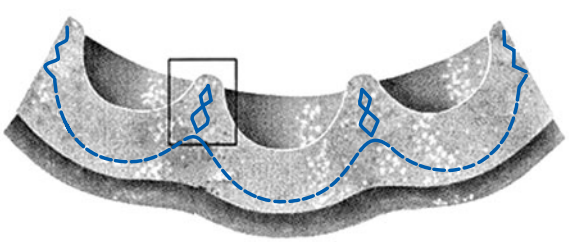

Figure 36-23. Unique construction of the Sorin Pericarbon Freedom Valve. Two sheets of bovine pericardium are sewn together and then formed into a cylindrical device with unique tension-relieving sutures at each commissure. (*Used with permission of Sorin Biomedica Cardio S.p.A., Saluggia, Italy.*)

treated with the No-React (Shelhigh Inc., Union, NJ) process. Initial experience from 1993 to 1995 in Hannover, Germany, showed this to be a hemodynamically attractive option in the small aortic root with shorter implant times compared to root enlargement procedures and low gradients compared to stented devices.[54] In a group of 247 patients operated on from 1990 to 2001 in Brazil with a mean follow-up of nearly 6 years, the Biocor stentless porcine valve performed extremely well, with mean gradients of 9.0 mm Hg and peak of 17 mm Hg. Freedom from reoperation was 99% and actuarial survival at 10 years 91%.[55]

Over a 10-year period, 112 patients had aortic valve replacement with the Biocor Stentless valve in Sweden.[56] The mean age was 78.5 and 31% had concomitant coronary surgery. Early mortality was 7%. Follow-up was 100% complete with a mean of 66 months. Using Swedish life tables for age and gender matching, these patients had no difference in actuarial survival from the normal population. Given the age of the patients, however, that translated to 5- and 9-year survivals of 74 ± 5% and 38 ± 7%, respectively. Freedom from reoperation was equal to freedom from structural degeneration at 96 ± 2% and 87 ± 6% at 5 and 9 years. Even though the average size implanted was only 23 mm, the transvalvular mean gradients at 9 years were very low at 7.3 ± 1.3 mm Hg. Slow progression of aortic regurgitation was the cause of reoperation in only two patients.

Shelhigh Superstentless and Shelhigh Bioconduit

A sister valve to the Biocor is the Shelhigh device, which shares the proprietary No-React tissue treatment. It is available in two forms, an isolated porcine aortic valve (Fig. 36-24), and a

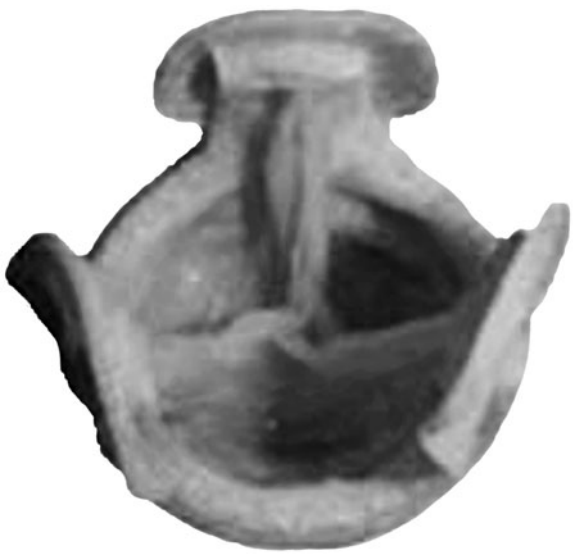

Figure 36-24. The Shelhigh Superstentless valve. This device requires only an annular suture line and fixation of each commissure to the aortic wall. Small patches of pericardium are placed at each commissure to facilitate attachment. (*Used with permission of Shelhigh, Inc., Union, NJ.*)

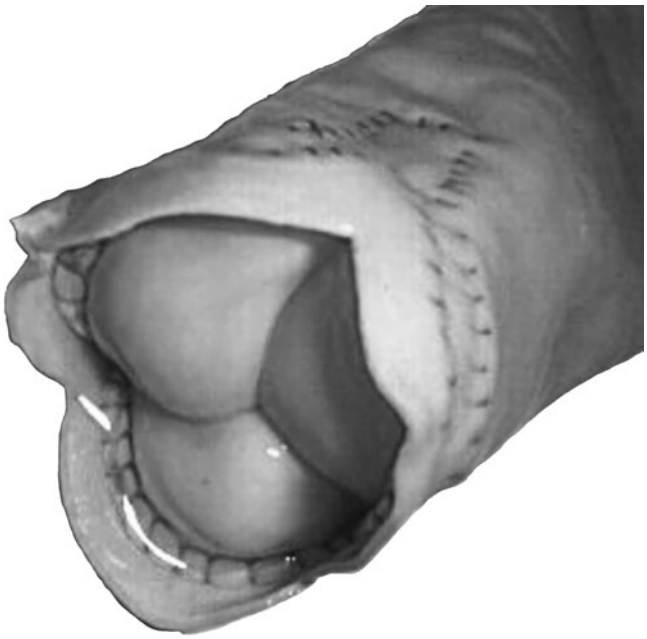

Figure 36-25. The Shelhigh Bioconduit. This shows the stentless porcine valve inside a pericardial tube without any cloth material. (*Used with permission of Shelhigh, Inc., Union, NJ.*)

valved conduit with a porcine valve enclosed in a bovine pericardial tube (Fig. 36-25). The basic valve is unusual in that it combines an annular suture line with simple commissural fixation without a formal distal suture line. This makes it technically easier to implant. The inflow end is reinforced with bovine pericardium and the commissural attachment patches are also bovine pericardium. The conduit version is made by suspending porcine leaflets in a long bovine pericardial tube to produce a valved conduit. Sizes from 21 to 31 mm are made. In Switzerland, 35 patients had complete aortic valve and root replacement with reimplantation of coronary arteries using this device.[57] There was only one early death, from persistent sepsis in the setting of methicillin-resistant *Staphylococcus aureus*. The hemostatic advantages of sewing to pericardial tissue were noted in this complex group of patients. Gradients were very low with means ranging from 14.2 down to 6.0 mm Hg, appropriate to the sizes of 21 to 29 mm. Only one patient had even minimal regurgitation. Important 1-year follow-up studies of aortic dimensions showed no dilatation of the pericardial tube in 15 patients. The potential disadvantage of a straight tube without sinuses of Valsalva in regard to leaflet wear and closing forces must await long-term follow-up evaluation.

3F Aortic Bioprosthesis

The 3F Aortic Bioprosthesis (3F Therapeutics, Lake Forest, CA) is a completely collapsible structure made from three equal pieces of equine pericardium joined together with a circular base reinforced with fabric and commissures equipped with small fabric patches for attachment to the aortic wall (Fig. 36-26). Initial clinical performance of this stentless valve was assessed in Frankfurt, Germany, in 24 patients. Contrary

Figure 36-26. The 3F Aortic Bioprosthesis. The device is made of three pieces of equine pericardium with a thin cloth inflow covering and attachment patches for each commissure. (*Used with permission of 3F Therapeutics, Lake Forest, CA.*)

to some of the bovine pericardial stentless devices these patients did show the typical early postoperative drop in transvalvular gradients to an average mean of 10.3 mm Hg and effective orifice area of 1.7 cm^2. The authors thought the device comparable to other stentless valves, but found its unique design a benefit in facilitating implantation.[58] The pliable nature of this valve was also felt to contribute to performance and ease of implantation at the Charité in Berlin, where 35 patients were equipped with this device. Cross-clamp times averaged under an hour and there was no mortality.[59] This device is not treated with any calcium mitigants and durability of equine as opposed to bovine pericardium has yet to be demonstrated.

SPECIAL SITUATIONS

Endocarditis

Endocarditis still presents surgeons with the dual challenge of adequate débridement of infected tissue and reconstruction with low risk of recurrent or persistent infection. In the aortic position, the aortic homograft has been a time-honored and sturdy option, but its limited availability makes the stentless bioprosthesis an attractive alternative. A number of reports have documented the versatility of this option. In a group of 25 patients with aortic annular abscess the Deutsches Herzzentrum Berlin used the Shelhigh Superstentless and its sister conduits and compared these to 68 historical controls whose endocarditis was treated with aortic homograft reconstruction. The operative mortality rates (16 versus 12%) were similar and recurrent infection afflicted 4% of each group.[60] The group in Osaka reported using the Freestyle root in five patients with complex aortic root endocarditis.[61] Five patients with similarly destructive root endocarditis were treated with Freestyle root replacement in Turkey without mortality or recurrent infection.[62] These reports of success are encouraging that the stentless devices may help fill the gap in these difficult situations.

Reoperation

Although experience is very limited, the Michigan group with extensive experience in stentless valve surgery reported experience with 10 patients who required reoperation, 7 for prosthetic valve endocarditis. These had all been implanted within the native aortic root, so it was possible to find a plane between the device and the native aortic wall by opening the distal suture line and using blunt dissection to separate this down to the proximal sewing ring. The proximal suture line was then divided sharply. Encouragingly, all patients survived reoperation.[63]

Ascending Aortic Aneurysm

In the setting of a true aneurysm of the ascending aorta (Fig. 36-27), complete resection of the abnormal tissue and replacement by a vascular graft is standard practice. The combination of these grafts factory-equipped with mechanical valves in various sizes is an option which is readily available, but results in the need for lifelong anticoagulation. In the elderly population and very active younger population, this option may not be desirable. The option of incorporating a Toronto SPV device into a vascular graft for this purpose was reported in 45 consecutive patients with no operative mortality.[64] Hemodynamics were excellent with mean gradients of only 8.5 mm Hg at

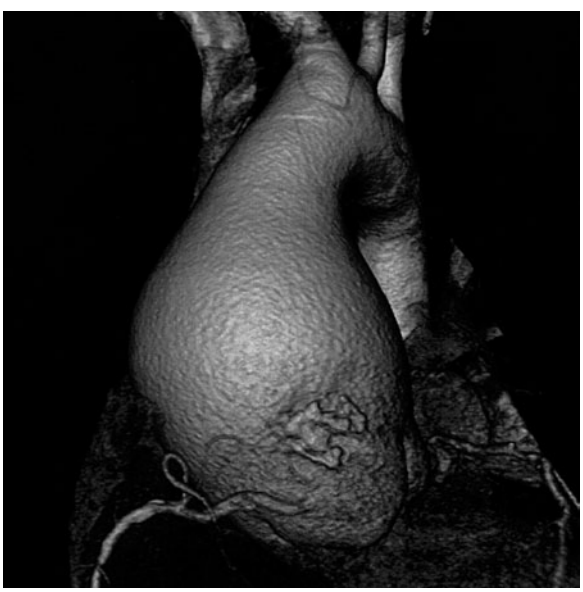

Figure 36-27. Aortic root aneurysm. This 64-slice CT reconstruction demonstrates a 7.9-cm diameter aneurysm in a 48-year-old male with aortic regurgitation through a three-leaflet aortic valve.

discharge and 8.0 mm Hg at follow-up which averaged 18 months.

The alternative of building a tissue valved conduit with a variety of valves and various size vascular grafts is an alternative that has been shown to be safe (mortality rate 5.1%) and durable (no reoperations for as long as 12 years) in 59 patients.[65] These patients were younger (mean 56 years) and mostly male (45), but 24 were emergency operations, predominantly type A dissections. The Toronto stentless valve was used inside a separate vascular graft in another German study to show an extremely safe and effective alternative method in 45 older patients (mean 69 years) with ascending aneurysm (42) or dissection (3) and no early mortality.[66] It is to this kind of alternative that the results of composite stentless root replacement must be compared.

A custom version of the Freestyle device with extended porcine aortic segment ("long neck") was used to replace the root and ascending aorta in six patients in Stuttgart, Germany.[67] This avoided the need for extension with a tubular graft and the potentially troublesome suture line between two nonliving structures. Advantages in cost, time, and hemostasis were realized, but it is extremely difficult to provide these conduits from a manufacturing standpoint. Very limited experience with the Shelhigh Bioconduit shows this, too, to be a possible option for complete biologic replacement of the root and ascending aorta.[68]

From Japan comes a report of using the Freestyle root replacement extended by a vascular graft. There were two early and three late deaths in this group of 24 patients with fairly long (210 minutes) ischemic times.[69] This technique was used successfully even in the setting of acute and chronic dissection in four patients at another Japanese institution.[70]

The simple composite alternative is very appealing and readily applicable. One can replace the root pathology with a stentless root bioprosthesis and extend it up to or into the arch with an appropriate diameter vascular graft (Fig. 36-28). This can often be a more timely way to do the operation. If the aorta can be clamped, work on the root can begin during cooling. The distal anastomoses of the graft to the arch can be done under circulatory arrest as soon as the temperature is low enough. This graft is then clamped and warming can proceed while the root reconstruction is completed.

Elderly

The perceived increase in risk of more complex procedures is particularly keenly felt when operating on elderly patients. John Pepper's group at the Royal Brompton Hospital in London retrospectively reviewed a group of 103 patients aged 75 to 91 (mean 79.8 years) who underwent stentless AVR.[71] (They included 29 patients with aortic homografts as well as 74 Toronto valves.) Although the group had multiple patients with multiple comorbidities and concomitant procedures, the overall 30-day mortality was just 11.6%. For elective cases it was 5.3% and for isolated, elective AVR only 2.5%. Mean follow-up was only 3.6 years, but actuarial survival was 52% at 5 years and 92% were in New York Heart Association functional class I or II despite their age. A multivariate model showed increasing age as the only independent predictor of mortality, both immediate and in follow-up.

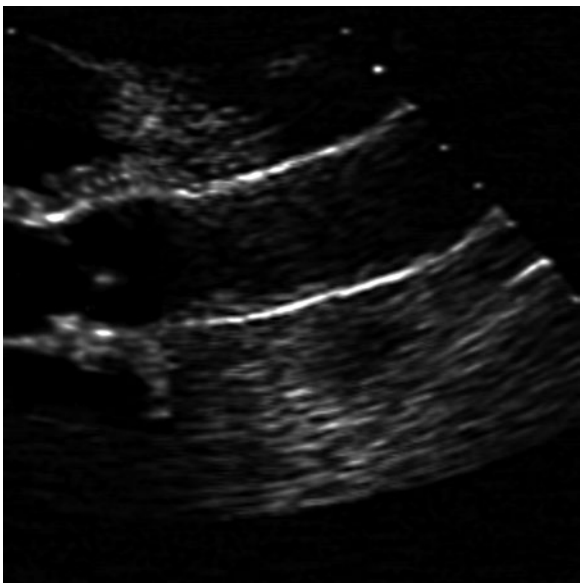

Figure 36-28. Composite reconstruction echocardiogram. The bright echodensity of the 26 mm vascular graft is seen attached to the distal end of a 29 mm Freestyle root replacement (long axis) of the patient shown in Fig. 36-27 on his fourth postoperative day when he was discharged home.

Poor Left Ventricular Function

In a small but very interesting study of stentless versus stented aortic valves in patients with poor left ventricular function (LVF), the Royal Brompton team in London demonstrated an immediate improvement in fractional shortening and decrease in LVM with the stentless but not the stented valves.[72] However, after a year the differences were not significant. One must always remember that long-term benefit is always dependent on short-term survival. Hence, the early difference may have a major impact in some of these sicker patients. This impact of residual obstructive gradients is dramatically demonstrated in the data from Quebec which demonstrated a very significant increase in short-term mortality with moderate or severe patient-prosthesis mismatch for AVR when EF was $<40\%$.[73] The risk in the group with moderate mismatch rose from 1.8 to 7.1%, and that for patients with severe mismatch went from 11.3 to 77.1%. Clearly, the combination of poor ventricular function and a replacement aortic valve that leaves significant obstruction is highly lethal. A small study in Italy compared stentless to stented or mechanical valves in 53 patients with LVEF $<35\%$. Despite the slightly longer cross-clamp times, the stentless aortic valve patients had significantly larger effective orifice areas and greater recovery of LVF without any increase in mortality.[74]

Diastolic Dysfunction

The problem of systolic dysfunction as an end-stage result of aortic stenosis is well recognized, but the earlier relaxation impairment of these hypertrophied ventricles is much more poorly understood and often ignored. The use of stentless valves has both a potential for increased long-term benefit and short-term risk in this setting. Complete removal of afterload by restoring normal size and flow to the left ventricular outflow tract (LVOT) with a stentless root replacement has immediate impact on left ventricular stroke work and maximal impact on LVM regression. Although the mechanism of diastolic dysfunction is poorly understood, the reduction of hypertrophy is of profound benefit to these patients. Those with long-standing interstitial fibrosis will benefit less, but removing the cause of hypertrophy as completely as possible seems an appropriate goal.

The problem comes from the fact that early after surgery, the stiff ventricle (often with hyperdynamic systolic function) (Figs. 36-29 and 36-30) can develop dynamic LVOT obstruction when the thick basal septum (albeit part of a concentric hypertrophy) catches the anterior mitral leaflet with systolic anterior motion as seen after some mitral valve repairs. This is most apt to occur in the setting of low systemic pressure, fast heart rate, and low-volume states. The worst possible scenario occurs with acute onset atrial fibrillation which causes all three of these effects. A stented valve holds the aortic annulus open, but a stentless valve does not provide such rigid resistance to dynamic LVOT obstruction. Hence, there is a much greater risk of disastrous consequences. This is most often seen in the elderly female patient with hypertension who is most likely to have diastolic dysfunction. (The unique impact of this condition was brought out by personal experience in the early part of the Freestyle investigation. Using the full root technique led to higher mortality rates, but a closer look at the deaths revealed all but one to be elderly female.)

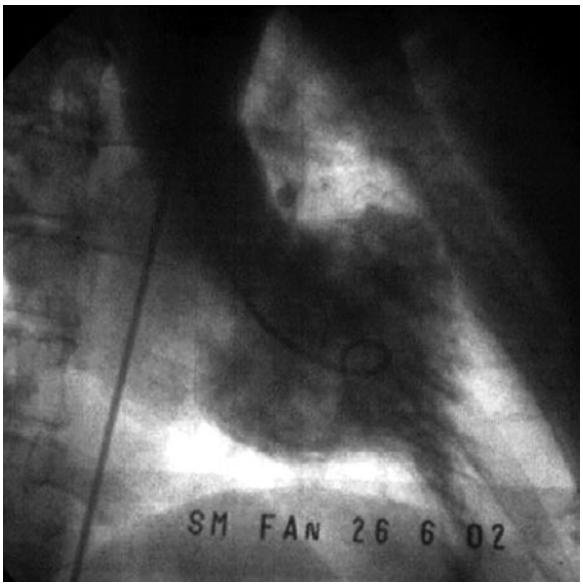

Figure 36-29. Hyperdynamic left ventricular function—diastole. Prominent papillary muscle shadows are seen in this hypertrophied ventricle, even in this diastolic frame.

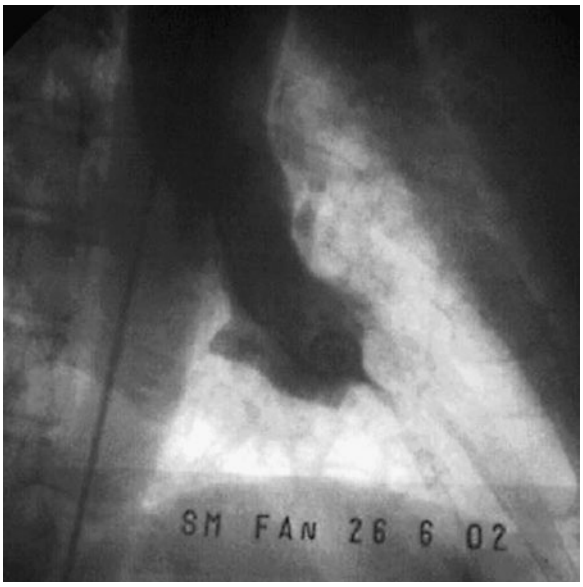

Figure 36-30. Hyperdynamic left ventricular function—systole. Complete distal cavity obliteration is apparent in systole.

Unfortunately, the clinical picture of hypertension, dyspnea, oliguria, and peripheral signs of low forward output trigger knee-jerk responses of inotropes, diuretics, afterload reduction, and digitalis. All of these (which are helpful in systolic heart failure) can be counterproductive to the stiff heart. The bottom line is that the left ventricle must be kept full even though the lungs may object. Prompt restoration of sinus rhythm makes perfect sense in the setting in which E:A reversal of mitral inflow underscores the importance of the atrial "kick" in these patients (Fig. 36-31). A strategy of loading these

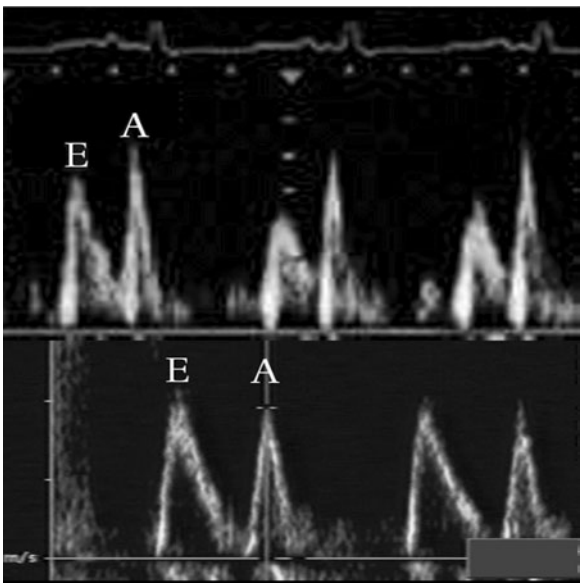

Figure 36-31. Mitral inflow patterns of abnormal relaxation. The lower panel shows nearly equal E and A waves, and the upper panel demonstrates clear reversal of the E:A ratio. With ventricular filling so dependent on atrial transport, new-onset atrial fibrillation can be devastating.

patients (on an outpatient basis) with amiodarone for a week prior to surgery might be advisable whenever possible to help prevent atrial fibrillation. Beta-blockers should also be used and perhaps verapamil or even disopyramide to treat the hyperdynamic left ventricle until its mass can be restored to more normal levels. Higher blood pressures should be tolerated, as this afterload helps prevent collapse of the LVOT. Lower cardiac indices must be accepted temporarily to avoid the counterproductive effects of using inotropes. Pulmonary artery pressures can be very misleading in these patients, as they can be very high in a setting in which the left ventricle is still underfilled. Echocardiography is essential in sorting out these issues and guiding therapy.

As a corollary to this issue, timing of AVR, particularly in older females, should be reconsidered. A Swedish study found that moderate to severe diastolic but not systolic dysfunction at the time of aortic valve surgery is predictive of long-term mortality risk and its significance tended to increase with time up to 12 years after AVR.[75] Waiting for the classic indication of symptomatology may be waiting for severe hypertrophy and its deadly diastolic consequences. Asking an 80-year-old woman with a valve area of 0.9 cm^2 to wait until she is 83 with an area of 0.7 cm^2 no longer makes sense but just multiplies risk. An EF of 85% should not be seen as good news, but rather as the "suicide" ventricle it really is. Guidelines need to be developed to encourage safer AVR at an earlier stage in the disease process. Clearly the durability of current devices is such that fear of structural deterioration should not delay surgery in these older patients.

FUTURE OF STENTLESS VALVES

It is ironic that one of the newest stentless valves is destined to be placed back on a stent and delivered to the aortic root by a catheter. It is also evident that the choice of equine pericardium for this purpose was made without any clinical experience or attempts to optimize the durability of this tissue with fixation or antimineralization technologies now used in the preparation of other surgically implanted alternatives.

More significant is the fact that adoption of stentless valves has been limited despite considerable enthusiasm and good data from the early adopters. The dual perceptions of increased surgical technical challenge and increased risk keep the low-volume valve surgeon from using these devices. Where possible, groups might benefit from consolidating specialized valve experience to fewer surgeons in order to optimize experience and outcomes. Training opportunities in and after residency must be provided to make the benefits of these devices more widely available to patients. With so much information freely accessible to the public electronically, more patients will come to surgical consultation already aware of stentless valve options. Their questions should not be dismissed but discussed intelligently. Continued careful trials of many alternatives must be encouraged to have the data to guide this joint decision-making process. Newer is not always better, but sometimes it really is. Surgeons of the twenty-first century must provide the answers to a lot of twentieth century questions.

Acknowledgment

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CHAPTER 37

Aortic Valve Repair and Aortic Valve–Sparing Operations

Tirone E. David

FUNCTIONAL ANATOMY OF THE AORTIC VALVE

The aortic valve is a complex structure that is best described as a functional and anatomic unit, the aortic root. The aortic root has four components: aortic annulus, aortic cusps, aortic sinuses, and sinotubular junction. In addition, the triangles beneath the commissures of the aortic valve, although part of the left ventricular outflow tract, are also important for valve function.

The aortic annulus unites the aortic cusps and aortic sinuses to the left ventricle. The aortic annulus is attached to the ventricular myocardium (interventricular septum) in approximately 45% of its circumference and to fibrous structures (anterior leaflet of the mitral valve and membranous septum) in the remaining 55% (Fig. 37-1). The aortic annulus has a scalloped shape. Histologic examination of the aortic annulus reveals that it is a fibrous structure with strands attaching it to the muscular interventricular septum and has a fibrous continuity with the mitral valve and membranous septum. The fibrous tissue that separates the aortic annulus from the anterior leaflet of the mitral valve is the intervalvular fibrous body. An important structure immediately below the membranous septum is the bundle of His. The atrioventricular node lies in the floor of the right atrium between the annulus of the septal leaflet of the tricuspid valve and the coronary sinus. This node gives origin to the bundle of His, which travels through the right fibrous trigone along the posterior edge of the membranous septum to the muscular interventricular septum. At this point the bundle of His divides into left and right bundle branches that extend subendocardially along both sides of the interventricular septum.

The aortic cusps are attached to the aortic annulus in a scalloped fashion (see Fig. 37-1). The aortic cusps have a semilunar shape whereby the length of the base is approximately 1.5 times longer than the length of the free margin, as illustrated in Fig. 37-2. There are three cusps and three aortic sinuses: left, right and noncoronary. The aortic sinuses are also referred to as sinuses of Valsalva. The left coronary artery arises from the left aortic sinus and the right coronary artery arises from the right aortic sinus. The left coronary artery orifice is closer to the aortic annulus than is the right coronary artery orifice. The highest point where two cusps meet is called the commissure, and it is located immediately below the sinotubular junction. The scalloped shape of the aortic annulus creates three triangular spaces underneath the commissures. The two triangles beneath the commissures of the noncoronary cusp are fibrous structures, whereas the triangular space beneath the commissure between the left and right cusps is muscular. These three triangles are seen in Fig. 37-1. The sinotubular junction is the end of the aortic root. It is an important component of the aortic root because the commissures of the aortic valve are immediately below it and changes in the sinotubular junction can affect the function of the aortic cusps.

The geometry of the aortic root and its anatomic components varies among individuals, but the geometry of these components is somewhat interrelated.[1–4] For instance, the larger the aortic cusps, the larger the diameters of the aortic annulus and sinotubular junction.[2] The aortic cusps are semilunar (crescent-shaped) and their bases are attached to the annulus; the free margins extend from commissure to commissure, and the cusps coapt centrally during diastole. The size of the aortic cusps varies among individuals and within the same person, but as a rule, the noncoronary cusp is slightly larger than the right and left. The left is usually the smallest of the three. Because of the crescent shape of the aortic cusps and the fact that their free margins extend from commissure to commissure, the diameter of the aortic valve orifice must be smaller than the length of the free margins. Indeed, anatomic studies of fresh human aortic roots demonstrated that the average length of the free margins of the aortic cusps was one-third longer than the diameter of

Figure 37-1. A photograph of a human left ventricular outflow tract and aortic root.

the aortic orifice.[1] The diameter of the aortic annulus is 15 to 20% larger than the diameter of the sinotubular junction in normal aortic roots of young persons, but these diameters tend to become equal in older ones (see Fig. 37-2). All components of the aortic root are very elastic and compliant in young patients but this compliance decreases with age as elastic fibers are replaced by fibrous tissue.

The aortic annulus, the aortic cusps, and the sinotubular junction play an important role in maintaining valve competence. On the other hand, the aortic sinuses play no role in valve competence,[5] but they are believed to be important in minimizing mechanical stress on the aortic cusps during the cardiac cycle.[6–7]

AORTIC VALVE PATHOLOGY IN ADULTS

Anatomically normal aortic cusps may become calcified late in life and cause aortic stenosis. This type of lesion is called dystrophic calcification, senile calcification, or degenerative calcification. The range of histopathologic lesions includes

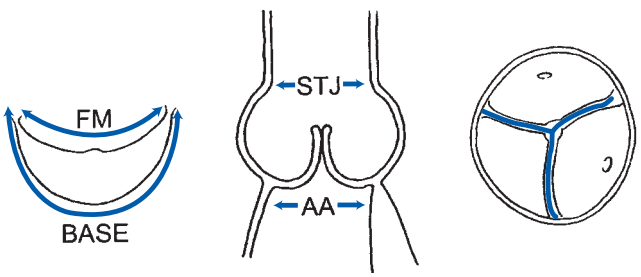

Figure 37-2. Geometric relationships of various components of the aortic root. The base of the aortic cusp is 1.5 times longer than its free margin (FM). The diameter of the aortic annulus (AA) is 10 to 15% larger than the diameter of the sinotubular junction (STJ) in children and young adults, but it tends to become equal with aging. Three semilunar cusps seal the aortic orifice. The height of the cusps must be longer than the radius of the aortic annulus.

calcification, chondroid and osseous metaplasia, neorevascularization, inflammation, and lipid deposition.[8] The pathogenesis of this lesion is not well understood. Aging is certainly the most important epidemiologic factor.[8–11] Degenerative calcification is an active inflammatory process with similarities and dissimilarities to atherosclerosis.[9–11] Aging and high levels of lipoprotein [a] were found to be correlated with aortic valve sclerosis.[9] Many studies have shown that treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the rate of progression of aortic valve stenosis,[12–13] but early results of a randomized trial did not confirm these findings.[14] Degenerative calcification of the aortic valve is the most common cause of aortic stenosis in elderly patients in North America.[15–16]

Bicuspid aortic valve occurs in 1 to 2% of the population and it is probably heritable.[17] It usually functions satisfactorily and does not cause hemodynamic problems until late in life when it becomes calcified and stenotic. Calcified bicuspid aortic valve is the second most common cause of aortic stenosis in elderly patients.[15] Bicuspid aortic valve can also cause aortic insufficiency, particularly in young patients in whom mild to moderate dilation of the aortic root is present.[18–19] Most patients with bicuspid aortic valve have three aortic sinuses. The two cusps are of different sizes and the larger one often contains a raphe instead of a commissure. The raphe extends from the mid-portion of the cusp to the aortic annulus, and its insertion in the aortic root is at a lower level than the other two commissures. Bicuspid aortic valves with two aortic sinuses and no raphe are uncommon. The right coronary is nondominant in most patients with bicuspid aortic valve.

Unicusp aortic valve is another congenital anomaly of the aortic valve. It often contains only one commissure and causes aortic stenosis. Bicuspid and unicusp aortic valves are frequently associated with premature degenerative changes of the media of the aortic root and ascending aorta. They increase the risk of aneurysms and type A aortic dissection.[20]

Quadricusp aortic valve is a rare anomaly that may cause aortic insufficiency. Three of the four cusps are usually of similar size and the other is hypoplastic.

Subaortic membranous ventricular septal defect (VSD) with aortic insufficiency is uncommon in adults. The interventricular septal defect (ISD) causes distortion of the aortic annulus, and the right aortic cusp is often elongated and may prolapse and cause aortic insufficiency.

Dilation of the aortic root is the most common cause of aortic insufficiency in North America.[15–16] Older patients with ascending aortic aneurysm may develop aortic insufficiency because of dilation of the sinotubular junction (Fig. 37-3). The aortic sinuses and aortic annulus may remain relatively normal in these patients. Aortic aneurysm in young patients usually begins with dilation of the aortic sinuses, which progresses into the sinotubular junction and ultimately aortic annulus. Annuloaortic ectasia is a term used to describe dilation of the aortic annulus. Aortic root aneurysm is common in patients with Marfan syndrome, which is an

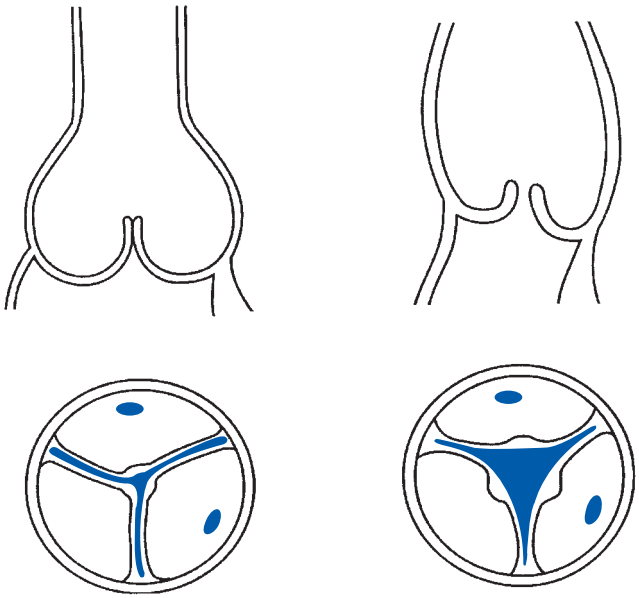

Figure 37-3. Dilation of the sinotubular junction causes aortic insufficiency because it displaces the commissures outward and prevents the cusps from coapting centrally.

autosomal dominant variably penetrant inherited disorder of the connective tissue that affects the cardiovascular, skeletal, ocular, and other systems. The prevalence is estimated to be around 1 in 3000 to 5000 individuals. It is caused by mutations in the gene that encodes fibrillin-1 on chromosome 15.

Aortic dissections involving the ascending aorta can cause aortic insufficiency because of preexisting aortic root aneurysm or by detachment of one or more commissures with consequent prolapse of the cusps.[21]

Numerous connective tissue disorders (e.g., ankylosing spondylitis, osteogenesis imperfecta, rheumatoid arthritis, Reiter syndrome, and lupus) can cause aortic insufficiency. The anorexigenic drugs phentermine and fenfluramine can also cause aortic insufficiency.[22]

Rheumatic aortic valve disease is still prevalent in developing countries. The rheumatic process causes fibrosis, thickening, and contraction of the aortic cusps, often with commissural fusion. In advanced cases, the cusps become calcified. It is possible that some postinflammatory aortic valve lesions are not rheumatic in origin.[23]

NATURAL HISTORY OF AORTIC VALVE DISEASE

Aortic Stenosis

Several studies showed that asymptomatic patients with aortic stenosis have a good prognosis.[24–25] Sudden death in asymptomatic patients is uncommon.[25] However, when symptoms develop, the prognosis becomes poor and the average survival is 2 to 3 years for patients with symptoms of angina and syncope, and 1 to 2 years for those with congestive heart failure (CHF).[26]

Aortic Insufficiency

The prognosis of symptomatic patients with aortic insufficiency is poor, with death occurring within 4 years after development of angina and within 2 years after the onset of CHF.[27]

Aortic Root Aneurysm

Aortic root aneurysm can cause aortic insufficiency, aortic dissections, or aortic root rupture. The degree of aortic insufficiency is dependent on dilation of the sinotubular junction and/or aortic annulus in patients with normal aortic cusps. If the cusps are abnormal, aortic insufficiency may be the dominant feature. The risk of aortic dissection and rupture is often related to the transverse diameter of the aortic sinuses. It is rare with diameters less than 50 mm except in cases of family history of dissection. The risk of dissection and/or rupture increases proportionally as the root dilates.

Ascending Aortic Aneurysm

Dilation of the ascending aorta increases the risk of dissection and/or rupture when its transverse diameter exceeds 50 mm. The median size of the ascending aortic aneurysm at the time of dissection or rupture was 59 mm in one study.[28] Dilation of the ascending aorta can cause secondary dilation of the sinotubular junction with consequent aortic insufficiency.[5]

DIAGNOSIS OF AORTIC VALVE DISEASE

Aortic Stenosis

Patients with aortic stenosis remain asymptomatic for many years. Symptoms usually appear late in the course of the disease. The symptoms are angina pectoris, syncope, and CHF. Coexisting coronary artery disease (CAD) is common in older patients, but more than half of all patients with aortic stenosis and angina pectoris have normal coronary arteries. The myocardial ischemia in these patients is the result of a combination of increased oxygen demands by the hypertrophic myocardium and a reduction of oxygen delivery resulting from the excessive compression of the coronary arteries.[29] Syncope is usually the result of cerebral hypoperfusion, but it can also be a result of arrhythmias such as transient ventricular fibrillation, atrial fibrillation, or transient heart block. Symptoms of CHF occur late in the course of this disease. Symptomatic patients with aortic stenosis are at risk of sudden death. Other less common symptoms are gastrointestinal bleeding (idiopathic or caused by angiodysplasia), infective endocarditis, and arterial thromboembolism.

On auscultation these patients have a harsh systolic murmur, sometimes with a thrill along the left sternal border,

often radiating to the neck. The second heart sound is soft, absent, or paradoxically split. The carotid pulses are diminished and delayed. The electrocardiogram reveals left ventricular hypertrophy in most patients with severe aortic stenosis. Echocardiography establishes the diagnosis; provides information regarding the ventricular function, ventricular thickness, and pulmonary hypertension; and estimates the aortic valve area and transvalvular gradient. Coronary angiography is an important part of the work-up in patients aged 40 years and older.

Aortic Insufficiency

The clinical presentation is dependent on the rapidity with which aortic insufficiency develops. Patients with chronic aortic insufficiency remain asymptomatic for many years while the heart slowly enlarges. Palpitations and head pounding may occur during exertion. Angina pectoris may occur, but it is not as common as with aortic stenosis. Syncope is rare. Symptoms of CHF are usually an indication of left ventricular dysfunction (LVD). Acute aortic insufficiency is frequently associated with cardiovascular collapse, with extreme fatigue, dyspnea, and hypotension resulting from reduced stroke volume and elevated left atrial pressure.

The major physical findings related to the wide pulse pressure are caused by the large stroke volume. The pulse is the water-hammer or collapsing type with a rapid rise and fall (Corrigan pulse). The patient's head may bob with each heartbeat (Musset sign). The systolic pressure is elevated and the diastolic pressure is low. A variety of peripheral artery auscultatory signs may be present: Traube sign (also known as "pistol shot sounds"), Muller sign (pulsations of the uvula), and Duroziez sign (a systolic murmur over the femoral artery when it is compressed proximally to where the stethoscope is placed). The apical impulse is prominent and displaced laterally. The aortic diastolic murmur is high pitched and decrescendo. The electrocardiogram usually demonstrates left ventricular hypertrophy. Chest x-ray demonstrates cardiomegaly. Echocardiography confirms the diagnosis and provides information regarding the cause of aortic insufficiency. Radionuclide imaging is useful in assessing the left ventricular function (LVF) at rest and during exercise, valuable information in asymptomatic patients. Coronary angiography is performed in older patients if surgery is being contemplated.

Aortic Root Aneurysm

Most patients with aortic root aneurysm are asymptomatic and have no physical signs if the aortic valve is competent. Some patients may complain of vague chest pain. Severe chest pain is suggestive of rapid expansion or intimal tear with dissection. Echocardiography establishes the diagnosis and gives information regarding the aortic cusps. Computed tomography (CT) scan and magnetic resonance imaging (MRI) of the chest are also diagnostic and useful to provide information regarding the thoracic aorta.

Ascending Aortic Aneurysm

Like patients with aortic root aneurysm, these patients usually remain asymptomatic until the aorta dissects or ruptures. Although echocardiography diagnoses ascending aortic aneurysm and gives information regarding the aortic cusps and root, a CT scan is necessary to determine the extent of the aneurysm. The transverse arch is often involved in patients with aneurysm of the ascending aorta.

INDICATIONS FOR AORTIC VALVE SURGERY

Aortic Stenosis

Patients with symptoms should undergo surgery. Asymptomatic patients with an aortic valve area of less than 0.6 cm^2 or a mean systolic gradient greater than 50 mm Hg with left ventricular hypertrophy should also be considered for surgery. An echocardiographic flow velocity across the aortic valve >4 m/s is also an indication for surgery.[30]

Aortic Insufficiency

Symptomatic patients should be operated on. Since aortic insufficiency may cause ventricular damage, asymptomatic patients should be operated on when ventricular function begins to deteriorate.[31] Assessment of ventricular function during exercise is useful to determine timing of surgery. Operation should be performed if left ventricular ejection fraction (LVEF) decreases during exercise.

Aortic Root Aneurysm

Since most patients with aortic root aneurysm are asymptomatic, surgery is recommended when the transverse diameter of the aortic root exceeds 55 mm.[32] If the aortic valve has normal cusps by echocardiography, surgery should be done when the aneurysm reaches 50 mm in diameter.[33] This size criterion is also used for patients with a family history of acute aortic dissection.[34]

SELECTION OF PATIENTS FOR AORTIC VALVE REPAIR

Only a small proportion of patients with aortic valve disease are candidates for aortic valve repair. Patients with advanced degenerative calcification of the aortic valve are best treated with aortic valve replacement; however, mildly or moderately stenotic aortic valves in patients in whom the primary indication for operation is myocardial revascularization are amenable to manual débridement to increase cusp mobility. The calcific deposits should be limited to small segments of one or two cusps and in proximity to the aortic annulus. Decalcification should be done mechanically and care must

be exercised to avoid damage to the cusps. The calcium on the annulus should also be removed to make it more pliable. Long-term therapy with statins may delay recurrence of the aortic stenosis. Ultrasound decalcification of aortic cusps was tried in the past and it failed because it causes scarring with retraction of the cusps with consequent aortic insufficiency within a few months after surgery.[35]

Most candidates for aortic valve repair have aortic insufficiency. Transesophageal echocardiography is the best diagnostic tool to study the aortic valve and the mechanism of aortic insufficiency. Each component of the aortic root must be carefully interrogated, in particular the aortic cusps. The number of cusps, their thickness, the appearance of their free margins, and the excursion of each cusp during the cardiac cycle must be examined in multiple views. The lines of coaptation of the aortic cusps should be interrogated by color Doppler imaging. The direction and size of the regurgitant jets should be recorded in many views. Information regarding the morphologic features of the aortic annulus, aortic sinuses, sinotubular junction, and ascending aorta should be obtained.

Obviously, the aortic cusps are the most important determinant of aortic valve repair. If the cusps are thin, mobile, and have smooth free margins, the feasibility of aortic valve repair is very high, including bicuspid aortic valve. Calcified or scarred and fibrotic aortic cusps preclude aortic valve repair unless glutaraldehyde-fixed pericardium is used for cusp augmentation.[36]

Patients with aortic root aneurysm often have normal or minimally stretched aortic cusps and reconstruction of the aortic root with preservation of the native aortic cusps is feasible. Larger aortic root aneurysms (e.g. >60 mm) often have overstretched, thinned out aortic cusps with stress fenestrations along the commissural areas and are not suitable for repair.

Patients with ascending aortic aneurysm and aortic insufficiency often have dilated sinotubular junction and normal or minimally altered aortic cusps. The aortic insufficiency is central and caused by outward displacement of the commissures of the aortic valve (see Fig. 37-3). Aortic valve repair is usually feasible in these patients.

Aortic insufficiency caused by prolapse of a single cusp in patients with tricuspid aortic valves is uncommon but correctable by means of aortic valve repair. Prolapse of one cusp in patients with bicuspid aortic valve is common and also suitable for repair.

TECHNIQUES OF AORTIC VALVE REPAIR

Cusp Perforation

Occasionally a cusp perforation is the sole reason for aortic insufficiency. The perforation may be iatrogenic, a sequela of healed endocarditis, or the result of resection of a papillary fibroelastoma. A simple patch of fresh or glutaraldehyde-fixed autologous pericardium is adequate to correct the problem. If fresh autologous pericardium is used, the patch should be larger than the defect because it retracts during healing. We use continuous 7-0 polypropylene to suture the patch around the defect on the aortic side of the cusp.

Cusp Extension

Cusp augmentation has been used to repair incompetent aortic valves due to rheumatic and congenital disease. Glutaraldehyde-fixed bovine or autologous pericardium has been used for this purpose.[36–37]

Cusp Prolapse

Cusp prolapse is due to elongation of the free margin. This is corrected by plication along the nodule of Arantius illustrated in Fig. 37-4. The degree of shortening is determined by examining the other cusps and the common level of coaptation.

Cusp with Stress Fenestration

Dilation of the sinotubular junction increases the mechanical stress along the free margin of the cusp and may cause a fenestration in the commissural area. This type of lesion has been successfully corrected by weaving a double layer of 6-0 expanded polytetrafluoroethylene suture along the free margin of the cusp as illustrated in Fig. 37-5.

Bicuspid Aortic Valve

The most commonly performed aortic valve repair in adults is for bicuspid aortic valve with prolapse of one cusp. Although the anatomic arrangement of the bicuspid aortic valve varies, most patients have an anterior cusp attached to the interventricular septum and a posterior cusp attached to the fibrous components of the left ventricular outflow tract (LVOT).

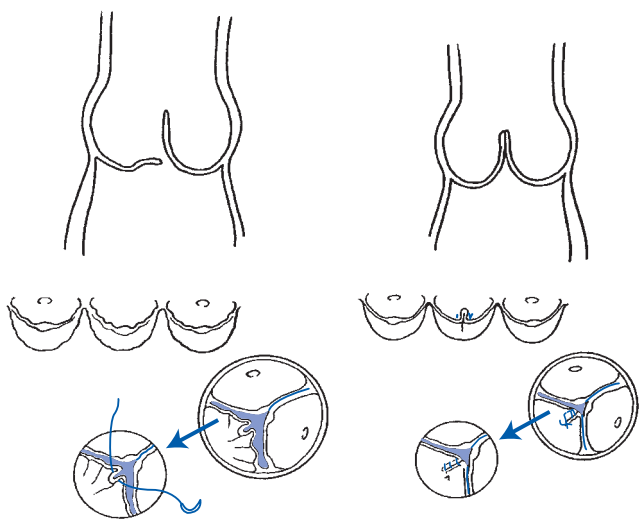

Figure 37-4. Repair of cusp prolapse. The free margin is shortened by plicating the area of the nodule of Arantius.

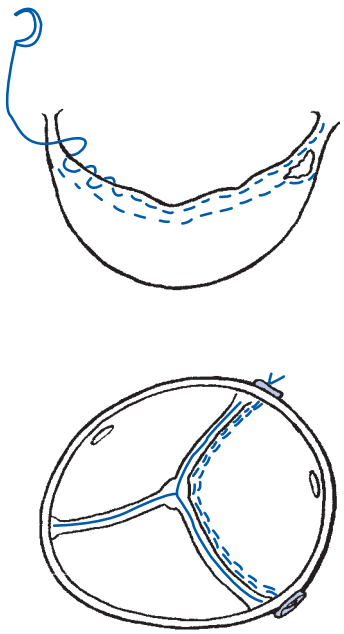

Figure 37-5. Reinforcement of the free margin with a double layer of 6-0 expanded polytetrafluoroethylene suture. This is often done in patients with stress fenestration.

The anterior cusp often contains a raphe at approximately where the commissure between the right and left cusps would be. This cusp is usually the one that is elongated and prolapsed. As long as the posterior cusp is normal, repair is feasible and relatively simple. The raphe is excised and the free margin of the anterior cusp is shortened with plicating sutures as illustrated in Fig. 37-6. The lengths of the free margins of both cusps should be similar and should coapt at the same level. Suspending the arterial walls immediately above the commissures and observing the level of coaptation of each cusp gives an estimate of the level of coaptation of the cusps.

Since most patients with incompetent bicuspid aortic valves have a dilated aortic annulus, an aortic valve–sparing operation may be a more appropriate procedure than simple cusp repair. However, if the aortic sinuses are not aneurysmal and the annulus is only mildly dilated, a reduction annuloplasty to increase the coaptation area of the cusps can be done. This is accomplished by plicating the subcommissural triangles using horizontal mattress sutures of 4-0 polypropylene with Teflon felt pledgets on the outside of the aortic root (Fig. 37-6). The suture is first passed from the outside to the inside of the aorta through the aortic annulus of both cusps 2 mm below their commissure. The same suture is passed again through the annulus and subcommissural triangle 4 or 5 mm below the first one and the ends are tied together over Teflon felt pledgets on the outside of the aorta.

AORTIC VALVE–SPARING OPERATIONS

Aortic valve–sparing operations include various procedures used to preserve the aortic cusps in patients with aortic root aneurysm or ascending aortic aneurysm with aortic insufficiency.[38–40] The complexity of these operations varies with the pathology of the aortic root. Elderly patients with ascending aortic aneurysm and aortic insufficiency often have dilated sinotubular junction, normal or minimally dilated aortic sinuses, and normal cusps, and all that is needed to restore valve function is reduction of the diameter of the sinotubular junction at the time of replacement of the ascending aorta. Younger patients with aortic root aneurysm

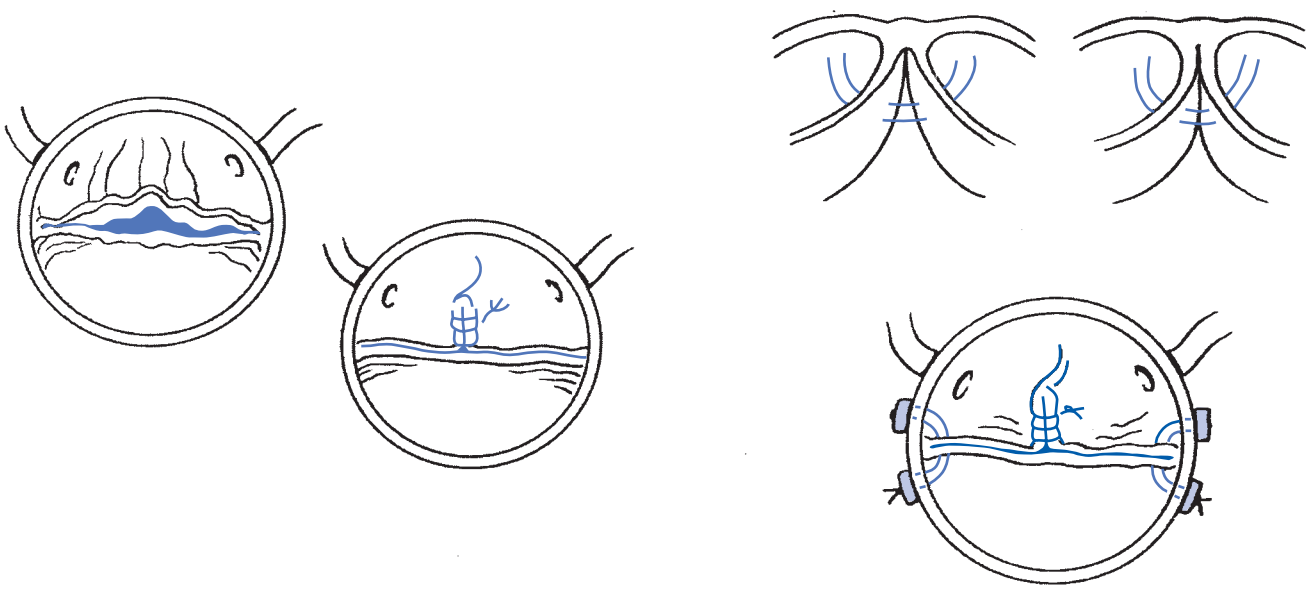

Figure 37-6. Repair of incompetent bicuspid aortic valve. The elongated cusp is shortened and the subcommissural triangles narrowed with sutures.

due to connective tissue disorders of the heart need more complex operations to save the aortic valve cusps.

Ascending Aortic Aneurysm with Aortic Insufficiency

Dilation

Dilation of the sinotubular junction displaces the commissures of the aortic valve outward and prevents the cusps from coapting during diastole (see Fig. 37-3). These patients are often in the sixth, seventh, and eighth decade of their lives and have ascending aortic aneurysms. The dilation of the sinotubular junction is asymmetrical, and often the commissures of the noncoronary aortic cusp are more affected than the other two. If the other components of the aortic root are normal, simple adjustment of the sinotubular junction restores valve competence. This is accomplished by transsecting the ascending aorta 5 mm above the sinotubular junction and pulling the three commissures upward and close to each other until the cusps coapt. The three commissures form an imaginary triangle. The diameter of a circle that contains this imaginary triangle is the diameter of the graft that should be used to reconstruct the sinotubular junction. Because the aortic cusps and sinuses have different sizes, this triangle is not always equilateral and the commissures must be spaced according to the length of the free margin of each cusp. The diameter of the graft and the space between commissures are determined by sizing the diameter of the circle that contains all three commissures with a transparent valve sizer, such as the one used for the Toronto SPV bioprosthesis (St. Jude Medical, St. Paul, Minn). That particular sizer has three equidistant marks, and one can determine the space between the commissures by comparing them to the distance between marks. The tubular Dacron graft is sutured right at the level of the sinotubular junction with a continuous 4-0 polypropylene suture (Fig. 37-7). If after adjusting the sinotubular junction the cusps do not coapt at the same level, one or more cusps may be elongated and the free margin has to be shortened as illustrated in Fig. 37-4. Aortic valve competence can be tested at this time by injecting cardioplegia into the graft under pressure and observing the left ventricle for distention.

If the noncoronary aortic sinus is dilated or altered by aortic dissection, a neo-sinus can be created by tailoring the graft with a tongue of tissue that is sutured directly to the aortic annulus as illustrated in Fig. 37-8. The height of the neo-sinus of Dacron should be 3 or 4 mm more than the diameter of the graft, and the width should be 3 or 4 mm more than the estimated intercommissural distance.

Grafts smaller than 24 mm in diameter should be avoided in adult patients because they may increase left ventricular afterload, particularly if long segments are used, such as with concomitant transverse arch replacement using the elephant trunk technique. If the estimated diameter of the sinotubular junction is less than 24 mm, a larger graft should be used and the end that is anastomosed to the aortic root to recreate the sinotubular junction should be reduced by plicating the graft in the area of the anastomosis.

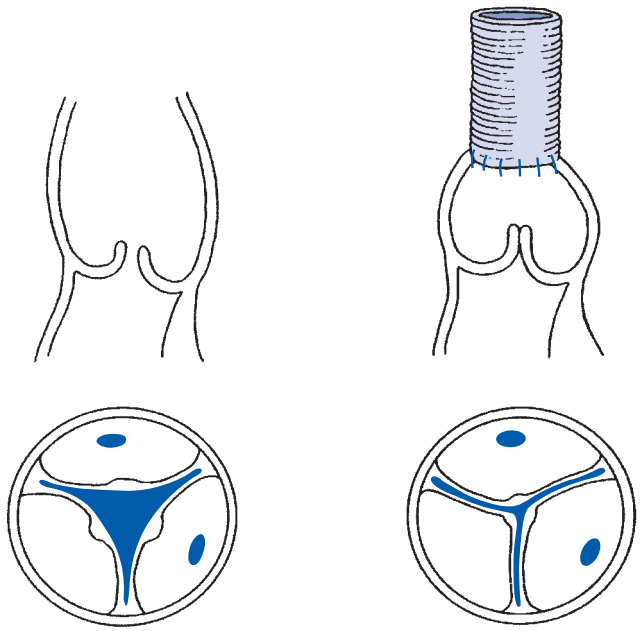

Figure 37-7. Dilation of the sinotubular junction causes aortic insufficiency. Correction of the dilation with a tubular Dacron graft of appropriate diameter corrects aortic insufficiency.

Aortic Root Aneurysm

The indication for surgery in patients with aortic root aneurysm is more often due to the diameter of the root at the level of the aortic sinuses than due to the severity of aortic

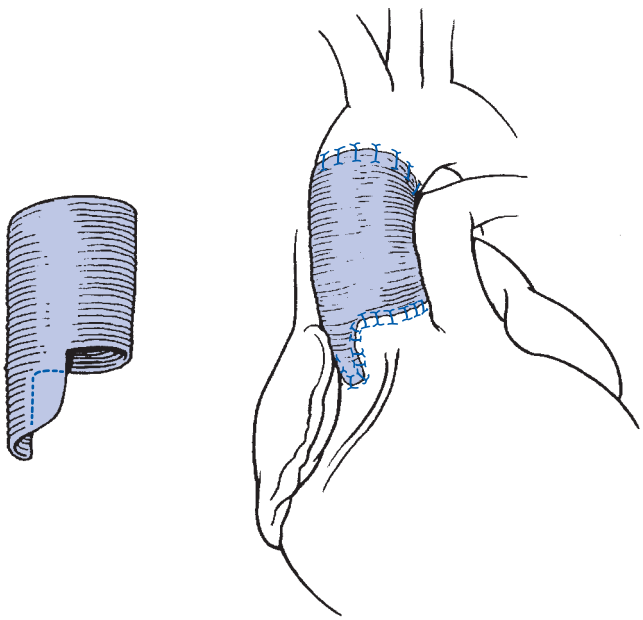

Figure 37-8. Correction of the sinotubular junction and replacement of the noncoronary aortic sinus.

insufficiency. Thus, a large proportion of patients have none, trace, or mild aortic insufficiency at the time of surgery. The aortic cusps are normal or minimally stretched in patients with aortic root aneurysm and mild aortic insufficiency. Even in those with severe aortic insufficiency one or more cusps may remain nearly normal. Stress fenestration along the commissural areas is common in the aortic cusps. In our experience, reinforcement with a double layer of 6-0 expanded polytetrafluoroethylene suture prevents cusp prolapse after the valve repair.

It is not always simple to determine if the free margin of a cusp is normal or elongated. The knowledge that the length of the base of the aortic cusp is 1.5 times longer than the length of its free margin is useful, but application of this anatomic finding requires some experience. Pulling upward on the commissures without causing distortion of the scallop-shaped annulus and observing the level of the nodule Arantius is a useful maneuver to assess cusp prolapse. Normally, the level of the central portion of the free margin should lie closer to the level of the commissures than to the level of the nadir of the aortic annulus. In our experience, almost one-half of all patients who had aortic valve–sparing operations had some degree of cusp prolapse that required shortening of the length of the free margin.

Assessing dilation of the aortic annulus is even more difficult than assessing cusp prolapse. The transverse diameter of the aortic annulus at its nadir is proportional to the area of the cusps, but the relationship between them is variable.[1] However, the transverse diameter of the aortic annulus has to be smaller than the average length of the free margins of the cusps, and the radius of the aortic annulus must be smaller than the average height of the cusps. Using these two parameters, it is possible to estimate whether the annulus is dilated or not.

There are two types of aortic valve–sparing operations for patients with aortic root aneurysm: remodeling of the aortic root and reimplantation of the aortic valve.[39]

Remodeling of the aortic root

The ascending aorta is transsected and the aortic root is dissected circumferentially down to the level of the aortic annulus. All three aortic sinuses are excised, leaving approximately 4 to 6 mm of arterial wall attached to the aortic annulus and around the coronary artery orifices as illustrated in Fig. 37-9. The three commissures are gently pulled vertically and approximated until the cusps coapt. The three commissures form a triangle and the diameter of the circle that contains that triangle is the diameter of the graft to be used for remodeling. In our experience, most grafts are 24, 26, or 28 mm in diameter. Here again the sizers of the Toronto SPV bioprosthesis are very useful to determine the diameter of the graft and also the distance between commissures because they may not be equidistant. The spaces in between the commissures are marked in one of the ends of the graft, and the graft is tailored to create three neo-aortic sinuses (Fig. 37-10). The heights of these neo-sinuses should be approximately equal to the diameter of the graft. The three commissures are

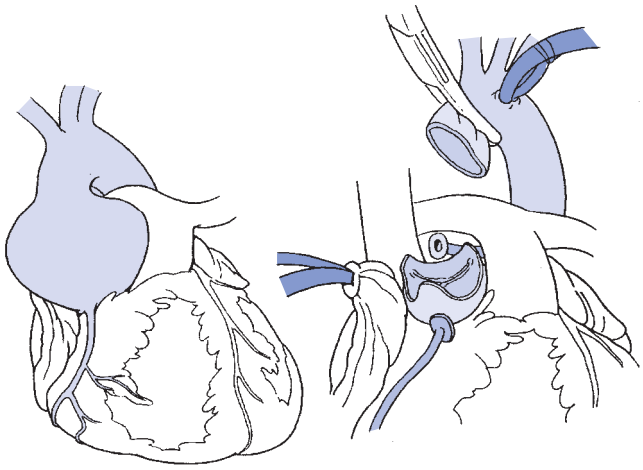

Figure 37-9. Remodeling of the aortic root. The aortic sinuses are excised leaving 4 to 6 mm of arterial wall attached to the aortic annulus and around the coronary arteries.

suspended in the graft (see Fig. 37-10), which is then sutured to the aortic annulus and remnants of the aortic wall with continuous 4-0 polypropylene sutures. The coronary arteries are reimplanted into their respective neo-sinuses. The aortic cusps are inspected to make sure that all three coapt at the same level and well above the nadir of the aortic annulus. If one or more cusps is prolapsing, the free margin is shortened as described above. If one or two cusps have stress fenestra-

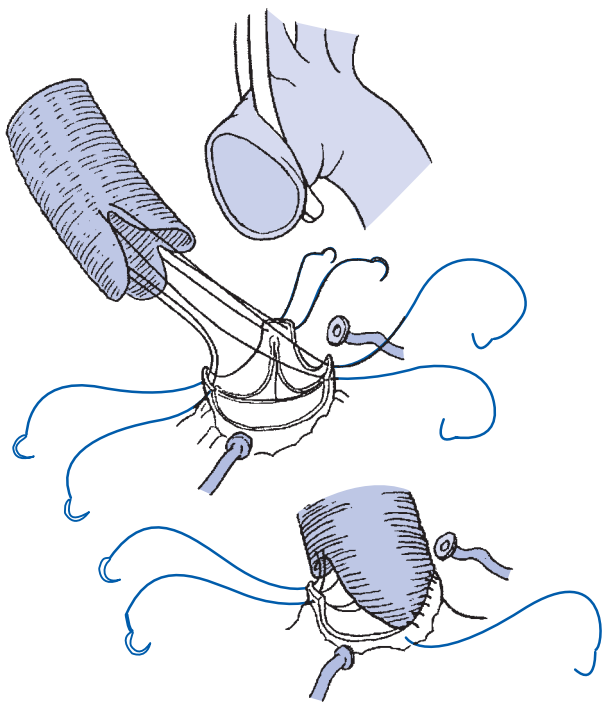

Figure 37-10. A graft of diameter equal to the diameter of the sinotubular junction is tailored to recreate three aortic sinuses. The three commissures are suspended into the tailored graft and the neo-aortic sinuses are sutured to the aortic annulus and remnants of arterial wall.

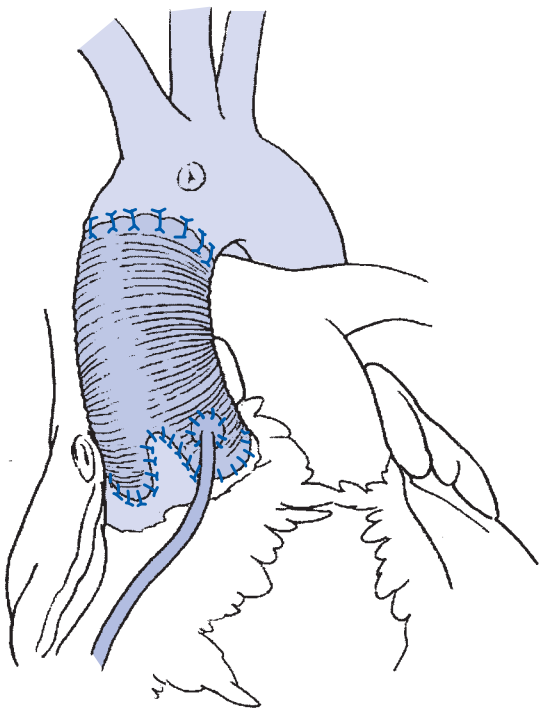

Figure 37-11. Remodeling of the aortic root. The coronary arteries are reimplanted into their respective neo-aortic sinuses and the graft anastomosed to the distal aorta.

tions, the free margin should be reinforced with a fine expanded polytetrafluoroethylene suture. Aortic valve competence can be assessed by injecting cardioplegia under pressure into the reconstructed aortic root and observing the left ventricle for distention or by turning the echocardiography machine on. The graft is then anastomosed to the distal ascending aorta or transverse aortic arch graft, depending on the extent of the aneurysm (Fig. 37-11).

Remodeling of the aortic root may be inappropriate for patients with Marfan syndrome or annuloaortic ectasia because the annulus may continue to dilate and cause aortic insufficiency.[33,40] An aortic annuloplasty along the fibrous component of the LVOT did not prevent late dilation of the aortic annulus in patients with Marfan syndrome.[33] Thus, reimplantation of the aortic valve may be a better operative procedure for patients with annuloaortic ectasia (Fig. 37-12).

Reimplantation of the aortic valve

This procedure can be performed in all patients with aortic root aneurysm, but it is particularly valuable in patients with annuloaortic ectasia and in those with acute type A aortic dissection.

This procedure is more difficult than remodeling of the aortic root because it requires greater knowledge of the functional anatomy of the aortic root since the aortic annulus, the aortic sinuses, the sinotubular junction, and even the aortic cusps are reconstructed. In the original description of this procedure, the aortic valve was reimplanted into a

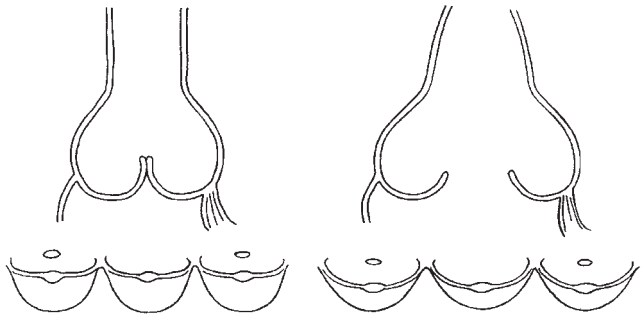

Figure 37-12. Annuloaortic ectasia. The subcommissural triangles of the noncoronary aortic cusp are flattened by dilation of the fibrous tissue.

tubular Dacron graft and no neo-aortic sinuses were created.[39–40] Some studies suggested that the presence of the aortic sinuses is important for normal cusp motion, and potentially, cusp durability.[6–7,42] Several modifications to the reimplantation procedure were introduced to create neo-aortic sinuses.[43] There is now a commercially available graft with sinuses;[44] however, it distorts the aortic annulus because the sinuses in that graft are spherical, and although crescent-shaped, the normal aortic annulus develops along a single horizontal plane.

Following is a description of this procedure as we have been performing it during the past decade with excellent functional results. The three aortic sinuses are excised as described for the remodeling procedure (see Fig. 37-9). Multiple horizontal mattress sutures of 2-0 or 3-0 polyester are passed from the inside to the outside of the LVOT, immediately below the nadir of the aortic annulus, through a single horizontal plane along the fibrous portion of the outflow tract and along its scalloped shape in the interventricular septum as illustrated in Fig. 37-13. If the fibrous portion is thin, sutures with Teflon felt pledgets should be used. A tubular Dacron graft of diameter equal to double the average height of the cusps is selected and three equidistant marks placed in one of its ends. A small triangular segment is cut off along the mark that corresponds to the subcommissural triangle of the left and right cusps (see Fig. 37-13). The sutures previously placed in the LVOT are now passed through the graft. The sutures should be spaced symmetrically if the aortic annulus is not dilated. If there is obvious dilation of the aortic annulus, the sutures should be spaced symmetrically along the muscular interventricular septum and the nadirs of the aortic annulus, but closer together beneath the subcommissural triangles of the noncoronary cusp, because that is where dilation occurs in patients with connective tissue disorders. The sutures are then tied on the outside of the graft. Care must be exercised not to purse-string this suture line. The graft is then cut to a length of approximately 5 cm and pulled gently, and the three commissures are also pulled vertically and temporarily secured to the graft with transfixing 4-0 polypropylene sutures, but they are not tied. Once the three commissures are suspended inside the graft, the

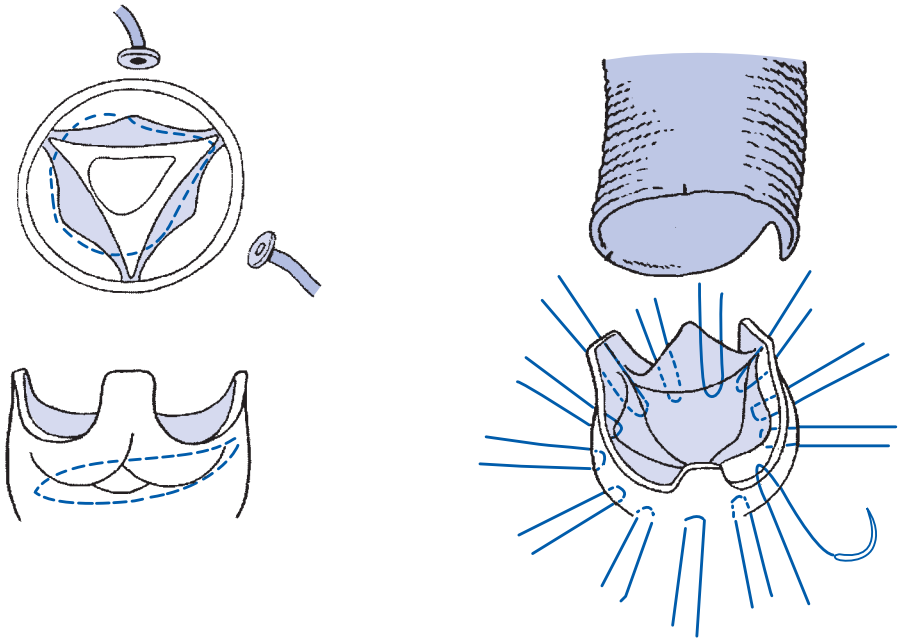

Figure 37-13. Reimplantation of the aortic valve. Sutures are passed below the aortic annulus in a single horizontal plane along the fibrous portion of the left ventricular outflow tract and following the scalloped shape of the aortic annulus along the muscular interventricular septum. These sutures are also passed from the inside to the outside of a tubular Dacron graft.

commissures and the cusps are inspected to make sure they are all correctly aligned. Next, the sutures are tied on the outside of the graft and used to secure the aortic annulus into the graft. This is accomplished by passing the suture sequentially from the inside to the outside right at the level of the annulus and from the outside to the inside at the level of the remnants of the arterial wall. We start at the level of the commissure and stop at the nadir of the aortic annulus where the sutures are tied together. The coronary arteries are reimplanted into their respective sinuses (Fig. 37-14). The coaptation of the aortic cusps is inspected and prolapse is corrected if necessary. It is important that the coaptation level is well above the aortic annulus. Neo-aortic sinuses are created by plicating the graft at the level of the commissure as illustrated in Fig. 37-15. Valve competence can be assessed by injecting cardioplegia into the graft and inspecting the ventricle for distention or by echocardiography. The mean graft size in our patients was 31 mm, range 26 to 34 mm.

RESULTS OF AORTIC VALVE REPAIR

Repair of Incompetent Bicuspid Aortic Valve

The largest published series on aortic valve repair for aortic insufficiency due to prolapse of bicuspid aortic valve came from Cleveland Clinic.[45–46] Casselman and colleagues reported on 94 patients with a mean age of 38 years. The freedom from reoperation was 84% at 7 years.[46] The only factor predictive of reoperation was residual aortic insufficiency at the time of repair.

We compared the clinical outcomes of aortic valve repair with those of aortic valve replacement with biologic valves in patients with incompetent bicuspid aortic valve in a case-match study.[47] The 5-year freedom from reoperation was 91 ± 5% for repair and 94 ± 6% for replacement (p = 0.2), whereas the freedom from moderate or severe aortic insufficiency was 79 ± 8% for repair and 94 ± 6% for

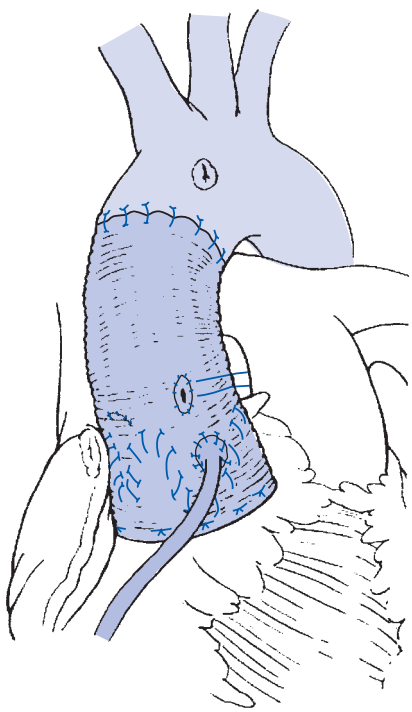

Figure 37-14. Reimplantation of the aortic valve. The commissures and the aortic annulus are sutured inside the graft and the coronary arteries reimplanted.

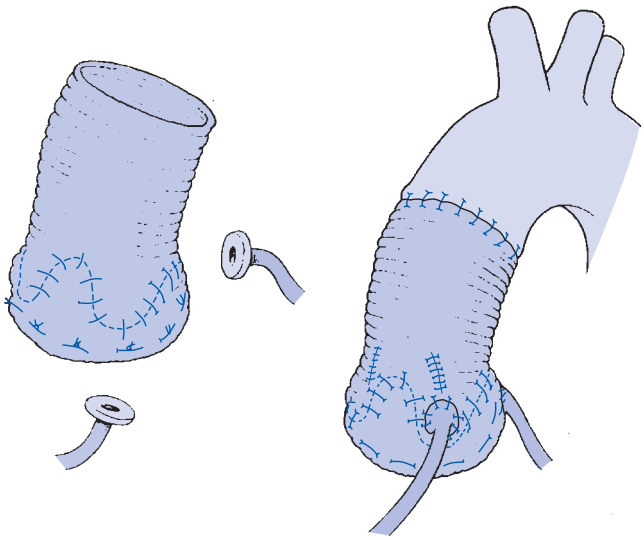

Figure 37-15. Reimplantation of the aortic valve. Neo-aortic sinuses can be created by plicating the graft in the spaces in between the commissures at the level of the sinotubular junction.

replacement ($p = 0.024$). That study indicated that freedom from reoperation underscored freedom from recurrent aortic insufficiency and that the clinical outcomes of aortic valve repair may not be superior to those for aortic valve replacement with biologic valves. In a subsequent study we compared the outcomes of simple aortic valve repair with those of aortic valve–sparing surgery for incompetent bicuspid aortic valve and concluded that since most patients have annuloaortic ectasia, aortic root reimplantation may be more appropriate than simple valve repair.[48] However, Aicher and associates reported a 5-year freedom from recurrent aortic insufficiency of 96%, and a freedom from reoperation of 98% after the remodeling procedure in patients with incompetent bicuspid aortic valve and dilated aortic root.[49]

The appropriateness of aortic valve repair in patients with incompetent bicuspid aortic valve remains unknown. Competent bicuspid aortic valves are durable because a large proportion of patients who require aortic valve replacement for aortic stenosis in their fifth, sixth, and seventh decades of life are found to have bicuspid aortic valve.[15] Thus, aortic valve repair for incompetent bicuspid aortic valves is a reasonable surgical approach in young adults, but the best type of repair remains to be determined. Based on our clinical experience, patient selection is probably even more important than the type of repair because of the heterogeneity of the pathology.

Ascending Aortic Aneurysm with Aortic Insufficiency

We recently reviewed our experience with aortic valve repair in patients with ascending aortic aneurysm, normal or minimally dilated aortic sinuses, and moderate or severe aortic insufficiency.[50] There were 103 patients whose mean age was 65 ± 12 years and 53% were men. The aneurysm extended into the transverse aortic arch in 60% of the patients and 20% had mega-aorta syndrome. The aortic valve repair consisted of adjusting the diameter of the sinotubular junction in all patients. In addition, repair of cusp prolapse was needed in 36 patients, and replacement of the noncoronary aortic sinus in 8. Associated procedures were: replacement of the transverse aortic arch in 62 patients, coronary artery bypass in 28, and mitral valve repair or replacement in 7. The follow-up was complete at 5.8 ± 2.3 years. There were 2 operative and 30 late deaths. The survival at 10 years was 54 ± 7%. Independent predictors of late death were transverse arch aneurysm, the use of elephant trunk technique to replace the arch, and mega-aorta syndrome. Only two patients required aortic valve replacement: one for endocarditis and one for severe aortic insufficiency. The freedom from aortic valve replacement at 10 years was 98%. Only one patient developed severe and six developed moderate aortic insufficiency during the follow-up. The freedom from severe or moderate aortic insufficiency at 10 years was 80 ± 7%. These findings suggest that aortic valve repair in these patients is an excellent alternative to valve replacement, and that the repair remains stable in most patients during the follow-up. Late survival was suboptimal because of the extensiveness of the vascular disease.

Aortic Root Aneurysm

We recently reported our experience with aortic valve–sparing operations for aortic root aneurysm in 220 patients.[51] Their mean age was 46 ± 15 years, 78% were men, and 40% had Marfan syndrome. In addition, 17% had type A aortic dissection, 7% had bicuspid aortic valve, and 22% had transverse arch aneurysm. Previous replacement of the ascending aorta had been done in 10 patients and the Ross procedure in 2. Sixteen patients had severe mitral insufficiency. Approximately one-half of the patients had moderate or severe aortic insufficiency before surgery. The technique of remodeling of the aortic root was used in 53 patients and the reimplantation of the aortic valve in 167. The follow-up was complete at 5.2 ± 3.7 years. All patients had echocardiographic studies during the follow-up. There were 3 operative and 13 late deaths. Patient survival at 10 years was 88 ± 3% and was similar to that of the general population of Ontario. Age >65 years, advanced functional class, and ejection fraction <40% were independent predictors of death. Seven patients developed moderate and five developed severe aortic insufficiency. Overall freedom from moderate or severe aortic insufficiency at 10 years was 85 ± 5%, but it was 94 ± 4% after reimplantation of the aortic valve and 75 ± 10% after remodeling of the aortic root ($p = 0.04$). Five patients required aortic valve replacement; the freedom from aortic valve replacement at 10 years was 95 ± 3%. One patient developed endocarditis 11 years postoperatively, and 8 suffered thromboembolic events. At the latest follow-up 88% of the patients were in functional class I and 10% were in class II. These findings suggested that reimplantation of the aortic

valve provides more stable aortic valve function than remodeling of the aortic root.

Yacoub and colleagues,[52] who exclusively used the remodeling of the aortic root to treat 158 patients with aortic root and ascending aortic aneurysms, reported a freedom from aortic valve replacement of 89% at 10 years, and moderate aortic insufficiency in one-third of the patients.

There were no other long-term studies on clinical outcomes of aortic valve–sparing operations at the time of this writing. There are several reports on early clinical and hemodynamic outcomes of these two types of aortic valve–sparing procedures.[41–42,49,52–58] Most comparative studies suggest that the reimplantation of the aortic valve provides a more stable aortic valve function than the remodeling of the aortic root.[41,54,56,57] Hemodynamic studies suggest that cusp motion and flow patterns across the reconstructed aortic root is more physiologic after remodeling of the aortic root than after reimplantation of the aortic valve.[7,42,44,55,58] In patients who had the reimplantation procedure, flow patterns and cusp motion are better with neo-aortic sinuses than without.[44,55,47] However, in our series of reimplantation of the aortic valve there was no difference in aortic valve function after 10 years in patients with a straight tube or with neo-aortic sinuses. Aortic sinuses seem to decrease the mechanical stress on the aortic cusps, but it is not clinically apparent during the first decade of follow-up.

Another important question regarding aortic valve–sparing operations is whether they are better than the Bentall procedure with mechanical valves.[59] There has been no randomized clinical trial comparing these two procedures for the treatment of aortic root aneurysms or ascending aortic aneurysm, but retrospective studies in patients with Marfan syndrome suggest that the outcomes may be similar.[33,60] In our series, the long-term survival was similar to that of the general population, and the rates of thromboembolism, bleeding, and endocarditis were much lower than what have been reported for mechanical valves.[59,61]

We believe that aortic valve–sparing operations offer an ideal method for treating patients with aortic root aneurysm and normal or minimally diseased aortic cusps. When correctly performed, they provide excellent results and are associated with very low rates of valve-related complications. However, as they are technically demanding operations, only surgeons with extensive experience in aortic surgery should perform them. The surgeon must have a sound knowledge of anatomy and pathology of the aortic valve and be able to apply the concepts of functional anatomy to create an anatomically and functionally satisfactory new aortic root.

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CHAPTER 38

Surgical Treatment of Aortic Valve Endocarditis

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DEFINITION

Infective endocarditis is a disease in which a microorganism colonizes a focus in the heart, producing fever, heart murmur, splenomegaly, embolic manifestations, and bacteremia or fungemia. Early diagnosis of this condition is extremely important because it almost invariably leads to devastating complications and death if not treated with antibiotics, combined or not with surgery.

EPIDEMIOLOGY

Predisposing factors for infective endocarditis are cardiac abnormalities that disrupt the endocardium by means of a jet injury, as well as the presence of blood-borne microorganisms that colonize these abnormal surfaces. Congenitally bicuspid aortic valve is the most common predisposing lesion for endocarditis of the aortic valve.[1] Other congenital abnormalities of the aortic valve, degenerative calcific aortic stenosis, aortic insufficiency secondary to connective tissue disorders, and rheumatic aortic valve disease, are also predisposing lesions for infection. Depending on the virulence of the offending microorganism, normal aortic valves can also be affected. Patients with prosthetic heart valves have a constant risk of developing infective endocarditis.

It is difficult to determine the incidence and prevalence of native aortic valve endocarditis in the general population because this disease is continuously changing.[2] The annual incidence of infective endocarditis is estimated to range from 1.7 to 7.0 episodes per 100,000 person-years in North America.[3–5]

Patients with prosthetic aortic valves are reported to have an incidence of infective endocarditis of 0.2 to 1.4 episodes per 100 patient-years, which varies with the type of aortic valves.[6–12] Approximately 1.4% of patients undergoing aortic valve replacement develop prosthetic valve endocarditis during the first postoperative year.[13]

The incidence of nosocomial endocarditis is increasing because more patients undergo invasive procedures. Infective endocarditis in hemodialysis patients is relatively infrequent, but it is associated with high mortality.[14]

Dental extractions have been demonstrated to produce bacteremia; however, even simple mastication, tooth brushing or cleaning, and oral irrigation can produce transient bacteremia. Endoscopic procedures may also produce bacteremia. Intravenous drug users are particularly susceptible to infective endocarditis, which often occurs in structurally normal heart valves.

PATHOGENESIS AND PATHOLOGY

In 1928, Grant and colleagues[15] theorized that platelet-fibrin thrombi on the heart valve served as a nidus for bacteria adherence. In 1963, Angrist and Oka[16] introduced the term "nonbacterial thrombotic endocarditis" to describe sterile vegetations on a heart valve and provided experimental animal evidence supporting the role of these vegetations in the pathogenesis of endocarditis. Experimental inoculation in animals with preexisting "nonbacterial thrombotic endocarditis" produced by mechanical abrasion of the endothelial covering of heart valves causes a prompt leukocytic infiltration of the thrombi.[17] As the microorganism multiplies, more leukocytes and thrombotic material accumulate in the area and a verrucous vegetation begins to form.

Depending on the virulence of the microorganism and the resistance of the host, the aortic valve can be destroyed and the infection may spread into the annulus and surrounding structures with abscess formation. The abscess may rupture into the pericardial cavity or into a cardiac cavity.

Infective endocarditis of the aortic valve not only causes destruction of the aortic cusps, paravalvular abscess, and cardiac fistulas, but also can cause coronary and systemic embolization of vegetations.[18] Cerebral infarction, either ischemic due to arterial occlusion or hemorrhagic due to rupture of the mycotic aneurysm, is common in these patients.[19,20] Mycotic aneurysms, infarcts, and abscesses of other organs such as spleen, liver, kidneys, and limbs are also common.[17] Aortic valve endocarditis with a large vegetation that prolapses into the left ventricle and comes in contact with the anterior leaflet of the mitral valve can cause secondary involvement of this valve.[21,22]

Infection of a mechanical heart valve is usually located in its sewing ring.[23,24] Infection of a porcine or pericardial valve may involve the cusps, the sewing ring, or both.[25,26] Infection in aortic valve homografts and pulmonary autografts resembles that of the native aortic valve: it begins in the aortic cusps and destroys them, causing aortic insufficiency, but it may also extend into surrounding structures.[27] Endocarditis after aortic root replacement with mechanical valves frequently causes dehiscence of the valve from the aortic annulus with consequent false aneurysm.[28]

MICROBIOLOGY

The microbiology of infective endocarditis of the aortic valve depends on whether the valve is native or prosthetic, and whether the infection is hospital- or community-acquired. *Staphylococcus aureus* and *Streptococcus viridans* are the most common microorganisms responsible for native aortic valve endocarditis.[29–33] *S. aureus* is extremely virulent and able to cause infection in patients with normal aortic valves. *S. viridans* is not as virulent and causes infection that often follows a protracted course. *Staphylococcus epidermidis* and various other streptococci can also cause endocarditis.

Endocarditis due to gram-negative bacteria is uncommon, but it is often resistant to antibiotic therapy and may cause serious complications. *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella* (the HACEK group) are gram-negative bacilli grouped together due to their characteristic fastidiousness requiring a prolonged incubation period before growth. Endocarditis due to the HACEK group is also uncommon. Fungal endocarditis is rare but extremely serious. *Candida albicans* and *Aspergillus fumigatus* are the usual agents.

The microbiology of prosthetic aortic valve endocarditis is different from that of the native valve.[24,29–34] Prosthetic valve endocarditis has been arbitrarily classified as *early* when it occurs within the first 2 months after surgery, and *late* when it occurs after 2 months.[35] However, it is possible that many cases of prosthetic valve endocarditis that occur during the first year after surgery are acquired at the time of implantation of the artificial heart valve. This may be particularly true when the infection is caused by the HACEK group of bacteria. Early prosthetic valve endocarditis is caused by contamination of the valve at the time of implantation by perioperative bacteremia.[13,34] *Staphylococcus epidermidis, S. aureus,* and *Enterococcus faecalis* are among the more common microorganisms responsible for early prosthetic valve endocarditis.[13,29–34] The sources of late prosthetic valve endocarditis are more difficult to determine. Bacteremia is probably the principal cause of late endocarditis. Although streptococci and staphylococci are commonly encountered in these patients, a myriad of microorganisms can cause late prosthetic valve endocarditis.[24,29,34]

Nosocomial infections are often caused by *S. aureus* or other staphylococci.

In a small proportion of cases of aortic valve endocarditis, no microorganism can be cultured from either the blood or surgical specimens.[29–34] This is called "culture-negative endocarditis," but it is important to rule out fastidious microorganisms and every effort should be made to identify them.

CLINICAL PRESENTATION AND DIAGNOSIS

It is helpful to classify infective endocarditis as acute and subacute because there are major differences between these two clinical presentations. Subacute endocarditis is often caused by less virulent microorganisms such as *S. viridans.* When this organism affects a diseased aortic valve, the clinical course is protracted and antibiotics alone cure most cases. On the other hand, acute endocarditis is frequently caused by a virulent microorganism such as *S. aureus* and may affect a normal aortic valve. The clinical course is acute, and antibiotics alone seldom cure the infection.

The onset of subacute endocarditis in most cases is subtle, with low-grade fever and malaise. Patients think they have the "flu" and are often treated with oral antibiotics for a week to 10 days with improvement of symptoms. However, in most cases the symptoms recur a few days after stopping antibiotics. In the majority of cases no predisposing factor is identified. An aortic valve murmur is present in nearly all patients because they have preexisting aortic valve disease. Splenomegaly is common. Clubbing of the fingers and toes may develop in long-standing cases. Skin and mucous membrane signs occur late in this form of endocarditis. Petechiae appear on any part of the body. Small areas of hemorrhage may be seen in the ocular fundi. Hemorrhages in the nail beds usually have a linear distribution near the distal end, hence the name splinter hemorrhages. Osler nodes are acute, tender, barely palpable nodular lesions in the pulp of the fingers and toes. Bacteria have been cultured from these lesions. Embolization of large vegetation fragments may cause dramatic clinical events such as acute myocardial infarction (AMI), stroke, or splenic or hepatic infarcts. Any other organ also may be involved. Destruction of the aortic cusps causes aortic insufficiency and heart failure. The blood pathology is not distinctive in subacute endocarditis. Anemia without reticulocytosis develops in patients untreated for more than a few weeks. The leukocyte count is moderately elevated. Blood cultures frequently identify the offending microorganism.

The clinical course of acute endocarditis is often fulminating. A preexisting source of bacteremia may be

identified. This form of endocarditis can present with all the symptoms and signs described under subacute endocarditis, but they are more acute and patients are often sicker with overwhelming signs of sepsis. Early metastatic infections are common. Two physical signs are seen only in acute endocarditis: the Janeway lesion (a painless red-blue hemorrhagic lesion a few millimeters in diameter found in the palms of the hands and in the soles of the feet) and the Roth spot (an oval pale area surrounded by hemorrhage near the optic disc). Acute endocarditis is common in patients with no preexisting aortic valve disease. Early cardiac decompensation due to aortic insufficiency is common. Paravalvular abscess is also common, and depending on the location of the abscess, the electrocardiogram may show an increased PR interval or heart block. The blood picture is one of acute sepsis. Blood culture often isolates the infecting agent.

Prosthetic valve endocarditis may present as acute or subacute endocarditis.

Doppler echocardiography is extremely useful in the diagnosis and management of infective endocarditis.[36–39] Transesophageal echocardiography is usually better than transthoracic echocardiography, and multiplane is better than monoplane for the diagnosis of endocarditis. Echocardiography can detect vegetations as small as 1 or 2 mm in size, but it is more reliable in native than in prosthetic valve endocarditis. It is more useful for tissue than for mechanical valves because of the acoustic shadowing of ball, disc, or leaflet motion of mechanical heart valves. Echocardiography is also extremely sensitive for detecting paravalvular abscess and cardiac fistulas.[39,40]

Clinical investigators from Duke University proposed certain criteria for confirming or rejecting the diagnosis of infective endocarditis.[41] These criteria have been confirmed by other investigators and their limitations addressed by others.[42–44] A modified version of the Duke criteria has been proposed[44] and it is shown in Table 38-1.

Table 38–1.

Modified Duke criteria for the diagnosis of infective endocarditis

Major criteria

- Blood culture positive for infective endocarditis
  Typical microorganisms consistent with infective endocarditis from two separate blood cultures: *Streptococcus viridans, S. bovis*
  HACEK group, *S. aureus,* or community-acquired enterococci, in the absence of a primary focus, or
  Microorganisms consistent with infective endocarditis from a persistently positive blood culture, defined as follows:
  At least two positive cultures of blood drawn >12 hours apart, or
  All of three or a majority of >4 separate cultures of blood (with the first and last samples drawn at least 1 hour apart)
  Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer to *C.burnetii* >1:800

- Evidence of endocardial involvement:
  Echocardiogram positive for infective endocarditis: TEE recommended in patients with prosthetic valves, rated at least as "possible endocarditis" by clinical criteria, or complicated endocarditis, such as endocarditis with paravalvular abscess;
  TTE as the first test in other patients as follows:
  Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation;
  Abscess;
  New partial dehiscence of prosthetic valve
  New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria

- Predisposition, predisposing heart condition, or injection drug use
- Fever
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctiva! hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above, or serological evidence of active infection with an organism consistent with infective endocarditis
- Echocardiographic minor criteria eliminated

Definite endocarditis = 2 major criteria, or I major + 3 minor criteria, or 5 minor criteria
Possible endocarditis = 1 major + 1 minor, or 3 minor criteria
HACEK group = Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.
Source: Used with permission from Li et al.[44]

Heart catheterization and coronary angiography increase the risk of embolization in patients with aortic valve vegetations and should be avoided. Newer computed tomography (CT) imaging techniques to diagnose coronary artery disease are useful in these patients.

TREATMENT

An appropriate antibiotic is the most important aspect of the management of patients with infective endocarditis.[18,29,30] Antibiotic therapy should be started soon after obtaining several blood cultures. The initial choice of antibiotics is based on clinical circumstances and the suspected source of infection. Patients who had recent dental work should receive antibiotics to counteract bacteria from the oral cavity; those who had recent urinary or colonic procedures should be treated with antibiotics that are effective against gram-negative bacteria.

Intravenous drug users are usually infected with *S. aureus* or *S. epidermidis*, and antibiotics should be chosen accordingly. Once the microorganism is identified by blood cultures and its sensitivity to specific antibiotics is known, antibiotic therapy is adjusted accordingly. A combination of two or three antibiotics that potentiate each other is often needed in the treatment of endocarditis caused by virulent microorganisms. Intravenous antibiotic therapy is continued for 6 weeks.

It is difficult to eradicate infection caused by virulent microorganisms with antibiotics alone because these microorganisms often destroy the native aortic valve very rapidly and cause aortic insufficiency and congestive heart failure (CHF). These infections are usually due to *S. aureus, Pseudomonas aeruginosa, Serratia marcescens*, or fungi.

Surveillance blood cultures are performed in 48 hours to monitor the efficacy of antibiotic therapy. The patient must be watched closely for signs of CHF, coronary and systemic embolization, and persistent infection. Daily electrocardiograms and frequent echocardiograms are performed during the first 2 weeks of treatment. With any evidence of increasing aortic insufficiency, enlarging vegetations, recurrent embolism, paravalvular abscess, or persistent infection, surgery should be immediately performed. It is important to operate on patients before they develop intractable heart failure, cardiogenic or septic shock, or extensive aortic root abscesses. Patients with vegetations larger than 10 mm present a clinical problem because they are more likely to develop serious complications and early surgery is justifiable.[36–38]

Anticoagulation is not effective in preventing embolization of vegetations in native and biologic valves and is associated with an increased risk of neurologic complications.[45,46]

Early surgical treatment should be considered in patients with signs of CHF, acute valve dysfunction, paravalvular abscess or cardiac fistulas, recurrent systemic embolization when aortic valve vegetations are present, and persistent sepsis despite adequate antibiotic therapy for more than 4 to 5 days. Prosthetic valve endocarditis is best treated by early surgery, particularly in patients with mechanical valves.[25,31,32] Acute endocarditis of the aortic valve due to *S. aureus* is also best treated with early surgery because of the destructive power of the bacteria.[29,30]

Patients with neurologic deficits should have CT or magnetic resonance imaging performed to determine if the cerebrovascular accident is ischemic or hemorrhagic. Ischemic damage is far more common than hemorrhagic damage, but both are associated with increased mortality and morbidity.[45–48] Mycotic aneurysms should be treated before valve surgery. Aortic valve replacement should be postponed for 2 weeks after an ischemic stroke and 4 weeks after a hemorrhagic stroke if possible.[48]

SURGICAL TREATMENT

Patients who need surgery are often very sick and may be in CHF. For this reason and because they often require complex and long surgical procedures, myocardial protection is of utmost importance. Another important aspect of surgery for endocarditis is avoidance of contamination of the surgical field, instruments, drapes, and gloves with vegetations and pus. Instruments used to extirpate contaminated areas in the heart should be discarded before reconstruction of the ventricle and aortic root begins. In addition, local drapes, suction equipment, and surgical gloves should all be changed.

When the infection is limited to the cusps of the native aortic valve or a bioprosthetic valve, complete removal of the valve and implantation of a biologic or mechanical valve usually resolves the problem. There is no evidence that bioprostheses are better than mechanical valves in patients with active infective endocarditis.[33] Some investigators believe that aortic valve homograft is ideal for patients with active endocarditis,[49–51] but the fact is that it can become infected like other valves.[52] Some surgeons favor the pulmonary autograft, particularly in young patients.[53]

If the aortic annulus is involved in the infective process, resection of the necrotic or inflamed area is needed before a prosthetic valve can be implanted. The defect created by the resection should be patched before a prosthetic valve is implanted. We prefer to use fresh autologous pericardium to patch small defects (1 or 2 cm wide) in the aortic root and LVOT, and glutaraldehyde-fixed bovine pericardium for larger defects.[54,55] Some surgeons also use Dacron fabric to reconstruct the aortic root.[55–57] Here again, aortic valve homograft is believed to be ideal for reconstruction of the aortic root and LVOT.[50,58–60] The mitral valve of the aortic valve homograft can be used to patch defects in the LVOT by correctly orienting the homograft. However, an aortic valve homograft is by no means a substitute for radical resection of all infected tissues, because persistent infection can occur with this biologic valve.[61,62] The pulmonary autograft has also been used in cases of extensive destruction of the aortic root,[63] but again, this valve is no substitute for radical resection of all infected tissues.

Surgery for aortic root abscess and/or cardiac fistulas is challenging. The most important aspect in the surgical treatment of these patients is radical resection of all infected tissues.[25,31,55] We believe that the type of valve implanted is less important than complete extirpation of all infected and edematous tissues.[55] These patients frequently require replacement of the entire aortic root and reconstruction of the surrounding structures that are also involved by the abscess. These operations must be individualized because the pathology of aortic root abscess is variable. Extensive resection and reconstruction may be needed.[54,55] Thus, patching of the interventricular septum, dome of the left atrium, intervalvular fibrous body, right atrium, and pulmonary artery may be necessary, as well as repair of the left and/or right coronary arteries. The aortic root is often replaced with a valved conduit.

Aortic root abscess extending into the intervalvular fibrous body or into a prosthetic mitral valve is particularly difficult to treat.[64] In these cases, the resection and reconstruction can be performed through the aortic root and dome of the atrium.[64,65] When an aortic valve homograft is used for this type of reconstruction, the anterior leaflet of the mitral valve of the homograft can be used as patch material for the new fibrous body between the aortic and mitral valves. Actually, aortic and mitral valve homografts in a single bloc of tissue have been used to treat this condition.[66]

Postoperative complications are common after surgery for active infective endocarditis. Septic patients may have severe coagulopathy and may bleed excessively after cardiopulmonary bypass. Antifibrinolytic agents, particularly aprotinin, should be used. Transfusion of platelets, cryoprecipitate, and fresh frozen plasma are often necessary to obtain hemostasis. Radical resection of aortic root abscess may cause heart block, for which a permanent pacemaker will be needed postoperatively. Depending on the patient's clinical condition before surgery, multiorgan failure may develop postoperatively. Neurologic deterioration may occur in patients with preexisting cerebral emboli. Pulmonary, splenic, hepatic, and other metastatic abscesses seldom require surgical treatment. Large metastatic abscesses may have to be drained, and in the case of the spleen, splenectomy should be performed because of the risk of rupture.[67]

Clinical Results

The prognosis of aortic valve endocarditis depends largely on when the disease is diagnosed, on the offending microorganism, and how promptly it is treated.[29,68] Patients with prosthetic aortic valve endocarditis have a more serious prognosis than patients with native aortic valve endocarditis,[29,30] and nosocomial infections are associated with higher mortality than community-acquired infections.[69–70] The results of surgery for infective endocarditis have improved significantly during the past three decades.[18] The operative mortality for patients with infection limited to the cusps of the aortic valve is largely dependent on the patients' presentation at the time of surgery, age, and comorbidities. Most reports indicate that the operative mortality is under 10%.[30–31] The operative mortality is higher for prosthetic valve endocarditis and ranges from 20 to 30%.[25,31–34] Surgery for aortic root abscess is also associated with higher operative mortality.[55–58]

The 10-year survival after surgery for infective endocarditis is around 50 to 60%.[31,32]

Patients operated on for active infective endocarditis have a higher risk of developing endocarditis again than do patients with prosthetic valves who never had endocarditis.[31,32] In a series from our unit, 8 of 122 patients developed recurrent infection after a mean interval of 47 months; freedom from recurrent endocarditis at 10 years was 79% ± 9%.[31] In most of these patients, a different microorganism caused the second episode of endocarditis.

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CHAPTER 39

Minimally Invasive Aortic Valve Surgery

Prem S. Shekar • Lawrence H. Cohn

Valvular heart disease has dominated cardiac surgery since its beginning along with coronary artery bypass grafting (CABG). Traditionally, valvular heart surgery has generally been performed via a full sternotomy incision with cardiopulmonary bypass. However, the increase in numbers of older patients and patients with multiple comorbidities has spurred the need for developing techniques that are less invasive in order to hasten postoperative recovery by reducing incisional pain, improving respiratory function, and producing an overall reduction in trauma. Indeed, the emergence of possible percutaneous options for management of valvular heart disease has demanded the development of alternative, more attractive surgical options.

REASONS AND PRINCIPLES: MINIMAL ACCESS AORTIC VALVE SURGERY

For purposes of simplicity, we will focus a large initial part of the discussion on patients undergoing primary aortic valve surgery. We will speak about reoperative minimal access aortic valve surgery toward the end of this chapter.

There are a variety of reasons to perform minimal access aortic valve surgery:

1. It provides a cosmetically superior incision.
2. There is reduced postoperative pain.
3. There is faster postoperative recovery.
4. There is improved postoperative respiratory function due to preservation of a part of the sternum and the integrity of the costal margin.
5. It can be performed with the same degree of ease and speed as a conventional operation, with no difference in mortality.
6. It provides access to the relevant parts of the heart and reduces dissection of other areas.
7. It greatly facilitates a reoperation at a later date, as the lower part of the pericardium remains closed.

The principles of these approaches are the same:

1. The ability to safely apply a stable aortic cross-clamp.
2. The ability to visualize the aortic valve completely and perform a successful replacement with standard techniques.
3. The ability to achieve the same degree of myocardial protection as through a midline sternotomy approach.
4. The ability to deal with issues of the aortic root, the ascending portion, and the arch of the aorta with relative ease and without conversion.
5. The ability to quickly convert to a standard midline sternotomy if compromising situations arise.

Minimal access aortic valve surgery can be safely performed if the following important adjuncts are available and criteria are met.

1. Experienced cardiac anesthesiologists are available.
2. Transesophageal echocardiography (TEE) is available in every case and an experienced echocardiographer is present to interpret findings.
3. The ability to place pulmonary artery catheters with pacing capabilities and transjugular coronary sinus catheters.
4. The ability to place percutaneous arterial and venous cardiopulmonary bypass cannulae.
5. The ability to use vacuum-assisted venous drainage on cardiopulmonary bypass.
6. Minimal access retractors and other relevant instruments that facilitate this surgery are available.
7. The ability to remotely monitor myocardial protection and distention by TEE.
8. Surgeons experienced with conventional aortic valve surgery and minimal access surgery are available.

There are at least four different minimal access surgical approaches to the aortic valve: (1) upper hemisternotomy, (2) right parasternal approach, (3) right anterior thoracotomy, and (4) transverse sternotomy.

THE UPPER HEMISTERNOTOMY APPROACH

This is undoubtedly the most popular of all minimal access approaches to the aortic valve, and has been popularized by the surgeons of the Cleveland Clinic and Brigham and Women's Hospital.[1,2]

It is performed through a 6- to 10-cm vertical midline incision over the upper part of the sternum, starting at or just above the level of the manubriosternal angle. The sternotomy is performed with the standard saw starting at the level of the sternal notch up to the level of the third or fourth intercostal space. The sternotomy is then continued into the right or left third or fourth intercostal space using a narrow-blade oscillating saw, taking care not to cut too deeply to avoid injuring mediastinal or pericardial structures (Fig. 39-1). The decision to cut into the third or fourth intercostal space can be made preoperatively with the chest x-ray being a guide to the amount of exposure you will need. We would favor the fourth interspace, as this almost always produces the most ideal exposure. It is very important to ensure that the sternotomy is absolutely midline and that the midline sternotomy is not carried beyond the level of the transverse portion. Failure to adhere to these principles will result in either a lateral fracture, resulting in three sternal fragments, or a continued lower extension of the midline fracture with retraction that produces severe intraoperative bleeding and difficulty in closure. There is no need to prophylactically divide the right or left internal mammary arteries (LIMAs) with this incision. If care is taken not to damage them, they will usually gently retract away.

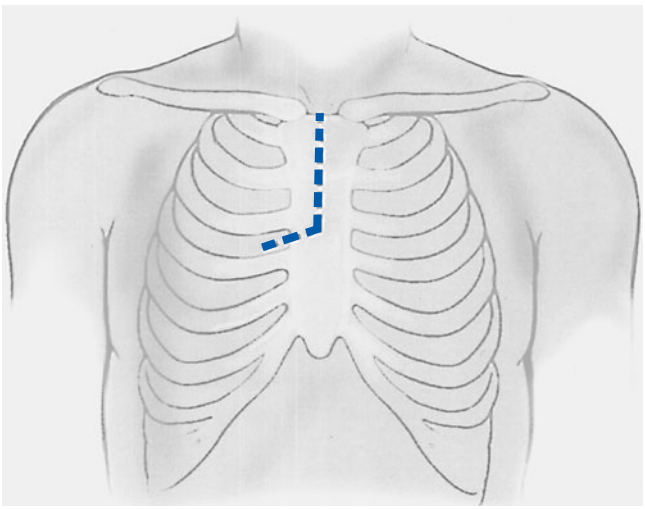

Figure 39-1. Incision for minimally invasive aortic valve surgery via upper hemisternotomy.

We use a Koros-Baxter retractor to retract the sternal edges. The pericardium is opened in the midline and carried inferiorly, and at least three pericardial stay sutures are applied to either side with the needles left on. The retractor is removed and the pericardium is tacked to the dermis of the skin and tied down. This facilitates exposure by elevating the pericardial contents forward into the operating field. The Koros-Baxter retractor is then replaced. Care must be taken when reopening the retractor, as sudden retraction with elevated cardiac structures could impede venous return causing a sudden drop in cardiac output which could lead to refractory arrhythmias in patients with severe aortic stenosis.

We perform an epiaortic ultrasound to exclude atheromatous disease in the ascending aorta before proceeding to systemic heparinization and ascending aortic cannulation in the standard fashion. We favor placement of a percutaneous venous cannula via the right or left femoral vein. There are a variety of custom long venous cannulae that are available (usually 20F or 22F) and they are inserted using the Seldinger technique. The cannula is guided into the right atrium and the tip can be placed in the superior vena cava under TEE guidance. Alternatively, when an adequate amount of the right atrial appendage is seen via the hemisternotomy incision, it may be directly cannulated with the appropriate cannula. We do not favor this approach unless there is difficulty with percutaneous cannulation, as it does increase clutter in this relatively small incision. The patient is then placed on cardiopulmonary bypass. We use tepid bypass with core cooling to 34 to 35°C. We cannot overemphasize the need for vacuum-assisted venous drainage to facilitate this operation.

A retrograde cardioplegia catheter can be placed in the coronary sinus via the right atrial appendage. This may require a minor adjustment to reduce the angulation of the catheter and its insertion can be facilitated by the use of TEE. Alternatively, this catheter can be placed by the anesthesiologists prior to incision via the transjugular route. Although we routinely use a transaortic left ventricular vent, a right superior pulmonary vein or a left atrial dome vent can be easily placed via this incision.

The operation then proceeds as usual. The aorta is cross-clamped and cardioplegia is delivered antegrade through the aortic root. Usually 1 L of cold blood cardioplegia is delivered. TEE is used to monitor left ventricular distention in patients who may have aortic insufficiency. Additional cardioplegia is delivered into the coronary sinus in a retrograde fashion and directly into the coronary arteries upon aortotomy. Standard aortic valve replacement is then carried out through an oblique aortotomy (Fig. 39-2). Upon completion of the procedure, the patient is rewarmed and the aortotomy is closed. A de-airing needle is placed in the ascending aorta before removal of the aortic cross-clamp and performance of appropriate de-airing maneuvers.

The heart nearly always recovers spontaneous sinus rhythm. If the heart goes into ventricular fibrillation, it will need to be cardioverted using the external defibrillator pads placed prior to commencement of the operation.

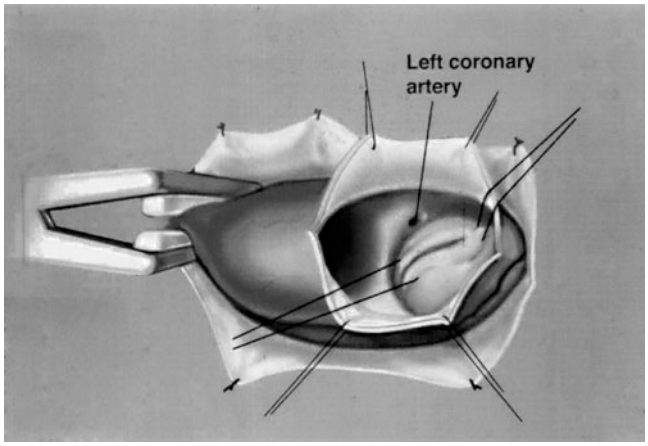

Figure 39-2. Exposure through an upper hemisternotomy incision.

Cardioversion can be facilitated by turning the cardiopulmonary bypass flows down to decompress the heart and appropriate drugs given. It is usually quite difficult to introduce internal defibrillator blades through this incision, although pediatric blades can sometimes be successfully placed. Appropriate preoperative placement of external defibrillator pads cannot be overemphasized. The heart is de-aired using TEE guidance. In the absence of the ability to reach in and agitate the heart, a combination of ventricular filling, table positioning, and external compression is used to successfully de-air the left heart. While this can always be successfully completed, patience may be an important part of facilitating this.

Prior to emergence from bypass, pacing wires and drainage tubes will have to be placed. Invariably, there is adequate atrial and ventricular myocardium exposed to place pacing wires. We usually bring these wires out in the right inframammary area through the right side. We place fluted silastic drains from a subxiphoid approach. It is very important to perform these placements with the heart decompressed on bypass in order to prevent injury. Small incisions are made in the subxiphoid area and long grabbing forceps are used to make two retrosternal tunnels, one of which will puncture the pericardium to facilitate placement of a pericardial drain, and the other will remain in the retrosternal plane. These are placed with a combination of tactile and visual control. In cases in which drains were not placed before removal from bypass and decannulation, we recommend opening the right or left pleural space and placement of transpleural drainage tubes. Placement of subxiphoid drains is not recommended after the heart is full. Weaning from cardiopulmonary bypass is then performed in the standard fashion followed by decannulation and protamine administration.

We usually leave the pericardium open. While checking the area for bleeding, some of the important sites to inspect are the coronary sinus due to the placement of the retrograde catheter (which will need full sternotomy conversion for control), areas of pacing wire placement and drainage tube entry (which may or may not require institution of bypass for visualization and control), sites of left ventricular vents, the lower edge of the sternotomy/pericardiotomy, and the internal mammary vessels on the side. The sternum is closed using three or four horizontal sternal wires and an oblique wire placed between the lower intact segment of the sternum and the angular segment of the incision.

Minimally invasive aortic valve replacement via the upper hemisternotomy approach was originally developed by Cosgrove and Sabik at the Cleveland Clinic[1] and soon after by Cohn and colleagues at the Brigham and Women's Hospital in Boston.[2] Gillinov and colleagues reported their excellent results in 365 cases by 2000[3] and today upper hemisternotomy is the approach of choice for isolated aortic valve surgery at the Cleveland Clinic. Mihaljevic[4] and colleagues from the Brigham group reported their experience with 1000 minimally invasive valve operations between 1996 and 2003, of which 526 were aortic valve procedures. They reported low levels of morbidity and mortality that were equal to or better than those seen with conventional techniques.

Recently, numerous authors have published their results with upper hemisternotomy minimal access aortic valve replacement. Most, if not all, report excellent outcomes. In their experience, Liu and associates[5] reported easier surgical access, less pain, shorter respiratory support time, lower blood loss, decreased incidence of infection and sternal dehiscence, and shorter hospital stay. In a prospective randomized study, Bonacchi and colleagues[6] reported similar findings in 2002. Sharony and coworkers[7] reported their experience with minimally invasive aortic valve surgery in the elderly and were able to demonstrate its safety in this fragile population with morbidity and mortality comparable to those of standard techniques.

THE RIGHT PARASTERNAL APPROACH

The first foray into the world of minimal access aortic valve surgery was with use of this approach. This approach seemed to be the most logical and elegant at a time when the focus was on the morbidity of the sternotomy, and surgeons were compelled to come up with this alternative.

This was performed via a vertical upper right parasternal incision. The second, third, and fourth costal cartilages were removed and the right internal mammary vessels were usually ligated and divided. It provided a similar approach to the aortic valve, and techniques of cannulation, cardiopulmonary bypass, myocardial protection, and valve replacement were the same. It soon gave way to the more elegant and simple upper hemisternotomy approach. One problem associated with the right parasternal approach was the high incidence of lung herniation, which was not only physiologically disturbing, but also was cosmetically disfiguring, and often required a second operation and mesh closure of the defect.

Cohn and colleagues[8] and Minale and associates[9] described their experiences with the right parasternal incision for aortic valve replacement in 1998. They reported low mortality and morbidity rates and recommended the approach for minimal access aortic valve surgery. Lung herniation led to hemisternotomy.

THE RIGHT ANTERIOR THORACOTOMY APPROACH

This incision is usually performed via the second right intercostal space. Due to the relatively high nature of the thoracotomy, it never continues around to become a true anterolateral thoracotomy. One can see why this would be unappealing for a female patient, as the incision would traverse horizontally across the upper part of the right breast which could lead to scarring and disfigurement. The incision is carried to the right sternal edge, and through this incision the right side of the aorta is easily visualized, and with strategically placed pericardial retraction sutures, the area of interest can easily be moved into the operative field. Aortic and venous cannulation could be performed centrally or peripherally. The rest of the operation is fairly routine as for any other minimal access aortic valve surgery. Special cross-clamps may be required to facilitate this procedure.

This operation is useful for patients requiring isolated aortic valve surgery in whom sternotomy needs to be avoided at all costs. A unique subset of such patients are those who are disabled and routinely ambulate with the use of shoulder crutches. These patients can ambulate early with their crutches without the risk of sternal dehiscence. Another possible subset of patients includes those with a heavily irradiated sternum.

The exposure via this incision could be optimized in cases with poor exposure by extending it across the sternum with a transverse sternotomy just below the manubriosternal angle. Reoperative aortic valve replacement is particularly difficult via this incision and the authors strongly discourage this approach for a reoperation.

Yakub and coworkers[10] and Benetti and colleagues[11] reported their results of minimally invasive aortic valve replacement via the right anterior thoracotomy approach. They reported excellent operative exposure and low mortality and morbidity. Minale and associates[12] reported a small series using a submammary right thoracotomy approach to aortic valve replacement in women with excellent results, especially cosmetically.

THE TRANSVERSE STERNOTOMY APPROACH

There are anecdotal reports of use of this incision for minimal access aortic valve surgery.

Typically an 8- to 10-cm transverse incision is made over the manubriosternal angle extending onto either side. Bilateral second costal cartilages are excised and both internal mammary pedicles are ligated and divided. A transverse sternotomy is performed across the sternal angle. The retractor is placed and the sternal edges are retracted in a craniocaudal plane. Adequate exposure is obtained through this incision to permit central aortic cannulation and a routine aortic valve replacement; however, venous cannulation, retrograde coronary sinus catheter placement, and left ventricular vent placement (except transaortic) may have to be performed percutaneously. Because the mammary arteries are sacrificed, this incision never gained much popularity.

Lee and associates,[13] De Amicis and colleagues,[14] and Aris and coworkers[15] reported that their small series with the transverse sternotomy approach yielded good results. However, Bridgewater and colleagues[16] reported an unacceptably high incidence of morbidity (i.e., re-exploration for bleeding, paravalvular leaks, and longer hospital stay) and mortality with this approach.

REOPERATIVE MINIMAL ACCESS AORTIC VALVE SURGERY

The Brigham and Women's Hospital routinely performs minimal access reoperative aortic valve replacement in patients who have previously undergone coronary artery bypass grafting or other cardiac surgery.

According to the STS database, patients requiring a reoperative aortic valve replacement following previous coronary artery bypass grafting have a mortality risk of about 8 to 12% with the procedure. The high risks are associated with the performance of a reoperation in an older patient with more comorbidities and patent or diseased bypass grafts.

There are several indications for this operation.

1. There is a definite subgroup of patients that has undergone coronary bypass surgery who had mild or no aortic stenosis at the time of their original operation, who will eventually progress to have severe aortic stenosis over time. This has sparked a discussion about the management of moderate aortic stenosis in those with coronary artery disease (CAD).[17]
2. These patients are older and sicker, and have many comorbid conditions.
3. They need a simple, safe, and effective operation.
4. The area of interest is the ascending aorta and aortic root.
5. Dissection of the rest of the heart and bypass grafts provides no additional benefit and can be potentially harmful.
6. Clipping the LIMA is not mandatory with alternative protection strategies.

Operative Strategy

Preoperatively, a computed tomogram of the chest with angiography and three-dimensional reconstruction is performed to ascertain the exact location of the old bypass grafts and their location relative to the sternum (especially the LIMA).[18] Coronary angiography and percutaneous coronary and graft intervention with drug-eluting stents are done as appropriate in order to optimize the revascularization as much as possible. Heart failure is controlled medically.

All cases need intraoperative TEE and a pulmonary artery catheter with atrial and ventricular pacing wire placement, and these should ideally be placed prior to incision. Accurate placement of external defibrillator pads is necessary, as internal paddles cannot be introduced in these cases.

All cases will need peripheral cannulation for cardiopulmonary bypass. We prefer right axillary and percutaneous femoral venous cannulation. Appropriate arterial line placement is needed to facilitate circulatory arrest and antegrade cerebral perfusion if required.[19] A standard upper hemisternotomy incision is made that extends into the right fourth intercostal space (Fig. 39-3). The anterior table split is performed using an oscillating saw, while the posterior table split is performed on cardiopulmonary bypass using straight Mayo scissors starting from the top down (preferably from the assistant's side of the table). When the LIMA graft is close to the left side or the middle of the sternum, a preplanned one- or two-third sternotomy to the right is performed. The right pleural space is widely opened. Only 5–10 mm of dissection is performed underneath the left sternal edge, enough to facilitate the placement of the Koros-Baxter retractor. The rest of the mediastinal and aortic dissection is performed on cardiopulmonary bypass. Care is taken not to injure the saphenous vein or radial arterial bypasses. It is not necessary to visualize the LIMA graft.

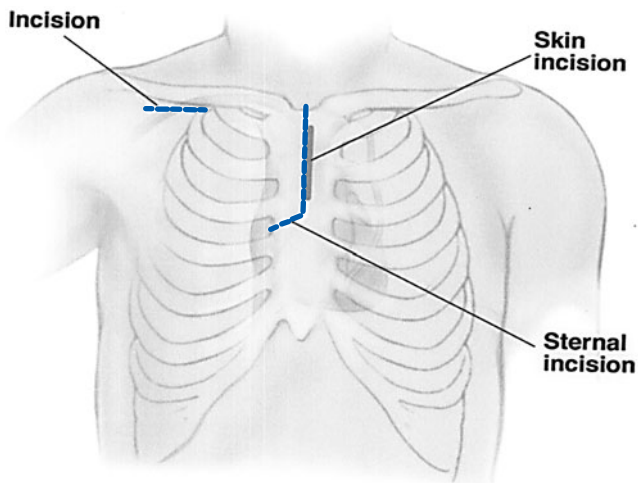

Figure 39-3. Incisions for reoperative minimal access aortic valve replacement.

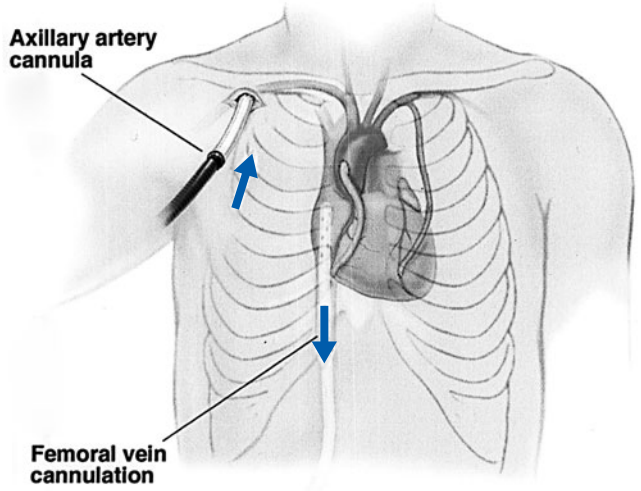

Figure 39-4. Setup for reoperation minimal access aortic valve replacement.

We start core cooling to 25°C only after it is possible to place an aortic cross-clamp. Moderate to deep hypothermia facilitates a low-flow state and reduces myocardial oxygen demand, which is important, as the LIMA will perfuse the heart for the duration of the operation. A retrograde coronary sinus catheter is placed through the right atrial appendage using TEE guidance. Usually, enough right atrial appendage can be seen to place this catheter. Alternatively, a transjugular catheter can be placed prior to incision. After cross-clamping the aorta, 1 L of antegrade cold blood cardioplegia is delivered through the aortic root (Fig. 39-4). Thereafter, 500 mL of cold retrograde blood cardioplegia is used. Simultaneously, systemic hyperkalemia is achieved by instilling 40 mEq of potassium into the cardiopulmonary bypass. Systemic hyperkalemia will achieve diastolic arrest in the left anterior descending artery territory that is perfused by the LIMA distal to the aortic cross-clamp. Throughout the operation, frequent doses of antegrade cardioplegia are delivered through the coronaries and grafts using perfusion cannulae, and 10 to 20 minute doses of retrograde cardioplegia are delivered as well. Systemic hyperkalemia is maintained at a level of 6.0 to 7.0 mEq/L. This will keep the myocardium fairly quiescent during the procedure. Needless to say, heavy doses of potassium may leave the patient with severe hyperkalemia that may not be cleared in the setting of renal dysfunction. In addition to being judicious in such cases, it is imperative that the perfusionists be able to provide ultrafiltration as well.

The aortotomy will be dictated by the location of previous bypass grafts. While in some cases a standard oblique aortotomy can be made, most cases will require a modified aortotomy like a lazy S or a lateral vertical aortotomy. The exposure should be adequate and expeditious valve replacement is the key to success. We aim to keep the cross-clamp time under 60 minutes. There will be continuous flow through the left main orifice due to perfusion from the

LIMA. During débridement and suture placement in the left coronary area, the bypass flows can be reduced or briefly turned off to facilitate exposure. Rewarming is started after the valve is seated. The aortotomy is closed in the standard fashion and a de-airing needle is placed before removal of the aortic cross-clamp. The heart often recovers spontaneous sinus rhythm. Defibrillation is achieved via the external pads if required. De-airing and weaning from cardiopulmonary bypass is as described before.

Drainage tubes are always placed through the right pleural space and subxiphoid placement is not possible and strongly discouraged. Rarely, when the right pleural space is completely fused, the silastic drain could be brought out in the supraclavicular area. It may be possible to place atrial pacing wires, but placement of ventricular wires is almost always quite difficult. We have routinely switched to the use of pulmonary artery catheter–based pacing leads with good success. Closure is fairly standard as described above and care must be taken during the placement of wires on the left side of the sternum and the oblique lower wire.

Byrne and associates[20,21] first published the Brigham experience with reoperative minimal access aortic valve replacement in patients who had previously undergone CABG or other cardiac surgery. Our experience has now grown to over 120 patients and we have had low mortality (<2%) and morbidity rates. This compares very favorably to the mortality and morbidity statistics of patients undergoing reoperation aortic valve replacement using standard techniques.

Conclusion

Minimally invasive aortic valve replacement is safer, effective, and reproducible and should be considered in especially elderly patients without CAD or after previous coronary bypass with intact grafts.

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CHAPTER 40

Percutaneous Aortic Valve Interventions

Michael J. Davidson • Donald S. Baim

The number of patients with clinically significant aortic stenosis (AS) or regurgitation—2 to 3% of the elderly population with calcific AS, including 1 to 2% with congenital bicuspid aortic valve disease—is far greater than the 50,000 annual surgical aortic valve replacements would suggest. Some patients with aortic valve disease defer surgery in light of mild symptoms, whereas others are deemed too ill to undergo cardiac surgery. The latter currently are treated expectantly or by balloon aortic valvuloplasty (BAV), but this 20-year-old technique offers poor magnitude and durability of the physiologic improvement in aortic valve orifice area.

Recent technological advances, however, now indicate that catheter techniques similar to those used for BAV can be used for *percutaneous aortic valve replacement*, avoiding open cardiac access or the use of cardiopulmonary bypass. This new era is truly in its infancy, with most relevant devices still in preclinical testing or phase I human clinical evaluation. As the technology matures, though, it is almost certain to alter the treatment landscape for aortic valve intervention significantly. Implementation of this new technology, however, is going to require close ongoing collaboration among cardiac surgeons, cardiac anesthesiologists, and interventional cardiologists.

Given the outstanding current results of open surgical valve replacement, the principal indication for percutaneous aortic valve intervention probably will remain those patients with severe disease who are deemed inoperable because of comorbid conditions. The broader application of these new percutaneous technologies to good surgical candidates will demand prospective, randomized clinical trials with demonstration of similar prolonged safety and efficacy to surgical valve replacement.

BALLOON AORTIC VALVULOPLASTY

Following successful percutaneous dilation of pulmonary and mitral valves, the first adult BAV was performed by Alain Cribier in 1985.[1] Early experience in the mid-1980s showed that BAV was safe, but it also showed that the technique provided a far smaller increment in aortic valve area (AVA) (i.e., from 0.6 to 0.9 cm^2) than provided by surgical valve replacement.[2,3] The basic technique has not changed significantly since this time, but the procedure has been aided by advances in guidewire and balloon design, as well as newer imaging modalities such as transesophageal and intracardiac echocardiography. The classic retrograde approach has been used most commonly but may present difficulty with crossing a severely stenotic valve or complications caused at the arterial entry site by insertion of large-caliber devices. The antegrade approach is a more recent alternative, in which left atrial access is obtained via the femoral vein using standard transseptal puncture, following which a balloon flotation catheter and guidewire are advanced through the mitral valve, to the left ventricular apex, and then through the aortic valve.

Once a 0.035 to 0.038 inch guidewire has been positioned appropriately using either approach, an 18 to 23 mm valvuloplasty balloon then is advanced over the wire and across the stenotic valve, and it is inflated with dilute contrast material (Fig. 40-1). Rapid ventricular pacing (i.e., 180 to 200 beats per minute) can be initiated to transiently lower cardiac output and allow balloon inflation without the risk of balloon migration. The mechanism of action initially was assumed to be reopening of fused valve commissures, but pathologic investigation reveals little commissural fusion, with the dominant mechanism being fracture of calcified nodules along the leaflets with elastic expansion of the aorta.[4] While nodule fracture allows initially greater leaflet mobility, the effect is modest and relatively short lived as the aorta recoils and the nodule fractures go on to heal.

Early enthusiasm for the technique stemmed from its relative ease compared with surgical valve replacement, and some proponents hoped that BAV might supplant many

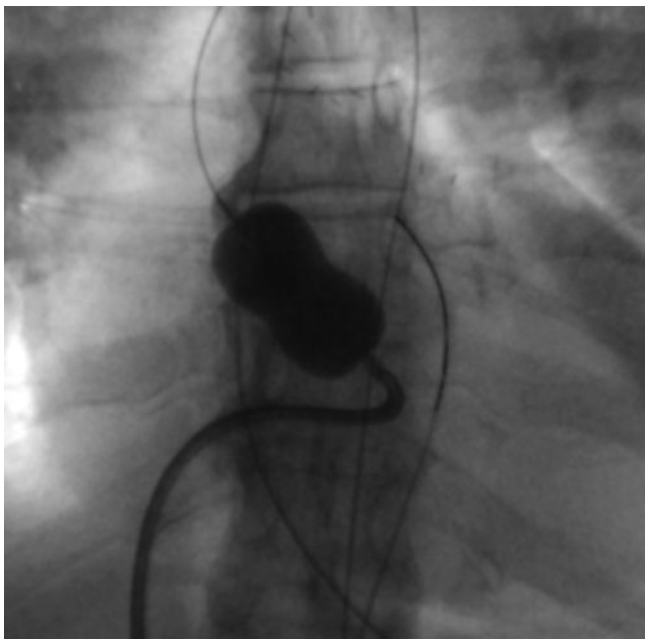

Figure 40-1. Percutaneous balloon aortic valvuloplasty using an antegrade transseptal approach. Native aortic valve calcium is visible at level of balloon "waist."

elective valve replacements. On average, however, AVA increased from 0.6 to 0.9 cm^2 and frequently reverted to severe stenosis over a matter of months. The overall 1-year survival was 65%, and the 1-year survival free of death, aortic valve replacement (AVR), or repeat BAV was 40%.[5] In addition, given the selected patient population, hospital mortality may be as high as 14%, with one-third having periprocedural complications,[3] including vascular access-site problems, arrhythmia, heart block, and stroke. At the present time, then, BAV is indicated only in select patients with severe AS and no surgical options. If stenosis recurs, repeat BAV can be performed.[6] BAV also may be used as a bridge to AVR in hemodynamically unstable patients or in those requiring urgent noncardiac surgery.[7]

VALVED STENTS

The impetus for the development of percutaneous AVRs thus lies in the need for an intervention that is more durable than BAV and that can be used in patients who are too high risk for surgical valve replacement. As in the percutaneous treatment of coronary artery disease (CAD), where simple balloon dilation was replaced by stent implantation to resist vessel recoil, the basic concept of percutaneous valve replacement hinges on the use of an outer stentlike structure to resist the tendency of the aortic annulus and diseased native leaflets to recoil following BAV. In addition, that stentlike structure is used to support three internal leaflets that together constitute a functioning valvular prosthesis. The first known embodiment of a stent-mounted valve was the

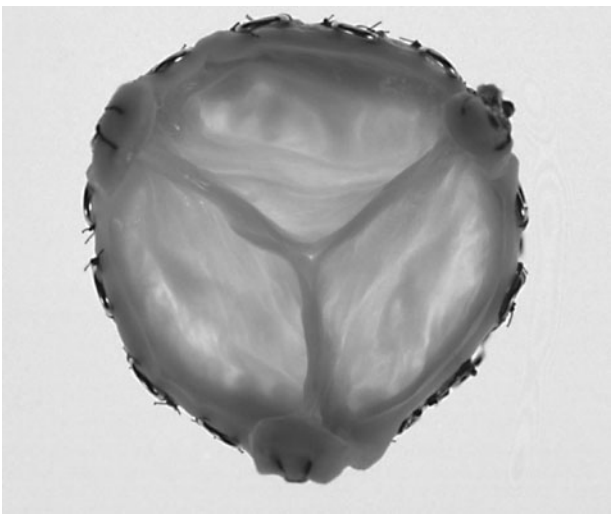

Figure 40-2. The Anderson valve consists of a trileaflet porcine valve mounted in a steel stent structure. The stent could be crimped onto a delivery balloon for percutaneous delivery. Initial use was in the heterotopic (i.e., Huffnagel) position.

Anderson valve, as described in 1992[7] (Fig. 40-2). While not initially optimized for orthotopic catheter-based valve replacement, the concept of a tissue valve mounted within a balloon-expandable stent formed the basis of subsequent percutaneous aortic valve intervention. Refinements in this concept ultimately led to the first human percutaneous aortic valve replacement, performed by Cribier in France in April 2002.[8]

Two devices are currently in active clinical use for percutaneous AVR: the balloon-expandable Cribier-Edwards valve and the self-expanding *Corevalve* prosthesis. A number of other second-generation devices are in various stages of development. All, however, face a common set of technical challenges.

PROCEDURAL AND DEVICE DESIGN CHALLENGES

The first procedural challenge concerns vascular access. The valved stents are, by necessity, significantly larger than most existing percutaneous cardiac catheters and devices. The first-generation delivery catheters are on the order of 22F to 24F, requiring direct femoral or iliac arterial access via surgical exposure if a retrograde approach is used. While an antegrade transseptal approach may enable percutaneous femoral venous access with some, the large sheath size still may predispose to vascular injury. While second-generation devices have reduced the size of the delivery catheter below 20F (by using the lower-profile self-expanding platform and by modifying the valve leaflets), issues with aortic, iliac, and femoral anatomy still may limit the retrograde introduction of even these smaller devices. Other options include retrograde implantation via axillary artery

cutdown or the descending thoracic aorta or antegrade introduction via minimally invasive or thoracoscopic left ventricular transapical puncture.[10] Overcoming vascular access issues is likely to be a central concern as device development continues.

A second design challenge for these devices is the potential for interference with other cardiac structures. The combination of fluoroscopy and transesophageal echocardiography offers limited control of the delivery catheter and makes precise three-dimensional (3-D) positioning difficult. Only the position of the valve prosthesis above the native aortic annulus can be adjusted, with no control of the orientation of the prosthetic leaflets relative to the native commissures. Unlike the pulmonary valve, a prosthesis within the aortic annulus has the potential to impede coronary flow, impinge on anterior mitral leaflet mobility, and apply pressure against the atrioventricular conduction system in the upper ventricular septum.[11,12] In current designs, avoiding interference with the coronary ostia relies on the calcified native aortic leaflets serving as "stand-off" from the coronary ostia; i.e., they preserve the space between the stent wall and the sinuses of Valsalva into which blood can flow from the ascending aorta to the coronary ostia. Rare cases have been described, however, where a large calcified nodule can block a coronary ostium or embolize calcium fragments into the coronary artery. Some stent architectures may extend to the tubular ascending aorta above the sinuses and potentially interfere with future catheter access to the coronary arteries and thus future catheter-based coronary artery interventions. Placement of the valve prosthesis too low in the left ventricular outflow tract (LVOT) can impede mitral leaflet mobility or cause heart block by impinging on the conduction system. Moreover, the first-generation devices are *single-shot implants*, with no possibility for recapture and repositioning, if needed. Second-generation designs, however, emphasize the ability to retrieve and reposition the device as needed during deployment. In addition, newer imaging modalities, including real-time computed tomography (CT) and magnetic resonance imaging (MRI) and 3-D echocardiography may aid in more accurate device placement.

The third challenge facing these devices is that of secure seating within the aortic annulus. First, the valve must be able to deploy accurately in the nonarrested heart. Initial approaches to this have included rapid ventricular pacing (at rates of up to 220 beats per minute) and the use of peripheral cardiopulmonary bypass to temporarily suspend left ventricular ejection. Each of these has potential pitfalls, and some second-generation devices thus are designed to allow stable seating of the valve prosthesis without interrupting cardiac output. Once the valve is placed, it must maintain a stable position within the annulus without risk of embolization. At this point, the valve is not retrievable, necessitating placement in a nonanatomic position (i.e., descending aorta) as a salvage maneuver. Moreover, the irregular surfaces of native calcified aortic leaflets may provide an advantage in serving as a "spacer" from the coronary ostia, but they also predispose to perivalvular leak (Fig. 40-3). In this sense, percutaneous AVR differs from open surgical AVR, where complete decalcification is performed prior to valve insertion to ensure proper valve seating. Options to improve sealing include the use of larger-diameter devices (i.e., 26 mm rather than 23 mm) to overstretch the aortic root into a rounder configuration or use of static or dynamic seals on the outside of the support stent to block potential paths for perivalvular leakage.

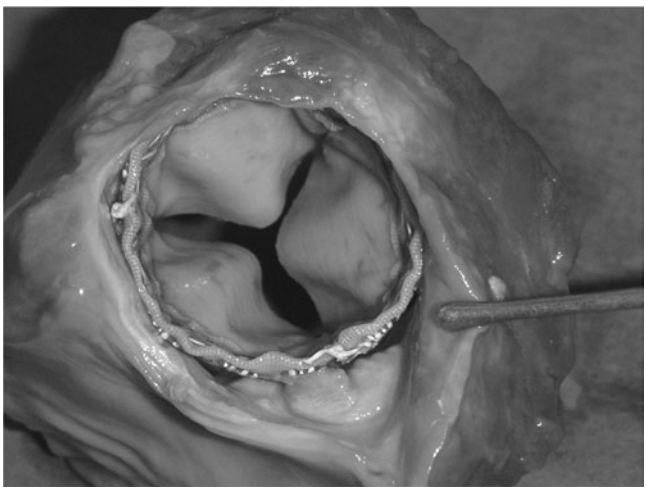

Figure 40-3. Postmortem specimen following placement of Cribier-Edwards valve. This patient suffered from severe perivalvular leak and resulting aortic regurgitation. The valve is positioned appropriately, but there is space present between the stent and the native valve leaflets.

Finally, the durability of these devices must be investigated thoroughly prior to their widespread use. While the initial applications have been in nonsurgical candidates with limited life expectancy, these valves may find use in a broader population. The biomaterials used for leaflet construction often have limited prior clinical application; these materials include equine and porcine pericardium, bovine jugular vein, and tissue-engineered leaflets. Furthermore, the long-term effects of bioprosthetic leaflets striking a rigid metal frame have not been established. Experience with aortic root replacement suggests that accelerated leaflet degradation may occur when valve cusps repeatedly strike a foreign surface.[13] In addition, if indications for these new devices move beyond nonsurgical candidates, the inevitable ingrowth of stent into aortic wall may preclude future simple surgical valve replacement and instead will necessitate full root replacement.

The initial clinical successes with these devices, however limited, have demonstrated that percutaneous AVR is possible and thereby have spawned an enormous professional and commercial impetus to overcome the challenges just described. The second-generation devices now in preclinical testing have begun to address many of the problems faced by early designs, and the pace of innovation in this arena is accelerating.

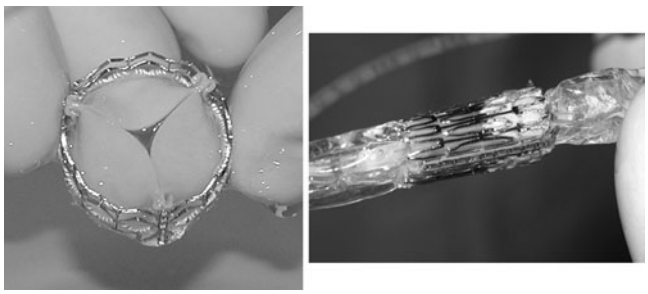

Figure 40-4. The Cribier-Edwards valve consists of three pericardial leaflets sewn to a stainless-steel stent. The valve is stored in the open position to avoid damage to the leaflets (*left panel*) and must be hand-crimped to the delivery balloon (*right panel*) immediately prior to implantation.

BALLOON-EXPANDABLE VALVES

The largest single-center experience to date has been reported from France by Alain Cribier using what is now termed the *Cribier-Edwards 23 mm balloon-expandable aortic valve prosthesis*[9,14,15] (Edwards Lifesciences, Irvine, CA) (Fig. 40-4). The valve consists of three pericardial leaflets (originally equine, now bovine) sewn inside a stentlike stainless-steel structure. The valve is stored in the open position to avoid damage to the leaflets and must be hand-crimped onto a deployment balloon catheter just prior to insertion. The initial approach in the most recent series from France almost exclusively has been antegrade. A transseptal puncture is performed, and a stiff guidewire is passed via the left ventricle and aortic valve into the descending aorta, where it is externalized through a femoral arterial sheath using a snare. After initial antegrade BAV over this wire, the Cribier-Edwards valve is crimped onto a Numed delivery balloon and advanced antegrade until it lies at the level of the native aortic valve calcifications. During rapid ventricular pacing, the balloon is inflated and deflated rapidly, leaving the prosthesis deployed at the level of the aortic annulus (once the valve has been deployed, it may not be retrieved or repositioned). Injection of contrast material into the aortic root confirms valve competence (Fig. 40-5).

Both the pilot phase of the clinical trial (termed I-REVIVE) and the subsequent trial (termed RECAST) have enrolled patients deemed not to be surgical candidates, having been turned down for valve replacement by two independent surgeons. Accordingly, this group of 40 patients had multiple comorbidities and had an average Euroscore of 13 and Parsonnet score of 47. Technical success was reported in 17 of the initial 20 patients (85%), with failures including two procedural deaths.[16] The mean gradient fell from 43 to 8.5 mm Hg, with AVA rising from 0.56 to 1.69 cm^2. This large effective orifice area is achieved by associated expansion of the aortic annulus and the absence of any struts or sewing ring so that it approaches the orifice of the best stentless surgical bioprosthetic valves. While no patients have experienced prosthetic valve dysfunction per se up to 26 months, moderate to severe perivalvular leak has been documented in one-half the patients.[16]

The North American experience with this approach, however, has been mixed. A small U.S. pilot study used an antegrade approach and the 23 mm Cribier-Edwards valve

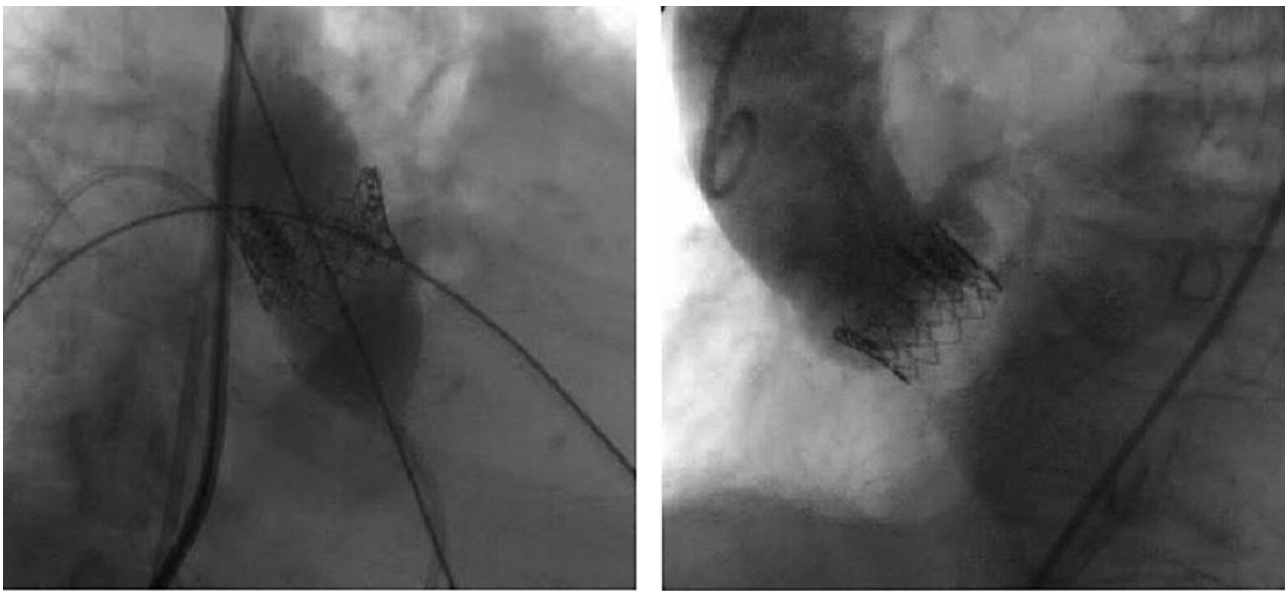

Figure 40-5. Fluoroscopic appearance of Cribier-Edwards valve placement. Stent is expanded by balloon at the level of the native aortic valve using calcification as a guide (*left panel*). Rapid ventricular pacing at 220 beats per minute transiently inhibits cardiac output to allow accurate valve placement. Aortic root injection after successful placement of the valve (*right panel*). Note nonobstructed flow to the coronary arteries and the presence of aortic insufficiency, suggesting perivalvular leak.

(analogous to that used in I-REVIVE and RECAST) but encountered a number of complications due to both the antegrade access and the limited valve size. Two cases of pericardial tamponade and two cases of injury to the anterior mitral leaflet caused periprocedural mortality, whereas several patients experienced significant perivalvular leak and valve migration. In contrast, a series of more than 20 insertions performed by Dr. John Webb in Vancouver, British Columbia, used the retrograde approach with a new, lower-profile deflectable delivery catheter that allows translation around the aortic arch and assists in crossing the stenotic valve. In addition, the Vancouver trial has used a larger 26 mm valve, which has reduced the number of perivalvular leaks. Complications have included two valve embolizations (treated by completing implantation in the descending aorta) and one case of fatal obstruction of the left main coronary artery owing to adverse positioning of a large calcified nodule during device expansion.[17] The U.S. pilot trial has resumed (December 2005) using a similar approach. The total experience with the Cribier-Edwards bioprosthesis—a first-generation device—demonstrates that percutaneous transcatheter AVR is possible but illustrates the significant technical challenges described earlier.

Additional balloon-expandable valved stents have been developed but have not yet entered clinical use.[18] Bonhoeffer and colleagues—the first to use valved stents successfully in humans—have modified the bovine jugular vein valve used in the pulmonary position for aortic use (Fig. 40-7C) and are in the stage of preclinical testing.[11] Other balloon-expandable valve stents likely will enter preclinical testing, but design emphasis has shifted toward self-expanding stent design because of the potentially lower device profile.

SELF-EXPANDING VALVES

A number of other devices have used a self-expanding frame rather than the balloon-expandable platform.[19–25] Of these, the Corevalve revalving system has undergone the largest amount of clinical application. This system uses a nitinol cage housing a valve constructed of porcine pericardial leaflets (Fig. 40-6). The delivery sheath is 21F and has been used in a retrograde fashion from surgical exposure of either the iliac artery, femoral artery, or axillary artery. The patients enrolled in this trial, like those receiving the Cribier-Edwards valve, have been deemed nonsurgical candidates, with an average Euroscore-predicted mortality of 22%. The technique uses peripheral cardiopulmonary bypass in lieu of rapid ventricular pacing for stable device deployment. To date, at least 20 patients have undergone attempted Corevalve placement by Dr. Eberhard Grube. Of the initial 21 patients, 17 had acute procedural success, and 10 of these were discharged from the hospital without major adverse cardiovascular events. There were seven periprocedural deaths (33%) in the early patients but a 90% procedural success rate and 10% mortality in the most recent 10 patients.[25]

Figure 40-6. The Corevalve system consists of pericardial leaflets attached to a self-expanding nitinol frame. In the deployed state. The flared distal end assists in anchoring in the ascending aorta. The stent covers the coronary ostia, but cell size is designed to allow later coronary catheterization.

A number of other devices using the self-expanding frame concept are in various stages of development and preclinical testing but have yet to be implanted in humans (Fig 40-7). These valve designs attempt to overcome several of the limitations faced by earlier generation valves, including embolization, perivalvular leak, inaccurate positioning, and unproven durability. The Sadra Lotus valve (Fig. 40-7A) uses a unique nitinol wire frame whose intrinsic self-expansion can be enhanced by active shortening of the axial length to generate considerable radial force to aid in seating. This can be reversed to allow the valve to be retrieved and repositioned during deployment, and the device includes an outer dynamic sealing system to reduce perivalvular leak. The AorTx design (Fig. 40-7B) suspends pericardial leaflets in a convex triangular nitinol frame that unrolls into a cylindrical shape to anchor in the annulus. This design is also repositionable and retrievable and may confer a leaflet durability advantage because the valve cusps do not come in contact with the frame during valve opening. Another design also achieves this goal but avoids the use of a metal frame altogether; the Direct Flow Medical device uses an inflatable cylindrical support that anchors within the native aortic valve. Additional self-expanding valves intended for aortic use have been developed for a direct left ventricular transapical approach via left thoracotomy or thoracoscopy.[10] While not currently adapted for catheter-based use, it is likely that these and other balloon-expandable valved stents will be modified for a percutaneous platform. Finally, while the vast majority of percutaneous AVR concepts have used biologic tissue for valve leaflets, some early preclinical attempts have been made to implant a mechanical prosthesis percutaneously.[26]

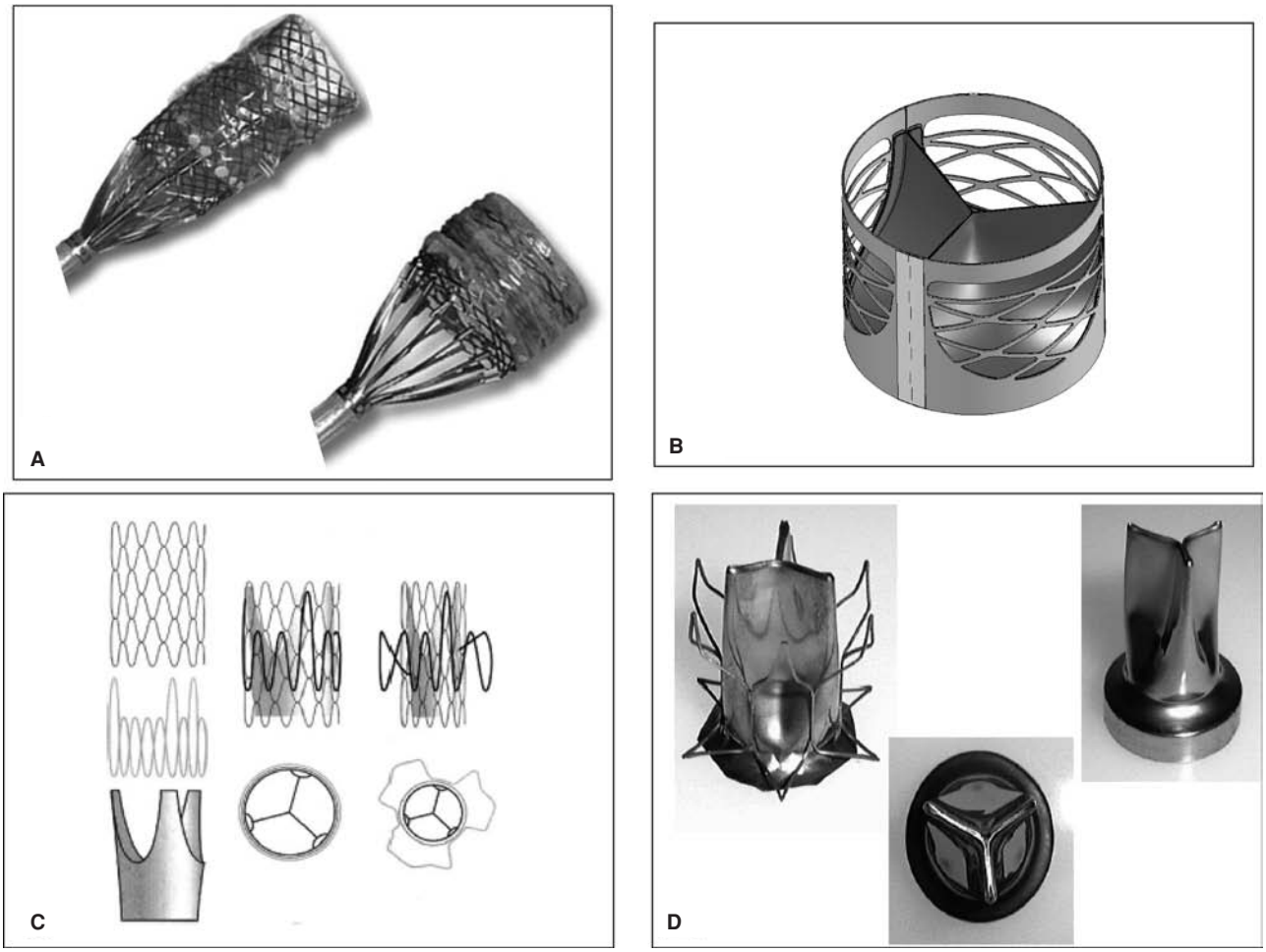

Figure 40-7. Percutaneous aortic valve replacement devices in preclinical development. (A) The Sadra self-expanding Lotus valve uses a nitinol frame that shortens as it is deployed, generating radial force for anchoring. (B) The AorTx valve uses a solid frame structure rather than traditional stent architecture to avoid damage to biologic leaflets. (C) The Bonhoeffer valve uses both self-expanding nitinol and balloon-expandable platinum-iridium components to achieve anchoring in the annulus. (D) The eNitinol thin membrane PercValve is a completely mechanical valve using nitinol leaflets that could become covered with native endothelium.

OTHER CONCEPTS

More radical designs include one by Palmaz and Bailey that uses nanoprocessing to create a valve consisting solely (including the leaflets) of nitinol (Fig. 40-7D). This might allow for rapid ingrowth of native endothelium and has the advantage of deliverability through a 10F sheath. A final percutaneous aortic valve intervention is that conceived at Corazon, which uses a chemical demineralization of the leaflets rather than valve replacement. This concept is to bathe the aortic valve in hydrochloric acid at a pH of 1 for 30 minutes to allow leaflet decalcification. This has been tested in humans during concomitant cardiac surgery, and a percutaneous embodiment was in development before initial capital was exhausted.

TRANSAPICAL APPROACH

The transapical approach offers to overcome vascular access issues as well as the challenges with crossing a stenotic valve and accurate positioning. A small left anterior thoracotomy is performed, and a sheath is placed in the left ventricular apex with a purse-string suture. A guidewire is passed through the native valve under fluoroscopic guidance, and the remainder of the procedure is performed in a manner similar to the transfemoral approach. This approach was validated initially in an animal model[10,27] and has been used clinically in at least 50 patients using the Cribier-Edwards valve.[28] While necessarily more invasive than a transfemoral approach, the shorter catheter length and antegrade approach may afford more stable control of the device for deployment.

CONCLUSION

Although definitive catheter-based AVR is clearly in its infancy (with a total of fewer than 200 patients treated worldwide over the past 3 years), it is clear that a number of percutaneous approaches can allow this procedure. The field is likely to develop rapidly over the next several years, with refinement of the early approaches and emergence of still newer technologies. Guided by clinical results, these devices ultimately may expand beyond the current target of patients with no surgical option to treat high-risk patients, patients with stenosis of a prior aortic valve bioprosthesis, or even as an alternative to surgery. Indeed, pilot studies of valved stent deployment inside previously placed bioprosthetic valves have been promising. Procedures likely will be performed by only a subgroup of "structural" cardiologists and surgeons who possess the training and skills to understand valve pathology more completely, to work transseptally, and to integrate fluoroscopic with 3-D transesophageal and intracardiac echocardiographic images. The remaining engineering obstacles do not appear to be insurmountable but clearly will require the close collaboration of interventional cardiologists with cardiac surgeons (who best understand the valve pathology and repair methods) and engineering teams who must turn these concepts into clinically usable devices.[29]

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PART

IVb

Valvular Heart Disease (Mitral)

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CHAPTER 41

Pathophysiology of Mitral Valve Disease

James I. Fann • Neil B. Ingels, Jr. • D. Craig Miller

THE NORMAL MITRAL VALVE

Anatomy

The mitral annulus is a pliable junctional zone of discontinuous fibrous and muscular tissue that joins the left atrium and left ventricle and anchors the hinge portion of the anterior and posterior mitral leaflets.[1–11] The annulus has two major collagenous structures: (1) the right fibrous trigone, which is part of the central fibrous body and is located at the intersection of the membranous septum, the mitral and tricuspid annulus, and the aortic annulus, and (2) the left fibrous trigone, which is located near the aortic annulus under the aortic left coronary cusp (Fig. 41-1). The anterior mitral leaflet spans the distance between the commissures (including the trigones) and is in direct fibrous continuity with the aortic annulus under the left and noncoronary aortic valve cusps, including the fibrous triangle between the left and noncoronary aortic valve cusps. Fine tendon-like collagen bundles, the fila of Henle, extend out circumferentially from each fibrous trigone a variable distance toward the corresponding side of the mitral orifice. The posterior half to two-thirds of the annulus, which subtends the posterior leaflet, is primarily muscular with little or no fibrous tissue.[10] This muscle is arranged mainly perpendicularly to the annulus, and a less prominent group of muscle fibers is arranged parallel to the annulus.

The mitral valve has two major leaflets, the larger anterior (or aortic or septal) leaflet and the smaller posterior (or mural) leaflet; the latter usually contains three or more scallops separated by fetal clefts or "subcommissures," which are developed to variable degrees in different individuals.[12] The portions of the leaflets near the free margin on the atrial surface are called the *rough zone,* with the remainder of the leaflet surface closer to the annulus being termed the *smooth* (or *bare* or *membranous*) *zone.* The ratio of the height of the rough zone to the height of the clear zone is 0.6 for the anterior leaflet and 1.4 for the posterior leaflet because the clear zone on the posterior scallops occupies only about 2 mm.[12] The two leaflets are separated by the posteromedial and anterolateral commissures, which usually are distinctly developed but occasionally are incomplete. Individual leaflet commissural scallops also can exist.

The histologic structure of the leaflets includes three layers: (1) the fibrosa, the solid collagenous core that is continuous with the chordae tendineae, (2) the spongiosa, which is on the atrial surface and forms the leaflet leading edge (it consists of few collagen fibers but has abundant proteoglycans, elastin, and mixed connective tissue cells), and (3) a thin fibroelastic covering of most of the leaflets.[10] On the atrial aspect of both leaflets, this surface (the atrialis) is rich in elastin. The ventricular side of the fibroelastic cover (the ventricularis) is much thicker, is confined mostly to the anterior leaflet, and is densely packed with elastin. The fibroelastic layers become thickened with advancing age owing to elaboration of more elastin and more collagen formation; similar accelerated changes also accompany the progression of myxomatous (degenerative or "floppy") mitral valvular disease. In addition to these complex connective tissue structures, the mitral leaflets contain myocardium, smooth muscle, contractile valvular interstitial cells, and blood vessels, as well as both adrenergic and cholinergic afferent and efferent nerves.[13–28] Leaflet contractile tissue is neurally controlled and may play a role in mitral valve function.[6,16–19,29–35] The atrial surface of the anterior leaflet exhibits a depolarizing electrocardiogram spike shortly before the onset of the QRS complex, and the resulting contraction of leaflet muscle, along with contraction of smooth muscle and valvular interstitial cells, possibly aids leaflet coaptation before the onset of systole, as well as stiffens the leaflet in response to rising left ventricular (LV) pressure.[16–19,33,35–39] Mitral leaflet stretch of 10% or more also leads to an action potential that initiates leaflet muscle contraction.[37,40]

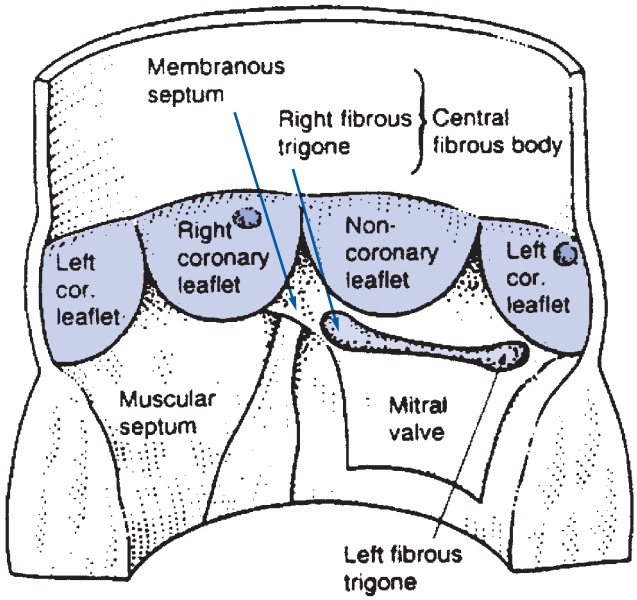


Figure 41-1. Diagram from a pathologic perspective with division of the septum illustrating the fibrous continuity between the mitral and aortic valves. (*Reproduced with permission from Anderson RH, Wilcox BR: The anatomy of the mitral valve, in Wells FC, Shapiro LM (eds): Mitral Valve Disease. Oxford, England, Butterworth-Heinemann, 1996; p 4.*)

Annular Size, Shape, and Dynamics

The average mitral annular cross-sectional area ranges from 5.0 to 11.4 cm^2 in normal human hearts (average is 7.6 cm^2).[41] The annular perimeter of the posterior leaflet is longer than that subtending the anterior leaflet by a ratio of 2:1; i.e., the posterior annulus circumscribes approximately two-thirds of the mitral annulus.[12] Annular area varies during the cardiac cycle and is influenced directly by both left atrial (LA) and LV contraction, size, and pressure.[4,42] The magnitude of change in mitral annular area is 20 to 40% during the cardiac cycle.[4,8,9,42–49] Annular size increases beginning in late systole and continues through isovolumic relaxation and into diastole; maximal annular area occurs in late diastole around the time of the P wave on the electrocardiogram.[4,8,44,46,47,50] Importantly, half to two-thirds of the total decrease in annular area occurs during atrial contraction (thus *presystolic*); this component of annular area change is smaller when the PR interval is short and is abolished completely when atrial fibrillation is present or when the ventricle is paced. Annular area decreases further (if LV end-diastolic volume is not abnormally elevated) to a minimum in early to middle systole.[4,7,8,42,44]

The normal human mitral annulus is roughly elliptical (or kidney-shaped), with greater eccentricity (i.e., being less circular) in systole than in diastole.[3,4,8,41,42,46,48,51] In its most elliptical configuration, the ratio of minor to major diameters is approximately 0.75. In three-dimensional space, the annulus is somewhat saddle-shaped (or, more precisely, a hyperbolic paraboloid), with the highest point (farthest from the LV apex) located anteriorly in the middle of the anterior leaflet; this point is termed the *fibrosa* in the echocardiography literature and the *saddle horn* by surgeons and is readily identified in echocardiographic images owing to the common junction with the aortic valve. The low points are located posteromedially and anterolaterally near the commissures, and another less prominent high point is located directly posterior.[4,52,53] The ratio of annular height to commissure-commissure width is highly conserved across species and thought to be an important modulator of systolic leaflet stresses.[54] During the cardiac cycle, annular regions adjacent to the posterior leaflet (where the leaflet attaches directly to the atrial and ventricular endocardium) move toward (during systole) and away (during diastole) from the relatively immobile anterior annulus.[4,48] Certain annular segments located near the left fibrous trigone (area of aortic-mitral continuity), however, actually may lengthen slightly during LV ejection, at least in canine and ovine hearts.[55]

The mitral annulus moves upward into the left atrium in diastole and toward the LV apex during systole; the duration, average rate, and magnitude of annular displacement correlate with (and perhaps influence) the rate of LA filling and emptying.[4,8,44,47,56,57] The annulus moves slightly during late diastole (2 to 4 mm toward the left atrium during atrial systole). This movement does not occur in the presence of atrial fibrillation and may be an atriogenic contractile property. The annulus moves a greater distance (3 to 16 mm toward the LV apex) during isovolumic contraction and ventricular ejection. This systolic motion, which aids subsequent LA filling, occurs in the presence or absence of atrial fibrillation and is related to the extent of ventricular emptying; thus it is likely driven by LV contraction.[4,8,46,47,56–62] Subsequently, the annulus moves very little during isovolumic relaxation but then exhibits rapid recoil back toward the left atrium in early diastole. This recoiling increases the net velocity of mitral inflow by as much as 20%.[9,47]

Dynamic Leaflet Motion

The posterior mitral leaflet is attached to thinner chordae tendineae than the anterior leaflet, and its motion is restrained by chordae during both systole and diastole.[12,56] Regions of both leaflets are concave toward the left ventricle during systole,[63–65] but leaflet shape is complex, and anterior leaflet curvature near the free margin actually may be convex to the left ventricle during systole, thus resulting in a sigmoid shape.[50,52,53,66] Leaflet opening does not start with the free margin but rather in the center of the leaflet; leaflet curvature flattens initially and then becomes reversed (making the leaflet convex toward the left ventricle) while the edges are still approximated.[50,64,65] The leading edge then moves into the left ventricle (like a traveling wave), and the leaflet straightens. The leaflet edges in the middle of the valve appear to separate before those portions closer to the commissures, and posterior leaflet opening occurs approximately 8 to 40 ms later.[65–68] Once reaching maximum opening, the edges exhibit a slow to-and-fro movement (like a flag flapping in a breeze) until another less forceful opening impulse

occurs, associated with the *a* wave. During late diastole, the leaflets move gradually away from the LV wall.

Valve closure starts with the leaflet bulging toward the atrium at its attachment point to the annulus. The closure rate of the anterior leaflet is almost twice that of the posterior leaflet, thereby ensuring arrival of both cusps at their closed positions simultaneously (since the anterior leaflet is opened more widely than the posterior leaflet at the onset of ventricular systole).[68] The anterior leaflet actually arrives at the plane of the annulus in a bulged shape (concave to the ventricle), but as the closing movement proceeds and the leaflet ascends toward the atrium, this curvature appears to run through the whole leaflet, from the annulus toward the edge, in a rolling manner. The leaflet edge is the last part of the leaflet to approach the annular plane. Leaflet curvature is more pronounced with the onset of systolic ejection.[64,65]

Mitral valve closure is completed 10 to 40 ms after the initial systolic rise of LV pressure, but leaflet opening motion actually may precede the diastolic pressure crossover point by up to 60 ms.[65,69,70] While the onset of mitral valve closure at the end of diastole appears to be initiated by atrial contraction, competent leaflet closure requires an increase in ventricular pressure above that in the atrium (irrespective of whether or not a normal atrial electrical and mechanical sequence is present) and a proper valve annular size to permit apposition of the valve leaflets at the onset of and during ventricular ejection.[16,42,68]

Chordae Tendineae and Papillary Muscles

Epicardial fibers in the left ventricle descend from the base of the heart and proceed inward at the apex to form the two papillary muscles, which are characterized by vertically oriented myocardial fibers.[11,71] The anterolateral papillary muscle usually has one major head and is a more prominent structure; the posteromedial papillary muscle can have two or more subheads and is flatter.[12] A loop from the papillary muscles to the mitral annulus is completed by the chordae tendineae continuing into the mitral leaflets, which then are attached to the annular ring. The distance from the tip of the human papillary muscle to its corresponding mitral annulus averages 23.5 mm from the tip of the anterolateral papillary muscle to the left trigone and 23.2 mm to the point between the anterior and middle scallops of the posterior leaflet.[72] The distance from the tip of the posteromedial papillary muscle to the right trigone is 23.5 mm and to the annular point between the middle and posteromedial scallops of the posterior leaflet is 23.5 mm. The posteromedial papillary muscle usually is supplied by the right coronary artery (or a dominant left circumflex artery in 10% of patients); the anterolateral papillary muscle is supplied by blood flow from both the left anterior descending and circumflex coronary arteries.[11,73,74]

The posteromedial and anterolateral papillary muscles give rise to chordae tendineae going to both leaflets[12] (Fig. 41-2). The chordae are divided classically and functionally into three groups.[11,75] First-order chordae originate near the papillary muscle tips, divide progressively, and insert on the leading edge of the leaflets; these primary chordae prevent valve-edge prolapse during systole. The second-order chordae (including two or more larger and less branched "strut" chordae) originate from the same location and tend to be thicker and fewer in number[12,75]; they insert on the ventricular surface of the leaflets at the junction of the rough

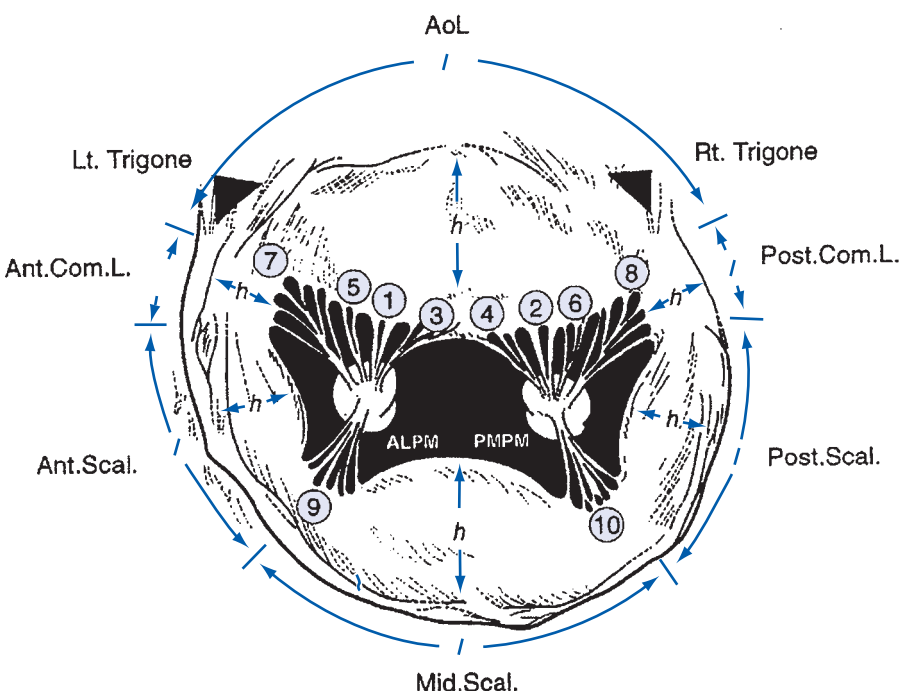


Figure 41-2. Mitral valve and subvalvular apparatus. ALPM = anterolateral papillary muscle; PMPM = posteromedial papillary muscle; AoL = aortic leaflet; Ant.Com.L. = anterior commissural leaflet; Post.Com.L. = posterior commissural leaflet; Ant.Scal. = anterior scallop; Mid.Scal. = middle scallop; h = height of leaflet; l = length of attachment of leaflet; Post.Scal. = posterior scallop; Rt.Trigone = right fibrous trigone; Lt.Trigone = left fibrous trigone; 1 = anterior main chorda; 2 = posterior main chorda; 3 = anterior paramedial chorda; 4 = posterior paramedial chorda; 5 = anterior paracommissural chorda; 6 = posterior paracommissural chorda; 7 = anterior commissural chorda; 8 = posterior commissural chorda; 9 = anterior cleft chorda; 10 = posterior cleft chorda. (*Reproduced with permission from Sakai T, Okita Y, Ueda Y, et al: Distance between mitral annulus and papillary muscles: anatomic study in normal human hearts. J Thorac Cardiovasc Surg 1999; 118: 636.*)

and clear zones, which is demarcated by a ridge corresponding to the line of leaflet coaptation. The second-order chordae (including the strut chordae) serve to anchor the valve, are more prominent on the anterior leaflet, and are important for optimal ventricular systolic function; second-order chordae also may arborize from large chordae that also give rise to first-order chordae. The third-order chordae, also called *tertiary* or *basal chordae,* originate directly from the trabeculae carneae of the ventricular wall, attach to the posterior leaflet near the annulus, and can be identified by their fan-shaped patterns.[75] Additionally, distinct commissural chordae and cleft chordae exist in the commissures. Chordae contain nerve fibers, and some chordae, considered to be immature forms, may contain muscle tissue.[17] In total, about 25 major chordal trunks (range 15 to 32) arise from the papillary muscles in humans, equally divided between those going to the anterior and posterior leaflets; on the other end, over 100 smaller individual chordae attach to the leaflets.[75] Recent studies of porcine mitral valves demonstrate that the chordae have different microstructures based on chordal type.[76] The presence of vessels characterizes the chordae as complex living components that work in coordination with the other elements of the valvular and subvalvular apparatus. The strut chordae on the anterior leaflet have an increased degree of vascularization compared with the other chordae. There also appears to be higher levels of DNA and collagen content in the anterior and posterior marginal chordae compared with the other chordae.[76]

During diastole, the papillary muscles form an inflow tract. During systole, they create an outflow tract that later becomes obliterated owing to systolic thickening of the papillary muscles, thereby augmenting LV ejection by volume displacement.[71] The contribution of the papillary muscles to LV chamber volume is 5 to 8% during diastole but 15 to 30% during systole.[71,77] The anterior and posterior papillary muscles contract simultaneously and are innervated by both sympathetic and parasympathetic (vagal) nerves.[78,79]

Previous analyses of papillary muscle function during the cardiac cycle yielded widely discordant results.[78,80–83] Although the papillary muscles shorten at some point during systole (by upwards of one-fourth their maximum length), this contraction may be isometric or substantially less than that of the LV free wall fibers.[80–82,84–87] In addition, there is no consensus as to the exact timing of papillary muscle contraction and elongation during the cardiac cycle.[78–80,82,83,85,86] Some workers suggest that the papillary muscles contract before the LV free wall so that the mitral valve leaflets are supported during early LV ejection[83]; others, however, report that papillary muscles lengthen during isovolumic contraction and shorten during ejection, as well as during isovolumic relaxation.[79,82] From the standpoint of electromechanics, although papillary muscle excitation occurs simultaneously with the rest of the endocardial surface of the ventricle, the papillary muscles may contract just after the onset of LV contraction.[78,85] Maximal shortening and elongation of the papillary muscle may follow thickening and thinning of an adjacent LV free wall segment.[85,86] Papillary muscle shortening throughout isovolumic relaxation may play a role in opening the mitral valve, and elongation in late diastole may be necessary to permit proper valve closure.[85]

It has been shown experimentally that both papillary muscles closely mimic general LV dynamics; i.e., the papillary muscles shorten during ejection, lengthen during diastole, and change length minimally during the isovolumic periods[80] (Fig. 41-3). These findings suggest that earlier studies suggesting that papillary muscle lengthen during isovolumic contraction and shorten during isovolumic relaxation may have been confounded by some form of myocardial injury or surgical trauma during instrumentation.[80]

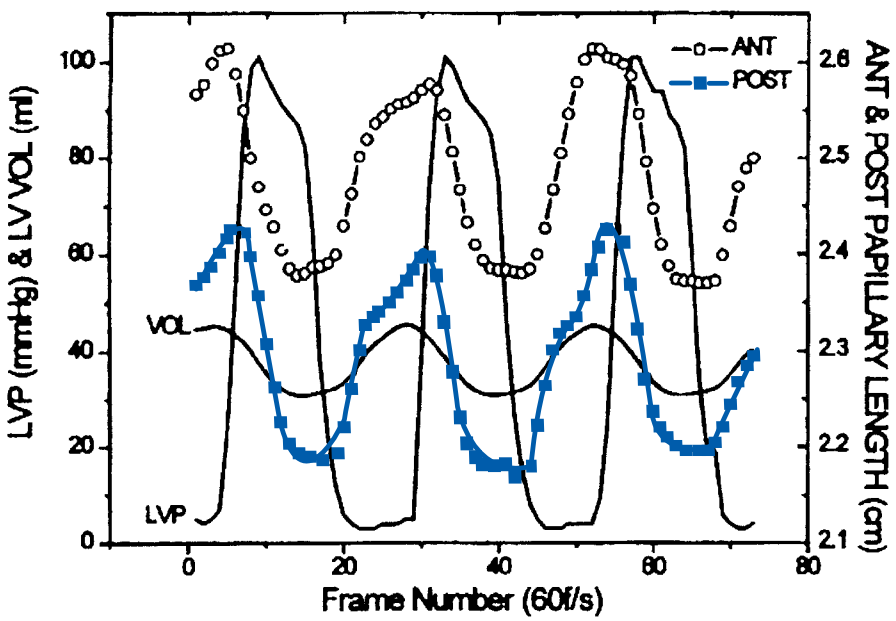


Figure 41-3. Graph showing typical dynamics of the left ventricle and papillary muscles. The papillary muscle lengths are temporally related closely to changes in LV volume (LV VOL). ANT = anterior papillary muscle; POST = posterior papillary muscle. (*Modified with permission from Rayhill SC, Daughters GT, Castro LJ, et al: Dynamics of normal and ischemic canine papillary muscles. Circ Res 1994; 74:1179.*)

MITRAL STENOSIS

Etiology

Mitral stenosis generally is the result of rheumatic heart disease.[88–94] Nonrheumatic causes of mitral stenosis or LV inflow obstruction include severe mitral annular and/or leaflet calcification, congenital mitral valve deformities, malignant carcinoid syndrome, neoplasm, LA thrombus, endocarditic vegetations, certain inherited metabolic diseases, and those cases related to previous commissurotomy or an implanted prosthesis[91–96] (Fig. 41-4). A definite history of rheumatic fever can be obtained in only about 50 to 60% of patients; women are affected more often than men by a 2:1 to 3:1 ratio. Nearly always acquired before age 20, rheumatic valvular disease becomes clinically evident one to three decades later. The association of pregnancy and the clinical onset of symptoms of mitral stenosis is common.

Approximately 20 million cases of rheumatic fever occur in third-world countries annually, with a correspondingly high incidence of advanced mitral stenosis later in life.[97] In the United States, western Europe, and other developed countries, the prevalence of mitral stenosis has decreased markedly. The etiologic agent for acute rheumatic fever is group A beta-hemolytic streptococcus, but the specific immunologic and inflammatory mechanisms leading to the valvulitis are less clear.[97–100] Streptococcal antigens cross-react with human tissues, known as *molecular mimicry,* and may stimulate immunologic responses. Differences in the cellular and extracellular proteins of the many strains of group A streptococcus may be important in the development of rheumatic heart disease. Components implicated in the organism's virulence include the hyaluronic acid capsule and the antigenic streptococcal M protein and its peptides.[97–99] Recent studies show mimicry between streptococcal antigens and heart tissue proteins, combined with high inflammatory cytokine and low interleukin 4 (IL-4) production, leads to the development of autoimmune reactions and cardiac tissue damage.[98,99] The chronic phase of rheumatic valve disease is associated with ongoing serum inflammatory mediators that correlate with the severity of valve involvement and scarring.[100] Along with the individual's immunologic responsiveness, other genetic factors are likely to be involved in the susceptibility to disease development or progression.

In addition to affecting the valves, rheumatic heart disease is a pancarditis affecting to various degrees the endocardium, myocardium, and pericardium[88–90] (Fig. 41-5). In rheumatic valvulitis, mitral valve involvement is the most common (isolated mitral stenosis is found in 40% of patients), followed by combined aortic and mitral valve disease, and least frequently, isolated aortic valve disease, with or without tricuspid involvement. Pathoanatomic changes characteristic of mitral valvulitis include commissural fusion, leaflet fibrosis with stiffening and retraction, and chordal fusion and shortening.[89] Leaflet stiffening and fibrosis can be exacerbated over time by increased flow turbulence.

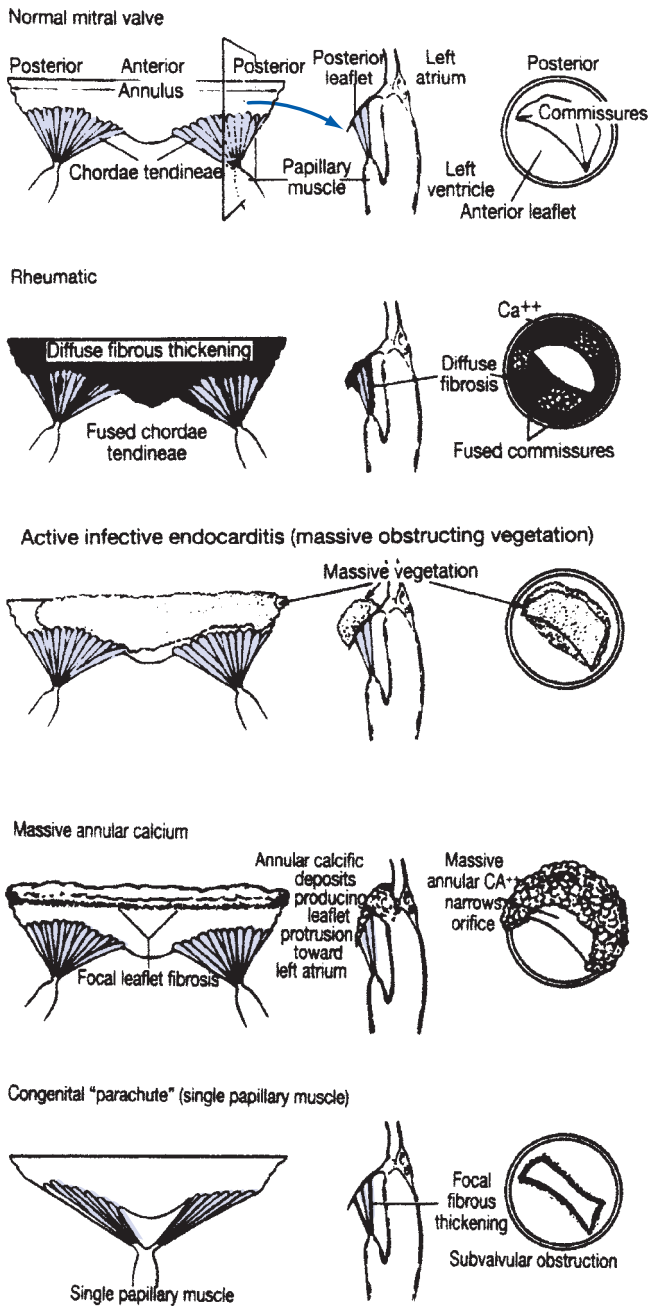


Figure 41-4. Diagrams demonstrating causes of mitral stenosis, including rheumatic heart disease, active infective endocarditis, massive mitral annular calcification, and congenital single papillary muscle syndrome. (*Modified from Waller BF, Howard J, Fess S: Pathology of mitral valve stenosis and pure mitral regurgitation, part I. Clin Cardiol 1994; 17:330. Copyrighted and reprinted with the permission of Clinical Cardiology Publishing Company, Inc., and/or the Foundation for Advances in Medicine and Science, Inc., Mahwah, NJ 07430-0832.*)

Valvular regurgitation can develop owing to chordal fusion and shortening. The chordae tendineae may become so retracted that the leaflets appear to insert directly into the papillary muscles. The degree of calcification varies; it is more common and of greater severity in men, older patients, and those with a higher transvalvular gradient.[90] In some

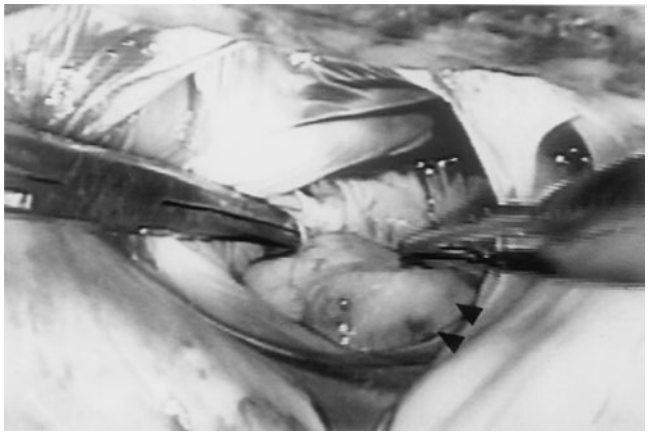


Figure 41-5. Intraoperative photograph of mitral stenosis as a result of rheumatic heart disease. The mitral leaflets are markedly restricted. The arrowheads point to the anterior leaflet near the anterolateral commissure.

cases, rheumatic myocarditis results in cardiac dilatation and progressive heart failure.

Mitral annular calcification may progress to mitral sclerosis and eventually stenosis in elderly patients.[96] The anterior leaflet can become thick and immobile; LV inflow obstruction also results from calcification of the posterior mitral valve leaflet. Calcific protrusions into the ventricle and extension of the calcium into the leaflets further narrow the valve orifice, resulting in mitral stenosis.[96] In these cases, the left ventricle typically is small, hypertrophied, and noncompliant.

Hemodynamics

In patients with mitral stenosis, an early, middle, and late diastolic transvalvular gradient is present between the left atrium and ventricle; as the degree of mitral stenosis worsens, a progressively higher gradient occurs, especially late in diastole.[91,101–103] The average left atrial pressure in patients with severe mitral stenosis may be in the range of 15 to 20 mm Hg at rest, with a mean transvalvular gradient of 10 to 15 mm Hg.[101,103] With exercise, the LA pressure and gradient rise substantially. LV end-diastolic pressure usually is normal.

Another physiologic measurement in patients with mitral stenosis is the (derived) cross-sectional valve area, which is calculated from the mean transvalvular pressure gradient and cardiac output. The transvalvular pressure gradient is a function of the square of the transvalvular flow rate; e.g., doubling the flow quadruples the gradient. At a given flow rate, a smaller valve area corresponds to a higher pressure gradient. Mitral transvalvular flow depends on cardiac output and heart rate. An increase in heart rate decreases the duration of transvalvular LV filling during diastole; the transvalvular mean gradient increases, and consequently, so does LA pressure.[102,104] A high transvalvular gradient may be associated with a normal cardiac output; conversely, if cardiac output is low, only a modest transvalvular gradient may be present.

Because of effective atrial contraction, the mean LA pressure in patients with mitral stenosis and normal sinus rhythm is lower than that in patients with atrial fibrillation.[105,106] Sinus rhythm further augments flow through the stenotic valve, thereby helping to maintain adequate forward cardiac output. The development of atrial fibrillation decreases cardiac output by 20% or more; atrial fibrillation with a rapid ventricular response can lead to acute dyspnea and pulmonary edema.[88,105,106]

Ventricular Adaptation

In patients with isolated mitral stenosis and restricted LV inflow, LV chamber size (end-diastolic volume) is normal or decreased, and the end-diastolic pressure typically is low.[91,107,108] The peak filling rate is reduced, as is stroke volume. Cardiac output thus is diminished as a result of inflow obstruction rather than LV pump failure.[109] LV mass is normal or slightly subnormal in the majority of these patients.[107] During exercise, the ejection fraction may increase slightly; however, LV filling is compromised by the shorter diastolic periods at higher heart rates, resulting in a smaller end-diastolic volume (or LV preload). Therefore, stroke volume and a blunted increase (or even decrease) in cardiac output can occur.[108]

Approximately 25 to 50% of patients with severe mitral stenosis have LV systolic dysfunction as a consequence of associated problems (e.g., mitral regurgitation, aortic valve disease, ischemic heart disease, rheumatic myocarditis or pancarditis, and myocardial fibrosis).[90,103,108] In these patients, LV end-systolic and end-diastolic volumes may be larger than normal. Also, because right ventricular afterload increases as pulmonary hypertension develops in these patients, right ventricular systolic performance deteriorates.[91,110] Clinically, however, increased right ventricular afterload as a result of mitral stenosis usually is associated with normal right ventricular contractility.[91]

Atrial Adaptation

In patients with mitral stenosis who are in normal sinus rhythm, the LA pressure tracing is characterized by an elevated mean LA pressure with a prominent *a* wave, which is followed by a gradual pressure decline.[88,106] The *a*-wave pressure largely reflects the kinetic energy dissipated in overcoming the resistance across the valve. Because of the stenotic valve, coordinated LA contraction is important in maintaining transvalvular flow.[106] The high LA pressure gradually leads to LA hypertrophy and dilatation, atrial fibrillation, and atrial thrombus formation.[90,108,111] The degree of LA enlargement and fibrosis does not correlate with the severity of the valvular stenosis partly because of the marked variation in duration of the stenotic lesion and atrial involvement by the underlying rheumatic inflammatory process.[108] Disorganization of atrial muscle fibers is associated with abnormal conduction velocities and inhomogeneous refractory periods. Premature atrial activation owing to increased

automaticity or reentry eventually may lead to atrial fibrillation, which is present in over half of patients with either pure mitral stenosis or mixed mitral stenosis and regurgitation.[111,112] Major determinants of atrial fibrillation in patients with rheumatic heart disease include older age and larger LA diameter.[111]

Pulmonary Changes

In patients with mild to moderate mitral stenosis, pulmonary vascular resistance is not increased, and pulmonary arterial pressure may remain normal at rest, rising only with exertion or increased heart rate.[101] In severe chronic mitral stenosis with elevated pulmonary vascular resistance, pulmonary arterial pressure is elevated at rest and can approach systemic pressure with exercise. A pulmonary arterial systolic pressure greater than 60 mm Hg significantly increases impedance to right ventricular emptying and produces high right ventricular end-diastolic and right atrial pressures.

LA hypertension produces pulmonary vasoconstriction, which exacerbates the elevated pulmonary vascular resistance.[90,110] As the mean LA pressure exceeds 30 mm Hg above oncotic pressure, transudation of fluid into the pulmonary interstitium occurs, leading to reduced lung compliance. Pulmonary hypertension develops as a result of passive transmission of high LA pressure, pulmonary venous hypertension, pulmonary arteriolar constriction, and eventually, pulmonary vascular obliterative changes. Early changes in the pulmonary vascular bed may be considered protective in that the elevated pulmonary vascular resistance protects the pulmonary capillary bed from excessively high pressures; however, the pulmonary hypertension worsens progressively, leading to right-sided heart failure, tricuspid insufficiency, and occasionally, pulmonic valve insufficiency.[91,110] Severe mitral stenosis ultimately causes irreversible pulmonary vascular changes; cardiac output is low at rest and remains subnormal during exercise.[101]

Clinical Evaluation

Because of the gradual development of mitral stenosis, patients may remain asymptomatic for many years.[88,101,112] Characteristic symptoms of mitral stenosis eventually develop and are associated primarily with pulmonary venous congestion or low cardiac output, e.g., dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea and fatigue. Dyspnea often is precipitated by events that elevate LA pressure, such as physical or emotional stress or atrial fibrillation. In patients with mild mitral stenosis, symptoms usually occur only with extreme exertion. With progressive stenosis (valve area between 1 and 2 cm^2), patients become symptomatic with less effort. When mitral valve area decreases to about 1 cm^2, symptoms become more pronounced. As pulmonary hypertension and right-sided heart failure subsequently develop, signs of tricuspid regurgitation, hepatomegaly, edema, and ascites can be found.

As a result of high LA pressure and increased pulmonary blood volume, hemoptysis may develop secondary to rupture of dilated bronchial veins (or submucosal varices).[88,110] Over time, pulmonary vascular resistance becomes higher, and the likelihood of hemoptysis decreases. Hemoptysis also may result from pulmonary infarction, which is a late complication of chronic heart failure. Acute pulmonary edema with pink frothy sputum can occur owing to rupture of alveolar capillaries.

Systemic thromboembolism, occurring in approximately 20% of patients, may be the first symptom of mitral stenosis; recurrent embolization occurs in 25% of patients.[88,113,114] The incidence of thromboembolic events is higher in patients with mitral stenosis or mixed mitral stenosis–mitral regurgitation than in those with pure mitral regurgitation. At least 40% of all clinically important embolic events involve the cerebral circulation, approximately 15% involve the visceral vessels, and 15% affect the lower extremities.[88,115] Embolization to coronary arteries may lead to angina, arrhythmias, or myocardial infarction; renal embolization can result in hypertension.[88] Factors that increase the risk of thromboembolic events include low cardiac output, LA dilatation, atrial fibrillation, left atrial thrombus, absence of tricuspid or aortic regurgitation, and the presence of echocardiographic "smoke" in the atrium, an indicator of stagnant flow. Patients with these risk factors should be anticoagulated.[88,113–115] If an episode of systemic embolization occurs in patients in sinus rhythm, infective endocarditis, which is more common in mild than in severe mitral stenosis, should be considered.

Patients with chronic mitral stenosis are often thin and frail (cardiac cachexia), indicative of long-standing low cardiac output, congestive heart failure, and inanition.[88] The peripheral arterial pulse generally is normal, except in patients with a decreased LV stroke volume, in which case the pulse amplitude is diminished. Heart size usually is normal, with a normal apical impulse on chest palpation. An apical diastolic thrill may be present. In patients with pulmonary hypertension, a right ventricular lift can be felt in the left parasternal region. Auscultatory findings include a presystolic murmur, a loud S_1, an opening snap, and an apical diastolic rumble.[88,116–118] The presystolic murmur, which occurs because of closing of the anterior mitral leaflet, is a consistent finding and begins earlier in those in sinus rhythm than in those in atrial fibrillation.[118] S_1 is accentuated in mitral stenosis when the leaflets are pliable but diminished in later phases of the disease when the leaflets are thickened or calcified. As pulmonary artery pressure becomes elevated, S_2 becomes prominent.[119] With progressive pulmonary hypertension, the normal splitting of S_2 narrows because of reduced pulmonary vascular compliance. Other signs of pulmonary hypertension include a murmur of tricuspid and/or pulmonic regurgitation and an S_4 originating from the right ventricle. Best heard at the apex, the early diastolic mitral opening snap is due to sudden tensing of the pliable leaflets during valve opening and is absent when the leaflets are rigid or immobile.[88,116,117] In mild mitral stenosis, the diastolic

rumble is soft and of short duration; a long or holodiastolic murmur indicates severe mitral stenosis. The intensity of the murmur does not necessarily correlate with the severity of the stenosis; indeed, no diastolic murmur may be detectable in patients with severe stenosis, calcified leaflets, or low cardiac output.[118]

On chest radiography, LA enlargement is the earliest change found in patients with mitral stenosis; it is suggested by posterior bulging of the left atrium seen on the lateral view, a double contour of the right heart border seen on the posteroanterior film, and elevation of the left main stem bronchus.[101] The overall cardiac size often is normal. Prominence of the pulmonary arteries coupled with LA enlargement may obliterate the normal concavity between the aorta and left ventricle to produce a straight left heart border. In the lung fields, pulmonary congestion may be recognized as distension of the pulmonary arteries and veins in the upper lung fields and pleural effusions. If mitral stenosis is severe, engorged pulmonary lymphatics are seen as distinct horizontal linear opacities in the lower lung fields (Kerley B lines).

The electrocardiogram is not accurate in assessing the severity of mitral stenosis and in many cases may be completely normal. In patients with severe mitral stenosis and in normal sinus rhythm, LA enlargement is the earliest change (a wide notched P wave in lead II and a biphasic P wave in lead V_1).[101,120] Atrial arrhythmias are more common in patients with advanced degrees of mitral stenosis. In those with pulmonary hypertension, right ventricular hypertrophy may develop and is associated with right-axis deviation, a tall R wave in V_1, and secondary ST-T-wave changes; however, the electrocardiogram is not a sensitive indicator of right ventricular hypertrophy or the degree of pulmonary hypertension.[120] Because multivalvular disease may be present in patients with rheumatic heart disease, signs of left and right ventricular hypertrophy can be identified on the electrocardiogram in cases of combined mitral and aortic stenosis. Right atrial enlargement and right ventricular dilatation and hypertrophy, however, also can mask the changes indicative of LV hypertrophy on the electrocardiographic tracing in patients with multivalvular disease.[120]

Echocardiography has become the primary diagnostic method for assessing mitral valve pathology and pathophysiology.[121–125] Cross-sectional valve area and LA and LV dimensions can be quantified using two-dimensional transthoracic echocardiography (TTE). Best appreciated in the parasternal long-axis view, the features of rheumatic mitral stenosis include reduced diastolic excursion of the leaflets and thickening or calcification of the valvular and subvalvular apparatus (Fig. 41-6). M-mode findings include thickening, reduced motion, and parallel movement of the anterior and posterior leaflets during diastole. The mitral valve area can be planimetered directly in the short-axis view, but this measurement has limited clinical value. Doppler echocardiography accurately determines peak and mean transvalvular mitral pressure gradients that correlate closely with cardiac catheterization measurements.[88,122] To estimate mitral valve area, the pressure half-time (time required for the initial diastolic gradient to decline by 50%) has been employed; the more prolonged the half-time, the more severe is the reduction in orifice area.[122] Using the pressure half-time determination, mitral valve area is equal to 220 (an empirical value) divided by the pressure half-time. Deriving mitral valve area using the pressure half-time method, however, generally has fallen out of favor. In patients with combined aortic regurgitation and mitral stenosis, the pressure half-time method may be unreliable because the regurgitant jet may interfere with the valve-area calculation.[122] The mean mitral gradient at rest and with bicycle or supine exercise measured using Doppler echocardiography is more useful clinically than estimating mitral valve area; the simultaneous increase in right ventricular systolic pressure (estimated from continuous-wave or pulse-wave Doppler envelopes of the tricuspid regurgitation signal) during exercise is also very revealing. Recently, the mitral separation index, which is the average of the maximum separation of the mitral leaflet tips in diastole in parasternal and apical four-chamber views, shows good correlation with mitral valve area measured by planimetry and pressure half-time and may be able to discriminate between hemodynamically significant and insignificant mitral stenosis.[126] TEE can provide even more information in the evaluation of mitral stenosis; it is better than the transthoracic approach for visualizing details of valvular pathology, such as valve mobility and thickness, subvalvular apparatus involvement, and extent of leaflet or commissural calcification.[122,124] TEE also is more reliable in detecting LA thrombi.

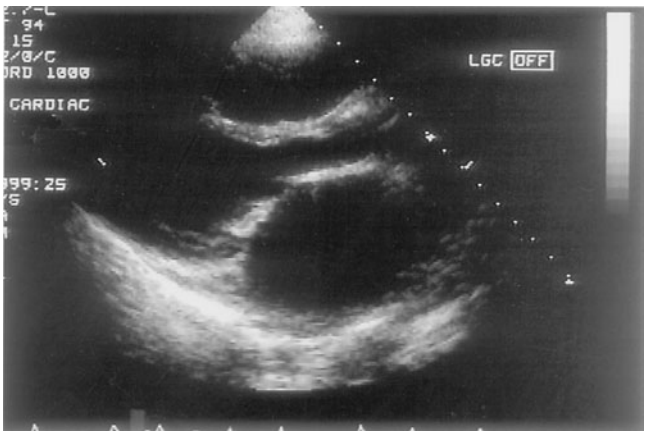


Figure 41-6. Echocardiogram (long axis) of a patient with severe mitral stenosis owing to rheumatic heart disease. A thickened, stenotic valve separates an enlarged left atrium (*right*) and the left ventricle (*left*) and outflow tract (*above*).

Three-dimensional echocardiography may facilitate spatial recognition of intracardiac structures and has been used to evaluate cardiac valvular and congenital heart disease using both real-time three-dimensional TTE as well as offline reconstructed TEE images.[127,128] The addition of color-flow Doppler to this modality has provided better visualization of regurgitant lesions and promises improved quantitative assessment of such lesions. Measurements of LV volume using three-dimensional echocardiography

correlate with those obtained using both contrast ventriculography and magnetic resonance imaging (MRI). Dynamic three-dimensional reconstruction currently is limited by the quality of the original two-dimensional cross-sectional images, which can be adversely affected by minimal patient movements, breathing, and cardiac arrhythmia.[128] Advances in transducers and software components will enhance image acquisition and image quality. Current MRI technology remains inferior for the depiction of valvular morphology and motion. Inherent constraints of MRI, such as pacemakers, morbid obesity, and claustrophobia, hinder the wide use of MRI in cardiac patients. Multidetector computed tomography (CT) may emerge as a technique that can evaluate both cardiac structure and function. Recent experience with gated multidetector CT has yielded good visualization of valve leaflets, commissures, and mitral annulus.[129] Main limitations of this technology include image noise, the time for postprocessing the acquired data, and the radiation dose.

Cardiac catheterization is not necessary to establish the diagnosis of mitral stenosis; however, it can provide information regarding coronary artery status.[130] Historically, left ventriculography permits assessment of the mitral valve and LV contractility and calculation of ejection fraction, but its role has been replaced by echocardiography. Left-sided heart catheterization allows determination of LV end-diastolic pressure; right-sided heart catheterization is performed to measure cardiac index and the degree of pulmonary hypertension. Rarely, cardiac catheterization is used to evaluate the reversibility of severe pulmonary hypertension using pharmacologic interventions, including inhaled nitric oxide when indicated.

Postoperative Outcome

Whereas LV systolic function is used to predict the natural history and postoperative prognosis of patients with other valvular lesions, there are few data linking LV function to outcome in those with mitral stenosis. Not surprisingly, the best indicator is related to the degree of clinical impairment. Surgical intervention (e.g., open mitral commissurotomy or mitral valve replacement) substantially improves the functional capacity and long-term survival of patients with mitral stenosis; 67 to 90% of patients are alive at 10 years.[120,131–133] If there is not excessive scarring of the subvalvular mitral apparatus, mitral valve replacement using chordal-sparing techniques should be performed in patients with rheumatic valve disease, particularly those with mixed stenotic and regurgitant lesions; this results in a reduction in LV end-systolic and end-diastolic volumes and preservation of LV systolic pump performance.[134,135] For those who undergo an open or surgical commissurotomy for advanced rheumatic disease, the rate of reoperation at 10 years is higher than in those who undergo mitral valve replacement (42% versus 4%).[133]

Generally, a valve area of 1 cm^2 is considered critical mitral stenosis and is associated with significant symptoms and morbidity. In physically active or larger patients, somewhat larger valve areas ($\leq$1.2 cm^2) may produce symptoms.[91] Despite a higher operative risk for patients with severe pulmonary hypertension and right-sided heart failure, these individuals usually improve postoperatively with a reduction in pulmonary vascular pressures.[91,136]

Summary

Mitral stenosis generally is due to rheumatic heart disease. In rheumatic valvulitis, the mitral valve is involved most commonly, followed by combined aortic and mitral valve disease. With worsening mitral stenosis, a progressively higher transvalvular pressure gradient occurs. Mitral transvalvular flow depends on cardiac output and heart rate; an increase in heart rate decreases the duration of transvalvular filling during diastole and reduces forward cardiac output, causing symptoms. In mild to moderate mitral stenosis, pulmonary vascular resistance may not be elevated; pulmonary arterial pressure may be normal at rest and rise only with exercise or increased heart rate. In patients with severe mitral stenosis with elevated pulmonary vascular resistance, the pulmonary arterial pressure usually is high at rest. Characteristic symptoms of mitral stenosis are associated with pulmonary venous congestion or low cardiac output. Echocardiography remains the best technique for assessing mitral valve pathology. Surgical intervention can improve the functional capacity and long-term survival of patients with mitral stenosis substantially.

MITRAL REGURGITATION

Etiology

The functional competence of the mitral valve relies on proper, coordinated interaction of the mitral annulus and leaflets, chordae tendineae, papillary muscles, left atrium, and left ventricle, what we refer to as the *valvular-ventricular complex.*[11,73,137–141] Normal LV geometry and alignment of papillary muscles and chordae tendineae permit leaflet coaptation and prevent prolapse during ventricular systole. Dysfunction of any one or more of the components of this valvular-ventricular complex can lead to mitral regurgitation. Regurgitation also can occur in diastole (*presystolic mitral regurgitation*) owing to delayed ventricular contraction or permanent pacing, but this phenomenon appears to have few clinical implications.[142]

Important causes of systolic mitral regurgitation include ischemic heart disease with ischemic mitral regurgitation (IMR), dilated cardiomyopathy [in which the general term *functional mitral regurgitation* (FMR) is used], myomatous degeneration, rheumatic valve disease, mitral annular calcification, infective endocarditis, congenital anomalies, endocardial fibrosis, and collagen-vascular disorders.[90,93,143–145] IMR is considered a specific subset of FMR.

In general, four different types of structural changes of the mitral valve apparatus may produce regurgitation: leaflet

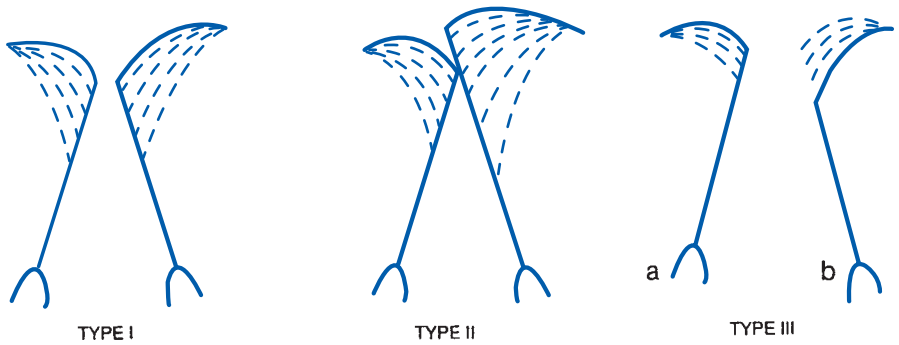


Figure 41-7. Carpentier's functional classification of the types of leaflet and chordal motion associated with mitral regurgitation. In type I, the leaflet motion is normal. Type II mitral regurgitation is due to leaflet prolapse or excessive motion. Type III (restricted leaflet motion) is subdivided into restriction during diastole (a) or systole (b). Type IIIb typically is seen in patients with ischemic mitral regurgitation. The course of the leaflets during the cardiac cycle is represented by the dotted lines. (*Modified with permission from Carpentier A: Cardiac valve surgery: The "French correction." J Thorac Cardiovasc Surg 1983; 86: 323.*)

retraction from fibrosis and calcification, annular dilatation, chordal abnormalities (including rupture, elongation, or shortening), and LV dysfunction with or without papillary muscle involvement.[11,73,146–153] Carpentier classified mitral regurgitation into three main pathoanatomic types based on leaflet and chordal motion: normal leaflet motion (type I), leaflet prolapse or excessive motion (type II), and restricted leaflet motion (type III).[146,147] Type III is further subdivided into types IIIa and IIIb based on leaflet restriction during diastole (type IIIa) in rheumatic disease or during systole (type IIIb) as seen in IMR (Fig. 41-7). Mitral regurgitation with normal leaflet motion can be the result of annular dilatation, which is often secondary to LV dilatation; as a rule, incomplete mitral leaflet coaptation is present at the free edges of the leaflets, e.g., patients with dilated cardiomyopathy or ischemic cardiomyopathy. Normal leaflet motion also includes patients with leaflet perforation secondary to endocarditis. Leaflet prolapse typically results from a floppy mitral valve with chordal elongation and/or rupture but can be seen in patients with coronary artery disease, who rarely have papillary muscle elongation or rupture. Mitral regurgitation owing to restricted leaflet motion is associated with rheumatic valve disease (types IIIa and IIIb), ischemic heart disease (IMR with type IIIb restricted systolic leaflet motion owing to apical tethering or tenting resulting from papillary muscle dislocation, with or without annular dilatation), and dilated cardiomyopathy (type IIIb plus annular dilatation).[147,148]

Functional and ischemic mitral regurgitation

Functional mitral regurgitation (FMR) is the result of incomplete mitral leaflet coaptation in the setting of LV dysfunction and dilatation with or without annular dilatation (e.g., dilated cardiomyopathy or ischemic cardiomyopathy).[149–153] Similar degrees of LV systolic dysfunction and dilatation also may be associated with long-standing mitral regurgitation as a consequence of chronic LV volume overload. Most commonly, the etiology of nonischemic cardiomyopathy is unknown or idiopathic; the second most common etiology is advanced valvular disease. FMR occurs in 40% of patients with heart failure owing to dilated cardiomyopathy.[153] The natural history is progressive valvular insufficiency and more volume overload, LV dilatation, and heart failure. In the past, FMR was thought to be associated with morphologically normal valve leaflets, but recent studies show that the leaflets are biochemically different, with extracellular matrix changes that may be influenced by the altered cardiac dimensions.[154,155] In recipient hearts obtained at the time of transplantation, mitral leaflets have up to 78% more deoxyribonucleic acid, 59% more glycosaminoglycans, 15% more collagen, but 7% less water than autopsy control leaflets.[154] Additionally, radially oriented anterior mitral leaflet strips from failing hearts are 61% stiffer and 23% less viscous.[155] The stiffness of circumferentially oriented anterior leaflet strips is 50% greater than that of control leaflets. Leaflet extensibility is reduced 35%, and the chordae are 16% stiffer. Thus it appears that the mitral valve in heart failure has altered intrinsic structural properties, suggesting that the permanently distended and fibrotic tissue is unable to stretch sufficiently to cover the valve orifice.[155] These findings of secondary leaflet and chordal remodeling argue that mitral regurgitation in these patients may not be purely functional and that these leaflets should not be considered normal morphologically.

IMR, a subset of FMR, is becoming widely appreciated as the population ages and more patients survive acute myocardial infarction. In those with acute myocardial infarction, IMR occurs in approximately 15% of patients with anterior wall involvement and up to 40% of patients with an inferior infarct.[92,93,156] Generally, the severity of mitral regurgitation is related to the size of the area of LV akinesia or dyskinesia. The pathophysiology of IMR is complex but becoming better defined.[146,149,150,156–169] Changes in global and regional LV function or geometry, alterations in mitral annular geometry, abnormal leaflet motion and malcoaptation,

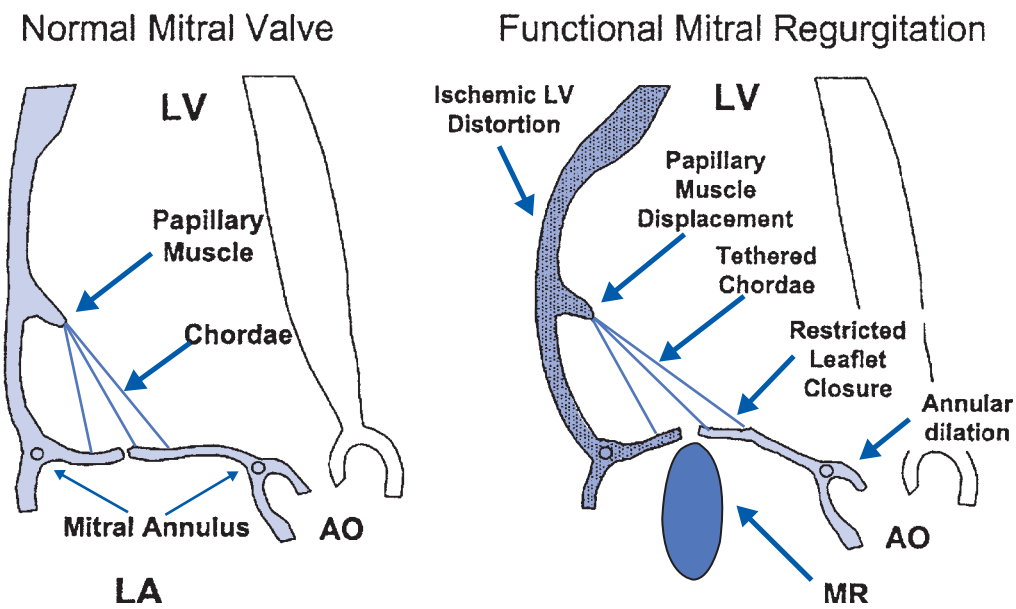


Figure 41-8. Mechanism of functional and ischemic mitral regurgitation. MR = mitral regurgitation; LA = left atrium; LV = left ventricle, AO = aorta. (*Modified with permission from Levine RA, Hung J: Ischemic mitral regurgitation, the dynamic lesion: Clues to the cure. J Am Coll Cardiol 2003; 42:1929.*)

increased interpapillary distance, and papillary muscle malalignment may lead to apical tethering or tenting of the leaflets and mitral incompetence associated with restricted systolic leaflet motion (type IIIb) (Fig. 41-8). Annular dilatation from LV enlargement may further cause incomplete mitral leaflet coaptation. Because of the interdependence of the numerous elements constituting the valvular-ventricular complex in IMR, perturbation of any specific component, such as LV function and geometry, annular geometry, leaflet motion, and papillary and chordal relationship, may result in dysfunction of the valvular-ventricular complex and cause mitral regurgitation.

LEFT VENTRICULAR FUNCTION AND GEOMETRY: Although LV dilatation and dysfunction are less pronounced in the setting of inferior myocardial infarction than in infarcts affecting the anterior wall, the incidence and severity of mitral regurgitation are greater in the former.[92,93,156,158,161] Over time, as the left ventricle dilates and changes shape after the ischemic event (postinfarction remodeling), the degree of IMR progresses.[151,152,161] Infarct size and location contribute to the anatomic manifestation of LV remodeling, with anteroapical infarcts leading to apical thinning and akinesia and inferior infarcts causing inferior akinesia or dyskinesia and progressive IMR. The development of IMR thus may be a manifestation of rather than a stimulus for progressive LV remodeling.[161] Mechanistically, the valve and subvalvular apparatus work in a tightly coupled and coordinated fashion. Geometric changes associated with ventricular remodeling, such as posteromedial papillary muscle dislocation in the lateral axis, may lead to leaflet tenting or tethering, as reflected by a larger distance from the middle of the anterior annulus (saddle horn or fibrosa, an echocardiographic landmark) to the posteromedial papillary muscle tip and increased annular diameter.[151,152,162,163] As a result of inferior myocardial infarction, the posteromedial papillary muscle tethering distance contributes to the mitral regurgitant jet area.[156] At the ventricular level, myocardial infarction associated with chronic IMR leads to greater perturbations in LV systolic torsion and diastolic recoil than myocardial infarction without chronic IMR.[170] These abnormalities may be linked to more LV dilatation, which possibly reduces the effectiveness of fiber shortening on torsion generation. Altered LV torsion and recoil thus are likely to contribute to the "ventricular disease" component of chronic IMR, with increased gradients of myocardial oxygen consumption adversely affecting cardiac efficiency and impaired early diastolic filling. Investigation of patients with ischemic heart disease using MRI has demonstrated mitral regurgitation, diminished LV systolic function, annular stretching (involving both the anterior and posterior annuli around the entire valve circumference), valvular dilatation in the septolateral axis (also known as the *anteroposterior axis,* which is perpendicular to the line of leaflet coaptation), flattening of the height of the annulus near the midanterior annular saddle horn, abnormal LV geometry and shape, and papillary muscle displacement responsible for leaflet tenting and IMR.[158]

ANNULAR GEOMETRY: In individuals with IMR, mitral annular area increases, septolateral annular dimension increases, the posteromedial papillary muscle is displaced in the lateral direction, and the posterior leaflet becomes apically tethered with restricted closing motion, all of which contribute to leaflet malcoaptation and IMR[159,162,163,168] (Fig. 41-9). LV dilatation and larger annular dimensions after inferior myocardial infarction require the mitral leaflets to cover

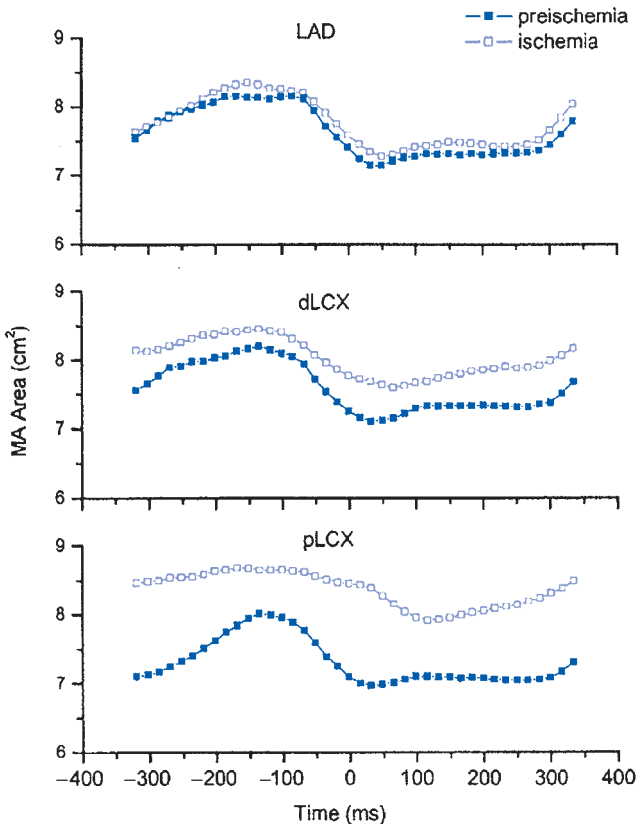


Figure 41-9. Average mitral annular area (in cm^2) before (*solid squares*) and during (*open circles*) acute LV ischemia induced by balloon occlusion of either the LAD artery (*top*), the dLCx coronary artery (*middle*), or the pLCx coronary artery (*bottom*). A 650-ms time interval centered at end-diastole ($t = 0$) is shown. MA = mitral annular; LAD = proximal left anterior descending artery; dLCx = distal to second obtuse marginal artery; pLCx = proximal to second obtuse marginal artery. (*Reproduced with permission from Timek TA et al: Ischemia in three left ventricular regions: Insights into the pathogenesis of acute ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2003; 125:559.*)

more area during closing, exceeding their normal redundancy or "reserve," which is exacerbated by restricted leaflet closure owing to apical tenting (type IIIb). Based on MRI, septolateral annular dilatation and diminished LV systolic function determine mitral systolic tenting area, which, in turn, is predictive of the severity of the IMR.[158] Additionally, the normal annulus has a distinctive saddle shape, which becomes accentuated during systole.[171–173] In IMR, this accentuation of the saddle shape, as measured by the annular height to commissural width ratio, is eliminated, suggesting an association between maintaining the saddle shape and valvular competence.[171] Thus deformation of the saddle shape of the annulus in conjunction with valve tenting contributes to the development of IMR.[172,173]

In patients with IMR, three-dimensional echocardiographic investigations show an increase in anterior and posterior annular perimeters and annular orifice area (9.1 cm^2 compared to 5.7 cm^2 normally) accompanied by an increase in the intertrigonal (anterior) annular distance and restriction of annular motion.[163] Furthermore, annular flattening with tenting of the leaflets, along with greater tenting lengths and volume, is appreciated.[172–174] The strongest echocardiographic determinant of leaflet tenting height is the distance from the tips of the papillary muscles to the saddle horn of the anterior mitral annulus; LV end-diastolic volume is only weakly correlated with tenting height.[175] The importance of annular size is pronounced in patients with dilated cardiomyopathy, in whom three-dimensional echocardiography showed that annular dilatation is the best predictor of FMR.[164] Additionally, mitral valve regurgitant volume correlates with annular area, LA volume, and LV end-diastolic volume.

LEAFLET MOTION: Acute IMR owing to proximal left circumflex artery occlusion in an animal model results in delayed valve closure in early systole (termed leaflet *loitering*) and increased leaflet edge separation throughout ejection in three leaflet coaptation sites across the valve, specifically near the anterior commissure, the valve center, and near the posterior commissure).[157,159] In addition, there is lateral displacement of the central scallop of the posterior leaflet, suggesting that interscallop malcoaptation can contribute to IMR in certain circumstances.[169] The primary geometric mechanism underlying scallop malcoaptation in acute IMR appears to be annular dilatation in the septolateral axis, which hinders leaflet coaptation by drawing the individual scallops apart.[169] Clinically, chronic IMR is associated with apical systolic restriction of the posterior leaflet, thereby effectively preventing competent valve closure. Chronic IMR is also associated with posterior leaflet displacement in the posterior direction and lateral displacement of both leaflets. When the position of each leaflet edge is assessed independently, the anterior leaflet is not displaced apically after inferior infarction, although with more time and further remodeling, apical restriction of this leaflet may occur.[162]

PAPILLARY MUSCLE AND CHORDAL RELATIONSHIPS: The papillary-annular distances in the LV long axis remain relatively constant in normal hearts throughout the cardiac cycle.[150] During acute ischemia, however, these distances change, which reflects repositioning or dislocation of the papillary muscle tips with respect to the mitral annulus; this can also contribute to apical tenting of the leaflets during systole.[146,150,162,165] With proximal circumflex artery occlusion and resulting IMR in an ovine model, the interpapillary distance and LV end-diastolic volume both increase. There is also increased mitral annular area and displacement of both (but predominantly the posterior) papillary muscle tips away from the septal annulus throughout ejection and at end-systole.[162,165] Posteromedial papillary muscle tip displacement probably results from failure of the ischemic posterior papillary muscle to shorten during systole, lengthening of the ischemic papillary muscle over time, and also dyskinesia of the ischemic LV wall subtending the papillary muscle. Since posterior papillary muscle displacement in the apical and posterior directions also occurs in sheep that did not develop substantial degrees of IMR, the additional posterior

papillary muscle displacement in the lateral direction is a dominant factor in the development of IMR.[162] In the setting of posterolateral ischemia, a larger distance from the papillary muscle tips to the midseptal annulus is an important determinant of mitral regurgitant volume. The nonischemic anterior papillary muscle also may play a role in apical leaflet restriction because this normally shortening anterior papillary muscle is displaced apically at end-systole relative to baseline. In sheep with mitral regurgitation, posterior papillary muscle tethering distance, papillary muscle depth, and papillary muscle angle are unchanged, and the anterior papillary muscle depth and papillary muscle angle decrease with decreasing ejection fraction.[165] Reduced systolic shortening of either papillary muscle in isolation, on the other hand, does not result in mitral regurgitation; thus the previous notion that papillary muscle dysfunction by itself is responsible for IMR is not correct. In fact, papillary muscle dysfunction paradoxically can decrease mitral regurgitation owing to inferobasal ischemia by reducing leaflet tethering to improve leaflet coaptation.[176] It is likely that a further insult to the LV wall underlying the papillary muscles is needed before valvular incompetence occurs. Finally, acute IMR owing to posterior LV ischemia is associated with focal chordal and leaflet tethering at the nonischemic commissural portion of the mitral valve and a paradoxical decrease of the chordal forces and relative prolapse at the ischemic site of the anterior leaflet.[166] Thus a combination of systolic annular dilatation and shape change and altered posteromedial (and possibly anterolateral) papillary muscle position and motion contributes to incomplete leaflet coaptation and IMR during acute inferior or posterolateral ischemia.

PAPILLARY MUSCLE ISCHEMIA: Papillary muscle dysfunction in patients with coronary artery disease has been thought to contribute to mitral regurgitation, although the significance of its role in IMR has been challenged.[11,73,74,92,93,150,162,165,176] The papillary muscles are particularly susceptible to ischemia, more so the posteromedial papillary muscle (generally supplied by the posterior descending artery) than the anterolateral papillary muscle (customarily supplied by branches of the left anterior descending and the circumflex arteries).[11,73,74,177] The posteromedial papillary muscle is perfused by one major coronary artery in 63% of cases and by two vessels in the remainder; on the other hand, the anterior papillary muscle has two-vessel perfusion in 71% of normal individuals.[74]

Myocardial infarction leading to papillary muscle dysfunction occurs more frequently when the blood supply to the papillary muscle is provided by one vessel, as is more often the case with the posteromedial papillary muscle after an inferior myocardial infarction. Also, coronary artery disease involving both the right and circumflex coronary arteries (as opposed to single-vessel disease) can cause posteromedial papillary muscle dysfunction.[177] Although papillary muscle necrosis can complicate myocardial infarction, frank rupture of a papillary muscle is rare. Total papillary muscle rupture usually is fatal owing to the resulting severe mitral regurgitation and LV pump failure; survival long enough to reach the operating room in reasonable condition is possible with rupture of one or two of the subheads of a papillary muscle, which is associated with a lesser degree of mitral regurgitation. Papillary muscle rupture usually occurs 2 to 7 days after myocardial infarction; without urgent surgery, approximately 50 to 75% of such patients may die within 24 hours.[178,179]

Myxomatous degeneration

Myxomatous degeneration of the mitral valve, also known as *floppy mitral valve* or *mitral valve prolapse,* is the most common cause of mitral regurgitation in patients undergoing surgical evaluation in the United States.[11,180–183] The etiology of mitral valve prolapse is both acquired (*fibroelastic deficiency* in older patients) and congenital or heritable, with excess spongy, weak fibroelastic connective tissue constituting the leaflets and chordae tendineae[90,184–187] (Fig. 41-10). Recent genotypic analyses show an autosomal dominant mitral valve prolapse locus mapped to chromosome 13.[187] Some degree of mitral valve prolapse is seen echocardiographically in 5 to 6% of the normal female population[184,185,188]; it can be familial or associated with hypertension. The risk of endocarditis is increased only if valvular regurgitation is present and accompanied by a murmur. Although mitral valve prolapse appears to be more widespread in women, severe mitral regurgitation owing to mitral valve prolapse is more common in men. Subtle signs of heart failure, usually manifest as declining stamina and fatigue, may be the presenting complaint in 25 to 40% of symptomatic patients with mitral valve prolapse. The syndrome of mitral valve prolapse includes palpitations, chest pain, syncope, and dyspnea; in younger patients, the initial clinical sign is a midsystolic click, which later evolves into a click followed by a late systolic murmur.[184,185] This latter scenario is seen typically in patients with Barlow syndrome, in which large amounts of excessive leaflet tissue and marked annular dilatation are coupled with extensive hooding and billowing of both leaflets.

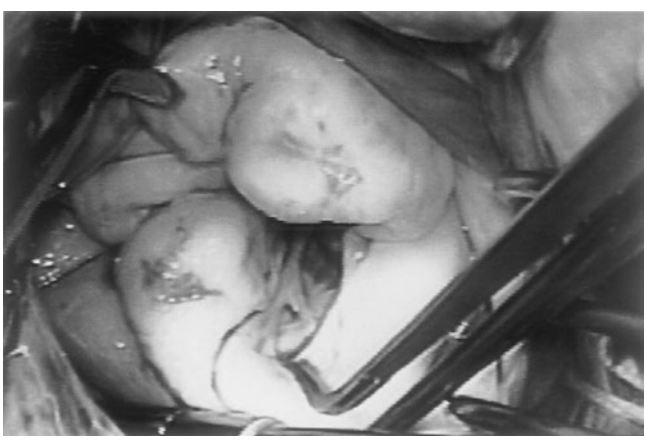


Figure 41-10. Intraoperative photograph of mitral regurgitation owing to floppy mitral valve.

Pathologically, the atrial aspect of the prolapsing mitral leaflet often is thickened focally, whereas the changes on the ventricular surface of the leaflet consist of connective tissue thickening primarily on the interchordal segments with proliferation of fibrous tissue into adjacent chordae and onto the ventricular endocardium.[90,184,186] Myxomatous degeneration commonly involves the annulus, resulting in annular thickening and dilatation. The leaflets become thickened, spongy in texture, and opaque, occasionally with yellow plaque formation. Histologically, elastic fiber and collagen fragmentation and disorganization are present, and acid mucopolysaccharide material accumulates in the leaflets. All these changes are very pronounced in young patients with the Barlow syndrome but can be minimal in older subjects with fibroelastic deficiency, in whom the leaflets are normal and thin (termed *pellucid* by Carpentier), with only minimal thickening of the chordae. It is important to recognize that these two distinct varieties of mitral valve prolapse exist and can be segregated on clinical grounds, even if pathologists have difficulty discriminating between the two. The main visual and pathologic difference is the extent and degree of degenerative changes. The surgical implications of these two distinct subtypes of mitral valve prolapse are noteworthy. Certain centers, such as the Mayo Clinic, encounter mainly elderly patients with coronary artery disease and fibroelastic deficiency (78% of their surgical "flail" leaflet population are over 60 years old and/or require concomitant coronary artery bypass grafting), in whom the valvular pathology is limited, and repair techniques, such as the small McGoon triangular excision of the middle scallop of the posterior leaflet, are applicable.[189] This is in contrast to other referral centers, where the majority of mitral valve prolapse patients are much younger and have the Barlow syndrome or severely myxomatous mitral valves, circumstances that demand much more extensive repair techniques. As a corollary, the long-term results after mitral repair also will differ substantially between these two cohorts owing to the adverse effects of advanced age and ischemic heart disease.

Only 5 to 10% of patients with mitral valve prolapse progress to severe mitral regurgitation, and the majority remain relatively asymptomatic.[184,185] Mechanisms accounting for severe mitral regurgitation in those with mitral valve prolapse include annular dilatation and rupture or elongation of the first-order chordae (58%), annular dilatation without chordal rupture (19%), and chordal rupture without annular dilatation (19%).[186] Chordal rupture probably is related to defective collagen, underlying papillary muscle fibrosis or dysfunction, or bacterial endocarditis.[11,73,90,92,93,144,190,191] Elongation without rupture of other first-order as well as many second-order chordae frequently accompanies chordal rupture. Chordal rupture typically is the culprit when mitral regurgitation develops acutely in patients without any previous symptoms of heart disease or suddenly becomes worse in those with known mitral valve prolapse.[92,144] Chordal rupture is evident in 14 to 23% of surgically excised purely regurgitant valve specimens; in 73 to 93% of these patients, the underlying pathology is degenerative or floppy mitral valve syndrome.[92,93,144] Posterior chordal rupture was the most frequent finding, followed by anterior chordal rupture and then combined anterior and posterior chordal rupture.[92,93,144]

Rheumatic disease

Although its incidence is decreasing in the United States, rheumatic fever remains a common cause of mitral regurgitation around the world.[11,92–94,143–145,192] It is unknown why rheumatic fever leads to valvular stenosis in some patients and pure regurgitation in others. The pathoanatomic changes of the purely regurgitant rheumatic valve differ from those in a stenotic valve. In chronic rheumatic mitral regurgitation, the valves have diffuse fibrous thickening of leaflets with minimal calcific deposits and relatively nonfused commissures; chordae tendineae usually are not extremely thickened or fused.[92,93] There also may be shortening of the chordae tendineae, fibrous infiltration of the papillary muscle, and asymmetric annular dilatation that develops primarily in the posteromedial portion. During the first episodes of rheumatic fever (average age is 9 years), patients may develop acute mitral regurgitation, which is related more frequently to prolapse of the anterior or posterior mitral valve leaflet.[192] Those with anterior leaflet prolapse tend to improve with medical management; however, those with prolapse of the posterior leaflet have a less favorable outcome and often require early surgical repair.[192]

Mitral annular calcification

Mitral annular calcification is a degenerative disorder that usually is confined to elderly individuals; most patients are older than 60 years of age, and women are affected more often than men.[11,96] The pathogenesis of mitral annular calcification is not known, but it appears to be a stress-induced phenomenon; annular calcification also can be associated with systemic hypertension, hypertrophic cardiomyopathy, aortic stenosis, and occasionally, advanced Barlow disease. Other predisposing conditions include chronic renal failure and diabetes mellitus. Aortic valve calcification is an associated finding in 50% of patients with severe mitral annular calcification.

The gross appearance of mitral annular calcification may vary from small, localized calcified spicules to massive, rigid bars up to 2 cm in thickness.[96] Initially, calcification begins at the midportion of the posterior annulus; as the process progresses, the leaflets become upwardly deformed, stretching the chordae tendineae, and a rigid curved bar of calcium surrounding the entire posterior annulus or even a complete ring of calcium may encircle the entire mitral orifice. Invasion of the calcific spurs into the LV myocardium and the conduction system can result in atrioventricular and/or intraventricular conduction defects. Annular calcification causes mitral regurgitation by displacing and immobilizing the mitral leaflets (thereby preventing their normal systolic coaptation) or impairing the presystolic sphincteric action of the annulus.[96] As the degree of mitral regurgitation

worsens over time, LV volume overload can lead to heart failure. Systemic embolization can occur if the annular calcific debris is extensive and friable.

Hemodynamics

The pathophysiology of acute mitral regurgitation differs from that of chronic mitral regurgitation. Acute regurgitation may result from spontaneous chordal rupture, myocardial ischemia or infarction, infective endocarditis, or chest trauma.[11,73,178,179,190] The clinical impact of acute mitral incompetence is modulated largely by the compliance of the left atrium and the pulmonary vasculature. In a normal left atrium with a relatively low compliance, acute mitral regurgitation results in high LA pressure, which can lead rapidly to pulmonary edema. Such is not the situation in patients with chronic mitral regurgitation, in whom compensatory changes over time increase LA and pulmonary venous compliance so that symptoms of pulmonary congestion may not occur for many years.

With mitral regurgitation, the impedance to LV emptying is lowered because the mitral orifice is in parallel with the LV outflow tract.[11,103,193] The volume of mitral regurgitation depends on the square root of the systolic pressure gradient between the left ventricle and the atrium, the time duration of regurgitation, and the effective regurgitant orifice (ERO).[11,175,194,195] The ERO is determined echocardiographically using two-dimensional color Doppler imaging to measure the cross-sectional area of the vena contracta, the proximal isovelocity surface area (PISA) method, or continuous-wave Doppler measuring the ratio of regurgitant volume to regurgitant time-velocity integral.[175,196] Regurgitation into the left atrium increases LA pressure and reduces forward cardiac output. LA pressure rises significantly during ventricular systole, followed by an abrupt decline in early diastole. LA pressure even may remain elevated at end-diastole (transient 5- to 10-mm Hg transvalvular gradient), representing a functional gradient associated with the increased diastolic flow rate.

If the mitral annulus is not rigid, various diagnostic and therapeutic interventions can alter ERO. Altered loading conditions (elevated preload and afterload) and decreased contractility result in progressive LV dilatation and a larger ERO.[197] When LV size is reduced by medical management (e.g., digoxin, diuretics, and most important, arteriolar vasodilators), ERO and regurgitant volume fall.[198,199] Stress echocardiography using an inotropic drug such as dobutamine usually decreases ERO and the degree of mitral regurgitation in patients with FMR and IMR because the LV chamber is smaller at beginning systole (or end diastole) and throughout systole secondary to enhanced LV contractility.[200]

Ventricular Adaptation

The loading conditions induced by mitral regurgitation promote more LV ejection because ventricular preload is increased, whereas afterload is normal or decreased owing to backward flow across the mitral valve. In terms of cardiac energetics, reduced LV impedance in patients with mitral regurgitation allows a greater proportion of contractile energy to be expended in myocardial fiber shortening than in tension development.[11,193] Because increased fiber shortening is less of a determinant of myocardial oxygen consumption than other components, such as tension (or pressure) development and heart rate, mitral regurgitation causes only small increases in myocardial oxygen consumption.[193] Simultaneous reductions in developed tension owing to lower LV systolic wall stress (or afterload) associated with mitral regurgitation allow the ventricle to adapt to the substantial regurgitant volume by increasing LV end-diastolic volume to maintain adequate forward output. Along with lower afterload, this substantial increase in preload (LV end-diastolic volume or, more precisely, LV end-diastolic wall stress) allows the heart to compensate for chronic mitral regurgitation for long periods of time before symptoms occur.[11,201,202] A fundamental response of the ventricle to increased preload is augmented stroke volume and stroke work, although effective forward stroke volume may be normal or even subnormal. High LV preload eventually leads to LV dilatation and shape changes of the ventricle, i.e., more spherical LV remodeling, owing to replication of sarcomeres in series as a consequence of chronic elevation of LV end-diastolic wall stress.[201,202] This is in contrast to LV hypertrophy secondary to chronic pressure overload (elevated systolic wall stress), which leads to sarcomere replication in parallel. In chronic mitral regurgitation, LV mass also increases; however, the degree of hypertrophy correlates with the amount of chamber dilatation so that the ratio of LV mass to end-diastolic volume remains in the normal range (unlike the situation in patients with LV pressure overload).[203–205] The contractile dysfunction that ultimately evolves owing to chronic LV volume overload is accompanied by increased myocyte length as well as reduced myofibril content.[202,203] The basic changes thus are a combination of myofibrillar loss and the absence of significant hypertrophy in response to the progressive decrease in ventricular pump function. Experimental work indicates that the defect is intrinsic to the myocyte per se, but changes in the extracellular matrix undoubtedly also play a role.[206] Conversely, in acute mitral regurgitation, the ratio of LV mass to end-diastolic volume is reduced because chamber dilatation occurs suddenly, and the LV wall becomes acutely thinned; this increase in LV end-diastolic volume is associated with sarcomere lengthening along the length-tension curve.[202]

After the initial compensatory phase, LV systolic contractility becomes progressively impaired with chronic mitral regurgitation.[204–207] Because of the low impedance during systole, however, ejection-phase indexes of LV systolic function, such as ejection fraction and fractional circumferential fiber shortening (%FSc), still can be normal even if severely depressed contractility is present.[206,208,209] An ejection fraction of less than 55 to 60% or %FSc less than 28% in the presence of severe mitral regurgitation indicates an advanced degree of myocardial dysfunction. The ejection-phase indexes commonly

used clinically to estimate LV pump performance, e.g., ejection fraction, %FSc, cardiac output, stroke volume, stroke work, etc. are all affected by changes in LV preload and afterload. It should be remembered that changes in LV loading conditions accompany all forms of valvular heart disease.

To avoid the pitfalls imposed by abnormal LV loading conditions, load-independent indexes of LV contractility [e.g., end-systolic elastance derived from the end-systolic pressure-volume relationship (ESPVR)] or preload-recruitable stroke work (PRSW, also termed *linearized Frank-Starling relationship*) are preferred to measure LV systolic function and mechanics in the setting of mitral regurgitation.[204,205,210–213] In hypertrophied and dilated hearts, as seen in chronic mitral regurgitation, however, the utility of end-systolic elastance may be limited owing to the geometric LV chamber shape and size changes and hypertrophy that occur; using the end-systolic stress-volume relationship in these circumstances is necessary. One other problem inherent in the use of end-systolic elastance or stress-volume data is that end-systole and end-ejection are dissociated in patients with mitral regurgitation. End-ejection is defined as minimum LV volume and end-systole as the instant when LV elastance reaches its maximal value. Because of this temporal dissociation of end-systole from minimal ventricular volume, end-ejection pressure-volume relations do not correlate with maximal elastance values derived using isochronal methods.[211] End-systolic dimension or LV end-systolic volume (LVESV) is less dependent on LV loading conditions than is ejection fraction, is a better measure of LV systolic contractile function, and varies directly and linearly with afterload.[210,214–217] The larger the LVESV becomes, the worse is the LV contractility. Correcting LVESV for chamber geometry, wall thickness and afterload [i.e., end-systolic wall stress (ESS)], and body size [LV end-systolic volume index (LVESVI)] provides good indexes of LV systolic function that are less influenced by loading conditions and variation in patient size.[214,215] Preoperative LVESV or LVESVI is a better predictor of postoperative outcome in terms of postoperative LV systolic performance and cardiac death than is ejection fraction, end-diastolic volume, or end-diastolic pressure.[217]

Based on load-independent indexes of LV contractility in experimental preparations of mitral regurgitation, the normalized end-systolic pressure-volume and end-systolic stress-volume relationships decline after 3 months of mitral regurgitation.[204] The LV preload-recruitable stroke work (the relation of stroke work to LV end-diastolic volume) and preload-recruitable pressure-volume area (the relation of stroke work to LV pressure-volume area) also decrease. The efficiency of energy transfer from pressure-volume area to external pressure-volume work at matched LV end-diastolic volume also falls. Furthermore, there is deterioration in ventriculoarterial coupling over time; i.e., a mismatch develops between the ventricle and the total (forward and regurgitant) vascular load. Although the overall (systemic plus LA) effective arterial elastance is decreased, there is a proportionally greater reduction in LV end-systolic elastance. Thus LV systolic mechanics become impaired along with deterioration in global LV energetics and efficiency, and a mismatch develops in coupling between the left ventricle and the arterial bed.[204] Further analysis shows that progression from acute to chronic mitral regurgitation (3 months) is associated with a decrease in maximum LV systolic torsional deformation from 6.3 to 4.7 degrees and a decrease in early diastolic LV recoil from +3.8 to –1.5 degrees[218] (Fig. 41-11). Because torsion is a mechanism by which the left ventricle equalizes transmural gradients of fiber strain and oxygen demand, a decrease in torsion in chronic mitral regurgitation may play a role in the inexorable and progressive decline of LV performance over time. Less systolic LV torsion would be associated with a larger transmural gradient of fiber strain and an imbalance of oxygen supply and demand such that decreased torsion may contribute to a deleterious feedback loop of ventricular mechanics.[218] The left ventricle responds to decreased forward cardiac output owing to mitral regurgitation by dilating. Ventricular dilatation tends to equalize the lengths of the endocardial and epicardial radii and thereby decreases systolic LV torsion. The associated increase in transmural gradient of fiber strain and oxygen supply-demand imbalance results in a further decrease in forward cardiac output, leading to more LV dilatation, thus continuing the vicious cycle.

LV diastolic function also is affected by chronic mitral regurgitation.[219–223] Diastolic inflow into the ventricle must increase as total stroke volume increases during evolution of mitral regurgitation during which the left ventricle dilates. With acute mitral regurgitation, mitral regurgitation enhances LV diastolic function by increasing the early diastolic filling rate and decreasing chamber stiffness. Flow across the mitral valve during early diastole is determined by the LA-LV pressure gradient, even though other factors, such as diastolic restoring forces and LV diastolic recoil (creating LV suction) during isovolumic relaxation also influence early LV filling.[219] In middle and late diastole, the lower LV chamber stiffness in patients with acute mitral regurgitation (evidenced by a shift of the LV diastolic pressure dimension or pressure-volume relationship to the right) allows the LV mean and end-diastolic pressures (and stresses) to remain in the normal range.

In patients with chronic mitral regurgitation and preserved ejection fraction, LV chamber stiffness is also lower, similar to that during acute mitral regurgitation; conversely, in those with impaired LV systolic function, chamber stiffness usually is normal.[221] During the period of passive filling, maximal rates of LV circumferential fiber lengthening and strain are increased only in those with a normal ejection fraction. The absence of augmented filling rate in patients with depressed LV systolic function probably reflects underlying myocyte abnormalities. In general, chronic mitral regurgitation causes a decrease in LV systolic contractile function but an increase in early diastolic function (as evidenced by an increase in early diastolic filling rate and a decrease in chamber stiffness).[222,224] The reduced chamber stiffness may be the result of altered ventricular geometry (more spherical or less eccentric shape); this shape change

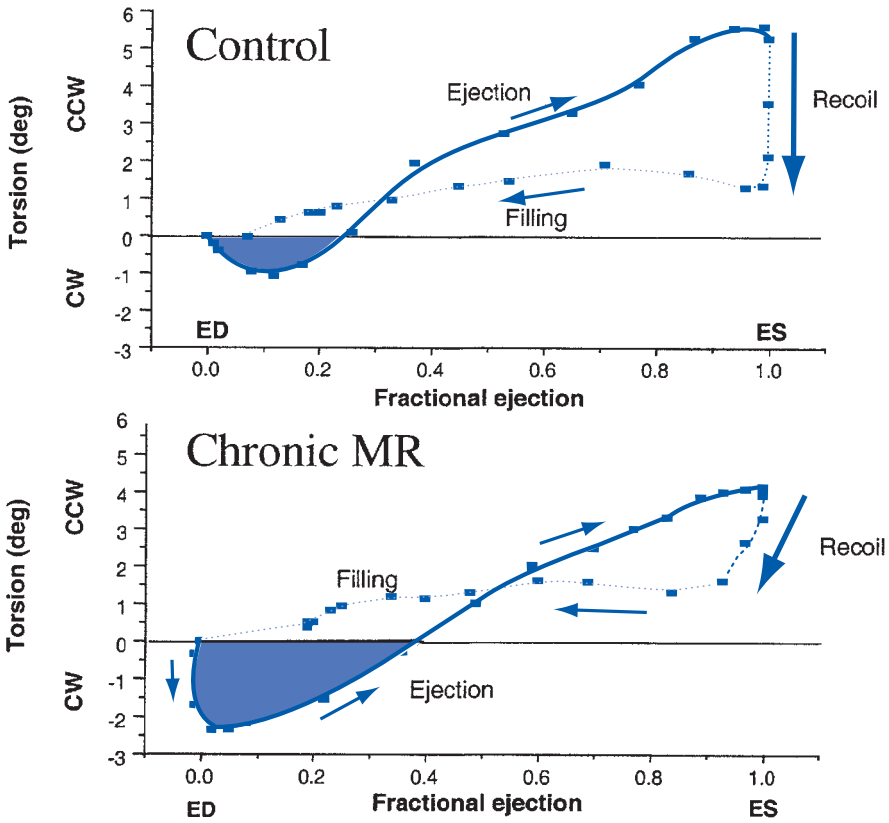


Figure 41-11. Torsional deformation versus fractional ejection with acute (*top*) and chronic (*bottom*) mitral regurgitation in a representative animal. With acute mitral regurgitation, systole (*solid line*) is characterized by a slight clockwise rotation followed be counterclockwise torsion that peaks at end-ejection. Early diastole (*dashed line*) shows steeper torsional recoil than middle to late diastole (*dotted line*). With chronic mitral regurgitation, the initial clockwise torsion is larger, the maximum positive torsion is decreased, and less recoil occurs during early diastole. (*Reproduced with permission from Tibayan FA, Yun KL, Lai DTM, et al: Torsional dynamics in the evolution from acute to chronic mitral regurgitation. J Heart Valve Dis 2002; 11:39.*)

can exacerbate the degree of mitral regurgitation by distorting annular dimensions and dislocating the papillary muscles.[221,225] Although the LV chamber stiffness is less owing to the change in geometry, the LV myocardium may be stiffer owing to myocyte hypertrophy and interstitial fibrosis.[221,222]

Regarding the impact of mitral regurgitation on right ventricular contractility, reduction in right ventricular systolic function is associated with a worse prognosis, emphasizing the adverse impact of pulmonary hypertension in this disease.[226] Patients with a right ventricular ejection fraction of less than 30% are at risk for a suboptimal outcome.

Atrial Adaptation

Regurgitant flow into the left atrium leads to progressive atrial enlargement, the degree of which does not correspond directly with the severity of mitral regurgitation.[107,193] Also, the LA *v* wave in mitral regurgitation does not correlate with LA volume. Compared with patients with mitral stenosis, LA size can be larger in patients with long-standing mitral regurgitation, but thrombus formation and systemic thromboembolization occur less frequently because of the absence of atrial stasis.[107,110] Atrial fibrillation occurs less often in those with mitral regurgitation than in individuals with mitral stenosis.[110]

LA compliance is an important component of the patient's overall hemodynamic status if mitral regurgitation is present.[11,190,193,227,228] With sudden development of mitral regurgitation owing to chordal rupture, papillary muscle infarction, or leaflet perforation, LA compliance is normal or reduced. The left atrium is not enlarged, but the mean LA pressure and *v* wave are high. Gradually, the LA myocardium becomes hypertrophied, proliferative changes develop in the pulmonary vasculature, and pulmonary vascular resistance rises. As the mitral regurgitation becomes chronic and more severe, LA compliance increases, and LA enlargement occurs. In patients with severe, long-standing mitral regurgitation, the left atrium is markedly enlarged, atrial compliance is increased, the atrial wall is fibrotic, but LA pressure remains normal or only slightly elevated.[227] In this situation, pulmonary artery pressure and pulmonary vascular resistance usually are still in the normal range or are elevated only modestly. Atrial fibrillation and a low cardiac output, however, can occur.

Pulmonary Changes

Because chronic mitral regurgitation is associated with LA enlargement and only mild elevations in LA pressure, pronounced increases in pulmonary vascular resistance usually do not develop. In patients with acute mitral regurgitation with normal or reduced LA compliance, a sudden increase in LA pressure initially elevates pulmonary vascular resistance, and occasionally, acute right-sided heart failure occurs.[11,190]

Pulmonary edema is seen less frequently in patients with chronic mitral regurgitation than in those with mitral stenosis because elevated LA pressure is uncommon. Pulmonary vascular resistance is higher more often in patients with mitral stenosis than in those with mitral regurgitation owing to the chronically elevated LA pressure in the former. In patients with IMR and heart failure, however, acute pulmonary edema is associated with the dynamic changes in IMR and the resulting increase in pulmonary vascular pressure.[229] Exercise-induced changes in ERO, transtricuspid pressure gradient, and LV ejection fraction are independently associated with the development of pulmonary edema.[229] From the standpoint of pulmonary parenchymal function and respiratory mechanics in patients with chronic mitral regurgitation, there is a decline in vital capacity, total lung capacity, forced expiratory volume, and maximal expiratory flow at 50% vital capacity.[230] These patients also may have a positive response to methacholine challenge; this bronchial hyperresponsiveness may result from increased vagal tone owing to long-standing pulmonary congestion.

Clinical Evaluation

Patients with mild to moderate mitral regurgitation may remain asymptomatic for many years as the left ventricle adapts to the increased workload and maintains normal forward cardiac output. Gradually, symptoms reflecting decreased cardiac output with physical activity and/or pulmonary congestion develop insidiously, such as weakness, fatigue, palpitations, and dyspnea on exertion. If right-sided heart failure appears late in the course of the disease, hepatomegaly, peripheral edema, and ascites occur and can be associated with rapid clinical deterioration.[112,114] Conversely, acute mitral regurgitation usually is associated with marked sudden pulmonary congestion and pulmonary edema. Patients with coronary artery disease can present with myocardial ischemia or infarction and associated mitral regurgitation. Acute papillary muscle rupture may mimic the presentation of a patient with a postinfarction ventricular septal defect.[231]

On physical examination, the cardiac impulse in patients with mitral regurgitation is hyperdynamic and displaced laterally; the forcefulness of the apical impulse is indicative of the degree of LV enlargement. In patients with chronic mitral regurgitation, S_1 usually is diminished. S_2 may be single, closely split, normally split, or even widely split as a consequence of the reduced resistance to LV ejection; a common finding is a widely split S_2 that results from shortening of LV systole and early closure of the aortic valve.[232] An S_3 gallop may be appreciated owing to the increased transmitral diastolic flow rate during the rapid filling phase. The apical systolic murmur of mitral regurgitation can be blowing, moderately harsh, or even soft and usually radiates to the axilla and left sternal border and occasionally to the neck or to the vertebral column.[232] The murmur is best appreciated in early systole in patients with FMR or IMR and can be difficult to discern even if a large degree of mitral regurgitation exists. With rupture of the posterior leaflet first-order chordae, the mitral regurgitation jet is directed superiorly and impinges on the atrial septum near the base of the aorta, which can produce a murmur heard best along the right sternal border and radiating to the neck.[232,233] In cases of ruptured anterior leaflet first-order chordae, the leakage is aimed laterally and toward the posterior LA wall; the murmur may be transmitted posteriorly. Although there is no correlation between the intensity of the systolic murmur and the hemodynamic severity of the mitral regurgitation, a holosystolic murmur is characteristic of more regurgitant flow.[232] Because of the relatively noncompliant left atrium in acute mitral regurgitation, the murmur is often early and midsystolic.[11] In patients with Barlow syndrome (severe bileaflet mitral billowing and prolapse), early in the disease process, a characteristic midsystolic click is heard, followed by a late systolic murmur; as the annulus and left ventricle dilate, the murmur over time becomes holosystolic, and the midsystolic click may become inaudible.

On chest radiography, cardiomegaly indicative of LV and LA enlargement is found commonly in patients with long-standing moderate to severe mitral regurgitation.[130] Acute mitral regurgitation often is not associated with an enlarged heart shadow and may produce only mild LA enlargement despite an elevated LA pressure. Chest x-ray findings of congested lung fields are less prominent in patients with mitral regurgitation than in those with mitral stenosis, but interstitial edema is seen frequently in individuals with acute mitral regurgitation and those with progressive LV failure secondary to chronic mitral regurgitation.

Changes on the electrocardiogram are not particularly useful and depend on the etiology, severity, and duration of the mitral regurgitation.[120,232] Atrial fibrillation can occur late in the natural history of the disease and usually causes sudden symptoms. In cases of chronic mitral regurgitation, LV volume overload leads to LA and LV dilatation and, eventually, to LV hypertrophy owing to the chronic volume overload. Electrocardiographic evidence of LV enlargement or hypertrophy occurs in half of patients, 15% have right ventricular hypertrophy owing to increased pulmonary vascular resistance, and 5% have combined left and right ventricular hypertrophy.[120] Ventricular arrhythmias may be noted on ambulatory Holter recordings, especially in patients with LV systolic dysfunction. In those with acute mitral regurgitation, LA and/or LV dilatation may not be evident, and the electrocardiogram may be normal or show only nonspecific findings, including sinus tachycardia or ST-T-wave alterations.[120] Findings of myocardial ischemia or infarction, more commonly noted in the inferior leads, may be present when acute mitral regurgitation is related to acute inferior myocardial infarction or myocardial ischemia; in these cases, first-degree AV block is a common coexisting finding.

In the majority of individuals with mitral valve prolapse, particularly those who are asymptomatic, the resting electrocardiogram is normal.[120,188,234] In symptomatic patients, a variety of ST-T-wave changes, including T-wave inversion and sometimes ST-segment depression, particularly

in the inferior leads, can be found.[184,188] QTc prolongation also may be seen. Arrhythmias may be observed on ambulatory electrocardiograms, including premature atrial contractions, supraventricular tachycardia, AV block, bradyarrhythmias, and premature ventricular contractions.[188] Atrial arrhythmias may be present in upwards of 14% of patients, and ventricular arrhythmias are present in 30% of patients.[147] Age correlates with the incidence of atrial arrhythmias; female gender and anterior mitral valve thickening are predictors of ventricular arrhythmias.[147]

Today, transthoracic echocardiography (TTE) is the clinical mainstay in patients with valvular heart disease, and real-time three-dimensional echocardiography is now used extensively for patients with mitral valve disease in many echocardiography laboratories. In those with chronic mitral regurgitation, echocardiography is used to follow the progression of LA and LV dilatation and changes in the amount of mitral regurgitation and leaflet morphology.[11,121,123,196,235] Two-dimensional echocardiography confirms chamber enlargement, and color Doppler imaging characterizes many features of the regurgitant leak(s). Two-dimensional echocardiography also identifies abnormalities in leaflet and chordal morphology and function, including myxomatous degeneration with or without leaflet prolapse, restricted systolic leaflet motion (as in IMR) or diastolic opening motion (as in rheumatic valve disease), lack of adequate coaptation owing to annular dilatation or rheumatic valvulitis (fused subvalvular apparatus), and leaflet destruction by endocarditis[11,122,196,235] (Fig. 41-12). Chordal rupture or elongation causing a flail leaflet is characterized by excessive motion of the leaflet tip backward into the left atrium beyond the normal saddle-shaped three-dimensional leaflet coaptation zone. Papillary muscle rupture following myocardial infarction and annular dilatation can be visualized by echocardiography (Fig. 41-13). Pulsed-wave or continuous-wave Doppler echocardiography tends to overestimate the severity of mitral regurgitation in patients with depressed LV ejection fraction and low cardiac output; it is extremely

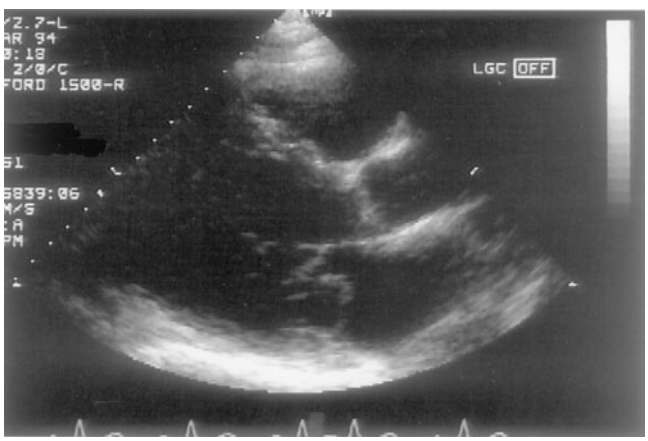


Figure 41-12. Echocardiogram (long-axis) of a patient with mitral regurgitation owing to floppy mitral valve. The leaflets billow back into the left atrium during systole.

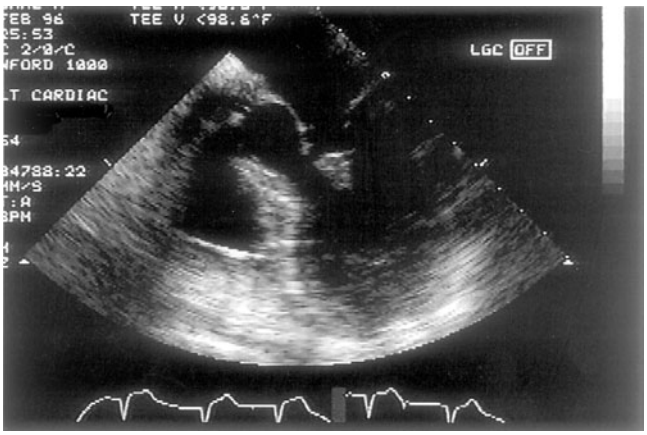


Figure 41-13. Echocardiogram (two-chamber view) of a patient with mitral regurgitation owing to ruptured papillary muscle.

sensitive and specific in diagnosing mild or severe mitral regurgitation but not as accurate in assessing the degree of mitral regurgitation.[11] The most commonly used method to assess the degree of regurgitation is two-dimensional color Doppler echocardiography, which permits visualization of the origin, extent, direction, duration, and velocity of disturbed backward flow of the regurgitant leak or leaks into the left atrium.[122,196,235,236] In patients with IMR or FMR, apical systolic tenting or tethering of the leaflets, tenting area and height, and leaflet opening angles can be quantitated, including important pathoanatomic differences between ischemic cardiomyopathy and idiopathic dilated cardiomyopathy[175,194,196,237] (Fig. 41-14). The cardinal distinctions between IMR and FMR in a recent study by Kwan and colleagues are (1) the pathologic changes are symmetric across the valve (from commissure to commissure) in patients with FMR and asymmetric in those with IMR, in whom the largest derangements are located on the medial side of the

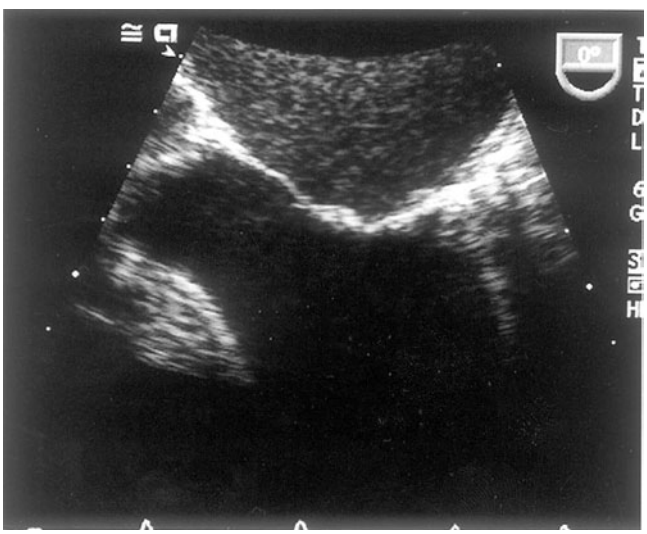


Figure 41-14. Echocardiogram of a patient with ischemic mitral regurgitation and apical systolic leaflet tenting.

valve, and (2) the magnitude of the changes is greater in the FMR group with idiopathic dilated cardiomyopathy than in those with IMR.[237] When the regurgitant leak is due in part or totally to annular dilatation, usually in the septolateral dimension (or clinically in the anteroposterior axis), the coaptation height of the anterior and posterior leaflets can be measured. Incomplete mitral leaflet coaptation is seen commonly in patients with FMR and IMR and can contribute to the mitral regurgitation in patients with long-standing prolapse. The regurgitation caused by annular dilatation and incomplete leaflet coaptation is directed straight back into the left atrium; successful repair includes restoring a normal amount of leaflet coaptation when an annuloplasty ring is used.

In any form of mitral regurgitation, ERO and regurgitant volume can be estimated quantitatively in many but not all patients using two-dimensional color Doppler echocardiography.[175,195,196] ERO has been demonstrated to be an important predictor of outcome in patients with mitral regurgitation treated medically and has been proposed as an indicator of when to proceed with mitral repair in asymptomatic patients with prolapse, which will be discussed below.[195] However, accurate quantification of the degree of mitral regurgitation using ERO and regurgitant volume is demanding and time-consuming and may not be possible at all institutions. The hemodynamic magnitude or severity of the mitral regurgitation also can be estimated semiquantitatively by calculating mitral and aortic stroke volumes, with regurgitant volume being the difference between these two stroke volumes. Notably, cardiac MRI is an accurate method to measure regurgitant volume and regurgitant fraction; it should be remembered that if aortic regurgitation also exists, the regurgitant volume and regurgitant fraction represent the combined effects of both valves leaking with respect to forward output.

Renewed interest in the timing of the regurgitant leak (and murmur) has helped clinicians discern subtle details about the pathologic mechanism(s) responsible for the mitral regurgitation (which then guide the specific mitral repair techniques used), infer information about the overall hemodynamic burden imposed by the LV volume overload, and predict the likelihood of successful and durable mitral repair. IMR is primarily an early-systolic leak, and the regurgitation in patients with FMR occurs during early and middle systole (biphasic pattern); prolapse is associated with late-systolic leaks. While detected by pulse-wave and continuous-wave Doppler echocardiography for years, the timing of the mitral regurgitation has become more widely appreciated owing to a resurgence of interest in color Doppler M-mode echocardiography, which has a much faster temporal resolution (sampling frequency) than does two-dimensional color Doppler echocardiography. Cardiac surgeons should study these color Doppler M-mode images regularly because the duration of the regurgitant leak is a major determinant of the overall magnitude of the regurgitation.

When necessary, such as when high-quality TTE images cannot be obtained owing to patient habitus or advanced emphysema, transesophageal echocardiography (TEE) provides superior image quality and can reveal additional anatomic and pathophysiologic information, including details of the valvular pathoanatomy and the mechanism, origin, direction, timing, and severity of the regurgitant leak.[11,123,196,235,238] TEE can detect small mitral vegetations, ruptured chordae, leaflet perforations or clefts, calcification, and other inflammatory changes and can be useful in patients with annular or leaflet calcification. TEE also is useful in patients with a previously implanted aortic valve prosthesis that can interfere with TTE assessment of mitral regurgitation owing to acoustic shadowing. Although intraoperative TEE during mitral valve repair is essential, a major limitation must always be remembered: The vascular unloading effects of general anesthesia downgrade the severity of mitral regurgitation.[239,240] The judgment about how much mitral regurgitation is present (and whether surgical repair is necessary) must be made on the basis of an awake TTE study when the patient has a normal ambulatory blood pressure. This concept is imperative in assessing the degree of mitral regurgitation in patients with IMR when deciding whether to add mitral valve surgery at the time of planned coronary artery bypass grafting. For patients in whom the degree of mitral regurgitation has been downgraded by the effects of anesthesia before or after valve repair, intraoperative TEE provocative testing using vasoconstrictor drugs with or without volume infusion is mandatory to guide surgical decision making. Testing consists of reproducing the patient's normal awake or active ambulatory hemodynamic condition with preload challenge and afterload augmentation.[239,240] Preload challenge is performed after aortic cannulation for cardiopulmonary bypass by rapidly infusing volume from the pump until the pulmonary capillary wedge pressure reaches 15 to 18 mm Hg. If severe mitral regurgitation is not produced, LV afterload is increased by intravenous boluses of phenylephrine until the arterial systolic pressure climbs to the 130- to 150-mm Hg range. In patients undergoing coronary artery bypass grafting, if both tests are negative, or if regurgitation is induced but associated with new regional LV systolic wall motion abnormalities (i.e., the regurgitation is due to acute ischemia of viable myocardium), the valve may not require visual inspection because coronary revascularization usually is all that is necessary if the inferior wall myocardium is viable. If these tests confirm the presence of moderate to severe mitral regurgitation, the valve is inspected and usually is repaired using an undersized annuloplasty ring specifically designed for IMR, e.g., Edwards ETlogix, Edwards Geoform, or St. Jude Medical RSR (rigid saddle ring), at the time of coronary revascularization. All these IMR rings are complete and rigid (made of titanium) with the septolateral dimension disproportionally downsized compared with the commissure-commissure annular dimension, thereby correcting the key abnormality (septolateral dilation) in IMR and FMR.

Real-time three-dimensional echocardiography is now available clinically and shows promise in the assessment of congenital and acquired valvular disease.[127] This technique

facilitates spatial recognition of moving intracardiac structures. In patients with mitral regurgitation, three-dimensional echocardiography is fairly accurate in elucidating the dynamic mechanisms of the regurgitant leak(s). The addition of color-flow Doppler to three-dimensional imaging provides improved visualization and may offer improved quantitative assessment of regurgitant valvular lesions.[127] Additionally, three-dimensional echocardiography may provide more insight into the geometric deformities of the mitral leaflets and annulus, maximum tenting site of the mitral leaflet, and quantitative measurements of mitral valve tenting and annular deformity in patients with IMR.

Historically, cardiac catheterization and left ventriculography have been used in the assessment of mitral regurgitation, but modern echocardiography has eliminated the need for left-sided heart catheterization in the vast majority of patients.[11,119,201] It usually is indicated only to determine coronary artery anatomy in older patients with prolapse prior to repair and those with IMR. Other techniques, such as calculating mitral regurgitant fraction (regurgitant volume determined as the difference between total LV angiographic stroke volume and the effective forward stroke volume measured by the Fick method), are limited. By measuring rest and exercise (supine bicycle) pulmonary artery pressures and cardiac output, right-sided heart catheterization can be useful occasionally to identify patients with primary myocardial disease who present with LV dilatation and relatively mild degrees of mitral regurgitation (who may not have a high likelihood of benefiting from mitral valve surgery) and those with severe mitral regurgitation who deny symptoms to see if they develop pulmonary hypertension with exercise.

MRI is a noninvasive modality that can be employed to assess the cardiovascular system, including cardiac structure and function.[241–243] Specialized MRI techniques, such as moving-slice velocity mapping, the control-volume method, or real-time color-flow MRI, have been used to evaluate and quantify the degree of mitral regurgitation. The presence of valvular regurgitation can be determined, LV volumes and mitral regurgitant fraction estimated, and information obtained concerning mitral and coronary anatomy. Quantitative MRI measurements, e.g., LV end-diastolic and end-systolic volumes and regurgitant fraction, correlate well with those determined at cardiac catheterization. Current MRI technology remains inferior to echocardiography for assessing valvular morphology and leaflet motion. Constraints of MRI, such as pacemakers or implantable cardiodefibrillators, morbid obesity, and claustrophobia, hamper the wider use of cardiac MRI. Recently, multidetector CT has emerged as an imaging technique that can fully evaluate both cardiac structure and function, including coronary artery anatomy; this new technology has yielded good visualization of valve leaflets, commissures, and mitral annulus.[129] Limitations still include image noise, requirement for a regular rhythm and a slow heart rate during imaging, time required for postprocessing data analysis, and radiation dose; nonetheless, this technology is very promising.

Postoperative LV Function and Surgical Outcomes

General

Successful mitral valve repair or replacement usually is associated with clinical improvement, augmented forward stroke volume with lower total stroke volume, smaller LV end-diastolic volume, and regression of LV hypertrophy.[182,244–246] Surgical correction of chronic mitral regurgitation can preserve LV contractility, particularly in patients with a normal preoperative ejection fraction who have minimal ventricular dilatation and those without significant coronary artery disease. On the other hand, in patients with impaired LV contractile function preoperatively, improvement in LV systolic function may not necessarily occur after operation.[245] An LVESVI exceeding 30 mL/m^2 is associated with decreased postoperative LV function.[217,245] Thus patients with chronic mitral regurgitation should be referred for mitral valve surgery when LVESVI does not exceed 40 to 50 mL/m^2 (or when LV end-systolic dimension is 4 cm or less according to the newly updated ACC/AHA 2006 guidelines[246]); otherwise, a poor outcome is likely.[217] LVESVI corrected for LV wall stress, a single-point ratio of end-systolic wall stress to end-systolic volume index, or ESS:LVESVI, is a good index of LV systolic function and accurately predicts surgical outcome in patients with mitral regurgitation.[214,215] Specifically, an ESS:LVESVI ratio of less than 2.6 portends a poor medium-term prognosis, whereas a normal or high ESS:LVESVI ratio is associated with a favorable outcome, suggesting that LV contractile function had been relatively preserved before operation.[215] Significant determinants of increased operative risk also include older age, higher New York Heart Association (NYHA) functional class, associated coronary artery disease, increased LV end-diastolic pressure, elevated LV end-diastolic volume index, elevated LV end-systolic dimension, reduced LV ESS index, depressed resting ejection fraction, decreased fractional shortening, reduced cardiac index, elevated capillary wedge or right ventricular end-diastolic pressure, concomitant operative procedures, and previous cardiac surgery.[217,245–252]

Experimentally, normalization of LV contractile function is associated with increased myocyte length, augmented myocyte cross-sectional area, and increased contractile protein content.[203] The abnormal LV diastolic properties (including early diastolic filling rate, myocardial relaxation, chamber stiffness, myocardial stiffness, and end-diastolic pressure) also may be reversible after mitral valve surgery.[222] If surgical correction of mitral regurgitation is carried out before the volume-overload cardiomyopathy reaches an irreversible stage, LV diastolic filling characteristics and systolic contractile function return toward normal values. Furthermore, LV volume and the LV volume:mass (or dimension:thickness) ratio usually normalize postoperatively, but mild LV hypertrophy may persist.[222]

The decline in ejection fraction after mitral valve replacement for chronic mitral regurgitation is believed to be a result of the postoperative increase in afterload, which

historically was thought to be secondary to closure of the low-resistance early-systolic "pop-off" into the left atrium and surgical excision of the subvalvular apparatus. A spherical mathematical model of the left ventricle has been used to define the relations between LV end-diastolic dimension, systolic wall stress, and ejection fraction.[253] This model has been validated in patients undergoing mitral valve replacement with or without chordal-sparing techniques; postoperative changes in systolic stress are related directly to changes in chamber size, and LV afterload may decrease postoperatively if chordal-preservation valve replacement techniques are used. In terms of exercise performance after mitral valve surgery for nonischemic mitral regurgitation, although patients generally report symptomatic improvement, cardiopulmonary exercise testing at 7 months actually is not better than preoperatively, and abnormal neurohumoral activation persists, probably reflective of incomplete recovery of LV contractility[254] (Table 41-1). Plasma renin activity, aldosterone, and atrial natriuretic peptide (ANP) decrease after surgery but are still elevated compared with control values. Neurohumoral activation may contribute to the impairment of exercise performance in patients with heart failure by limiting exercise-induced vasodilatation or by contributing to maldistribution of peripheral blood flow.[254] With respect to long-term clinical outcome, risk factors portending postoperative cardiac deterioration include larger LV end-diastolic dimension, increased LV end-systolic dimension, increased LVESV, diminished fractional shortening, reduced LV ESS index, large LA size, decreased LV wall thickness/cavity dimension at end-systole, and associated coronary artery disease.[217,247,250,251,255]

Patients with mitral regurgitation owing to flail leaflet frequently are asymptomatic, yet this entity is associated with a risk of progressive LV dysfunction and a suboptimal prognosis if not treated surgically. If treated conservatively with medical management, mitral regurgitation owing to flail leaflet is associated with high annual mortality risk (6.3%) and morbidity rates.[183,256] In these patients, the strategy of early operation results in improved long-term survival. Mitral valve repair for patients with myxomatous mitral regurgitation is feasible in the large majority of patients in certain experienced centers and offers excellent early and late functional results.[182,257–259] Because fewer complications and lower operative mortality risk are associated with valve repair compared with valve replacement in this patient population, operation should be considered earlier in the natural history of the disease if the pathologic anatomy is judged favorable for valve repair.[147,182,183,247,256,257,260,261] For instance, in a recent study from Toronto, patients undergoing mitral valve repair for floppy mitral valve disease had a 15-year survival rate of 61% for all patients and 76% for asymptomatic patients, along with a freedom from reoperation rate of 91%[182] (Fig. 41-15). Predictors of late death included age, NYHA functional class, ejection fraction greater than 40%, preoperative stroke or transient ischemic attack, previous cardiac surgery, and severe obstructive lung disease. Early mitral repair in asymptomatic patients with degenerative mitral regurgitation thus is recommended if valve repair can be performed reliably with low operative mortality and morbidity rates.[182]

A landmark study published in 2005 from the Mayo Clinic focused on the management of asymptomatic patients with organic mitral regurgitation.[195] Four hundred fifty-six asymptomatic patients with at least mild holosystolic mitral regurgitation defined echocardiographically were enrolled prospectively from 1991 to 2000. Follow-up averaged 2.7 years under medical management and 5.1 years under medical and surgical management. At entry, baseline ejection fraction was 70%, LV end-systolic dimension was 3.4 ± 6 cm, LV end-diastolic dimension was 5.6 ± 8 cm,

Table 41–1.

Neurohormone Levels Before and After Surgery

	Before	After	Controls ($n = 24$)
Norepinephrine (pg/L)	520 (400–650)*	430 (380–610)*	130 (100–260)
PRA (ng/mL/h)	3.1 (2.0–4.5)*	1.2 (0.9–2.2)*†	0.88 (0.56–1.22)
Aldosterone (pg/mL)	160 (118–180)*	93 (58–133)*†	78 (49–107)
ANP (pmol/L)	75 (47–128)*	62 (48–79)*†	14 (8–21)
Endothelin-1 (mpol/L)	2.1 (1.9–2.4)*	1.8 (1.6–2.2)	1.7 (1.2–2.1)

Data are median value (95% confidence interval).
ANP = atrial natriuretic peptide; PRA = plasma renal activity.
**$p < .05$ versus control.*
†$p < .05$ after versus before.
Reproduced with permission from Le Tourneau T, de Groote P, Millaire A, et al: Effect of mitral valve surgery on exercise capacity, ventricular ejection fraction and neurohumoral activation in patients with severe mitral regurgitation. J Am Coll Cardiol 2000; 36:2263.

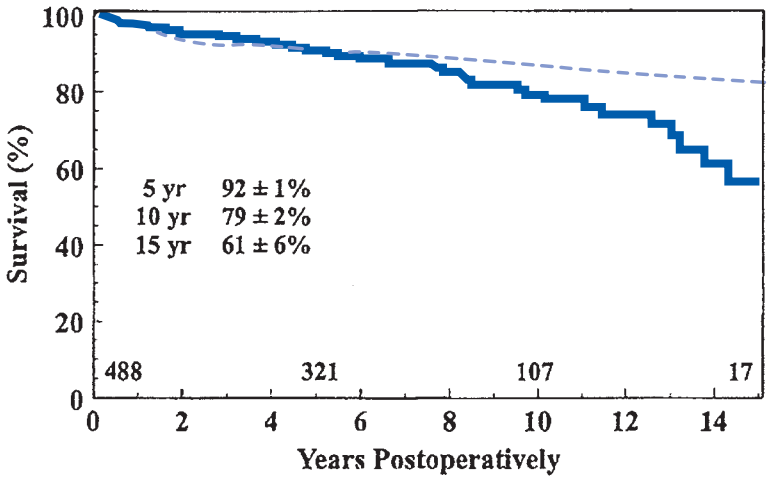


Figure 41-15. Survival after mitral valve repair in comparison with that in the general population matched for age and sex, as depicted by the dashed line. (*Reproduced with permission from David TE et al: Late outcomes of mitral valve repair for floppy valves: Implications for asymptomatic patients. J Thorac Cardiovasc Surg 2003; 125:1143.*)

LVESVI was 33 ± 130 mL/m^2, and regurgitant volume was 66 ± 40 mL/beat. Management was at the discretion of the primary physician, including when to proceed to valve surgery. At 5 years, 54% of patients had been operated on after an average of 1.2 ± 2 years of medical treatment when symptoms occurred or when worrisome echocardiographic findings were detected (based on 1998 ACC/AHA valve disease practice guidelines). Among the 230 patients who underwent a mitral valve procedure, 209 (91%) received a valve repair. Operative mortality rate was low at 1%. The patients were stratified by degree of regurgitation; mild, moderate, and severe were defined as regurgitant volumes of less than 30, 30 to 59, and 60 or more mL/beat, and ERO was defined as less than 20, 20 to 39, and 40 or greater mm^2, respectively. For the medically treated patients, 5-year survival compared with U.S. Census life tables was significantly inferior for those with moderate regurgitation (ERO of 20 to 39 mm^2, 66% versus 84%) and severe regurgitation (ERO of 40 mm^2 or more, 58% versus 78%).[195] Independent risk factors for death in the medically treated patients were advancing age, diabetes mellitus, and larger ERO. Even when adjusted for age, gender, diabetes, atrial fibrillation, and ejection fraction, ERO still predicted survival. The influence of ERO also held true for predicting cardiac deaths and all cardiac events. The 5-year cardiac death rate was 36% for patients with an ERO of 40 mm^2 or greater compared with 20% for those with an ERO of 20 to 39 mm^2 and only 3% for those with an ERO of less than 20 mm^2. Mitral valve operation was an independent determinant of fewer deaths, cardiac deaths, and cardiac events, especially in those with a larger ERO.[195] This important study, which focuses on the predictive effects of the severity of the regurgitation instead of the response of the ventricle, has prompted a rethinking in our approach to asymptomatic patients with mitral regurgitation. All asymptomatic patients with an ERO of 40 mm^2 or greater should be referred for consideration of early surgical repair. Those with an ERO in the 20 to 39 mm^2 range should be monitored closely using serial echocardiography. Finally, those with the smallest ERO (<20 mm^2) can be followed more conservatively and are at low risk of developing cardiac complications while being managed medically. Despite the valuable information in this study, future larger prospective trials are necessary to validate these results. Notably, the critical ERO threshold for mitral regurgitation owing to degenerative disease and prolapse (40 mm^2) in patients with preserved LV systolic function is twice the 20 mm^2 critical value of ERO that predicts an adverse outcome in patients with LV systolic dysfunction and IMR or FMR (see below).[175,194] In other words, it only takes a regurgitant orifice one-half as large to portend an unfavorable outcome if one has impaired LV function owing to ischemic or idiopathic cardiomyopathy.

When a large preoperative LVESVI or echocardiographic end-systolic dimension indicates the presence of LV systolic dysfunction, every effort should be made to repair the valve, or at least preserve all chordae tendineae (to both the anterior and posterior leaflets) if valve replacement is necessary.[246,262] Importantly, these surgical technical details have been emphasized in the 2006 update of the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines; furthermore, these guidelines state how important it is that patients with mitral regurgitation be referred to surgical centers that have demonstrated track records of excellence for mitral repair, including long-term repair durability.[246] In the United Kingdom, this thrust emphasizing surgical quality and reliability has reached the point where standards for mitral repair best practice have been promulgated with recommended regionalization of surgical expertise and minimum surgeon and hospital annual volume benchmarks.[263] The recently updated ACC/ AHA practice guidelines include an overall strategy in the management of patients with severe chronic mitral regurgitation, incorporating symptoms, LV systolic function, reparability of the valve, and the likelihood of total chordal preservation if valve replacement were necessary[246]

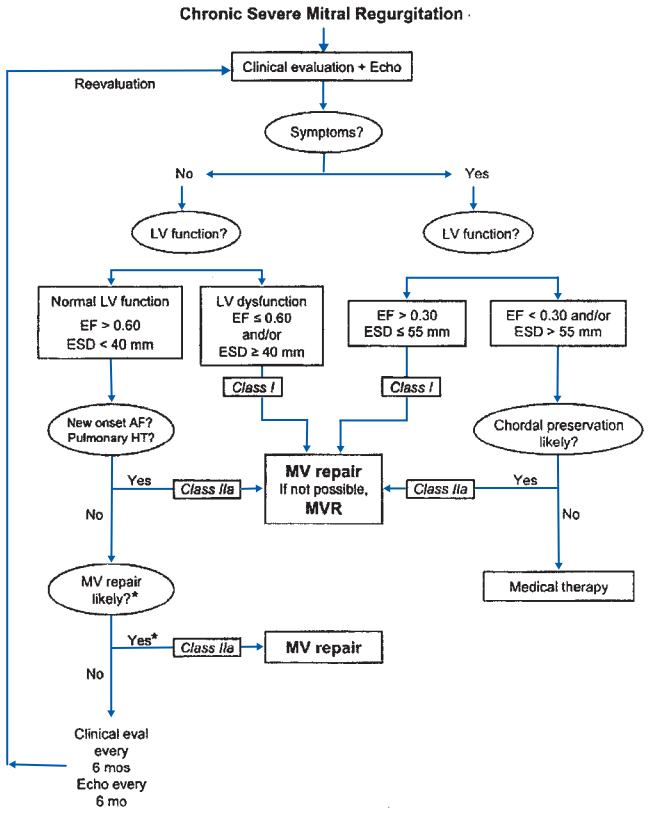


Figure 41-16. Management strategy for patients with chronic severe mitral regurgitation. *Mitral valve repair may be performed in asymptomatic patients with normal left ventricular function if performed by an experienced surgical team and if the likelihood of successful repair is greater than 90%. MV = mitral valve; LV = left ventricular; AF = atrial fibrillation; EF = ejection fraction; ESD = end-systolic dimension; eval = evaluation; HT = hypertension; MVR = mitral valve replacement. (*Reproduced with permission from Bonow RO et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. J Am Coll Cardiol 2006; 48:e1.*)

(Fig. 41-16). It is noteworthy that the threshold for LV end-systolic dimension for when to consider operation is now 4 cm, smaller than the 4.5-cm criterion in the previous 1998 guidelines. Needless to say, to reach consensus on this controversial issue has been an arduous challenge and is based on scientific evidence supporting each decision step. The defined strategy is thoughtful and should be studied.

Because many patients with a substantial mitral regurgitation report no symptoms, and because symptoms have been the mainstay of when to consider surgical repair, cardiopulmonary exercise testing has been used to evaluate asymptomatic patients with organic mitral regurgitation (owing to prolapse in 93% of cases) at the Mayo Clinic.[264] Of 134 asymptomatic patients with an average ejection fraction of 73%, 57% had severe mitral regurgitation with a regurgitant volume of 68 ± 24 mL/beat (range of 30 to 146 mL/beat) and an ERO of 35 ± 14 mm^2 (range 14 to 83 mm^2). Surprisingly, functional capacity was markedly reduced (defined as 84% or less than expected) in 19% of these "asymptomatic" patients. Those with impaired functional capacity were roughly equally distributed according to regurgitant volume of less than or greater than 60 mL/beat and ERO of less than or greater than 40 mm^2. When patients with extraneous reasons for impaired functional capacity were excluded, 14% had a reduced functional capacity, and their regurgitant volume and ERO were larger than those with a normal functional capacity. Determinants of reduced functional capacity were impaired LV diastolic function, lower forward stroke volume, and atrial fibrillation; ERO had no significant influence on functional capacity.[264] Thus it was the consequences of chronic mitral regurgitation and not the magnitude of the leak that predicted impaired functional capacity. Follow-up at over 2 years revealed that 66% of patients with impaired functional capacity sustained some adverse event or required mitral surgery (versus 29% of those with normal functional capacity) after adjusting for age, ERO, gender, and ejection fraction. Although the results need to be validated prospectively, this evidence argues that asymptomatic patients with substantial mitral regurgitation should undergo periodic cardiopulmonary exercise testing to detect subclinical impairment in functional capacity and that mitral valve repair should be recommended to those with impaired capacity.

Even after mitral valve surgery for chronic mitral regurgitation, some patients continue to be limited by heart failure symptoms and have a less than optimal long-term postoperative outcome. Based on evidence from the Mayo Clinic, the incidence of congestive heart failure in patients who survive surgery (combined series of valve repair and valve replacement) for pure mitral regurgitation has been 23%, 33%, and 37% at 5, 10, and 14 years.[266] Valve repair is not a predictor of decreased incidence of congestive heart failure; however, using a combined endpoint of congestive heart failure and death, valve repair compared with valve replacement in patients with mitral regurgitation appears to confer a survival advantage. Patient survival after the first episode of congestive heart failure is dismal, being only 44% at 5 years. Causes of congestive heart failure include LV dysfunction in two-thirds of patients and valvular problems in the remaining one-third. Predictors of postoperative heart failure are lower preoperative ejection fraction, coronary artery disease, and higher NYHA functional class.[266] Importantly, preoperative functional class III/IV symptoms are associated with markedly decreased postoperative medium- and long-term survival independent of all other baseline characteristics.[267]

Despite the trend of advocating earlier operation for patients with chronic mitral regurgitation even if they are minimally symptomatic or asymptomatic if the valve is reparable, some clinicians still adhere to the earlier, more conservative ACC/AHA practice guidelines. The cardiology unit at the Medical University of Vienna followed 132 asymptomatic patients with severe degenerative mitral regurgitation for a median of 69 months between 1995 and 2002.[268] Indications for operation were consistent with the 1998 ACC/AHA practice guidelines, including onset of symptoms or, if asymptomatic, the development of LV

enlargement (LV end-systolic dimension greater than 4.5 cm, or greater than 2.6 cm/m^2), LV systolic dysfunction (ejection fraction of less than 60%), pulmonary hypertension (pulmonary systolic pressure greater than 50 mm Hg), or recurrent atrial fibrillation. Thirty-eight of the 132 patients ultimately developed an indication for mitral surgery, yielding an actuarial freedom from surgery of 55% at 8 years. Of the 34 patients who underwent surgery, 83% received valve repair. There were no operative deaths. All patients benefited symptomatically, but 4 of 35 patients had impaired LV function postoperatively that was judged to be secondary to valve replacement (chordal preservation technique not stated) in 2 and coronary artery disease after repair in 2. The conclusion was that it was safe to treat patients with severe degenerative mitral regurgitation medically as long as they were monitored carefully on a regular basis.[268] Although vigilance and close follow-up were the key to safe patient management in the Vienna experience, an editorialist noted that this level of care might not be available or reliably accessible to many patients.[269] The editorialist also highlighted the importance of the timing and duration of the "severe" mitral regurgitation in terms of the overall volume overload imposed on the left ventricle and wondered if the regurgitation in the study patients was as severe as the investigators believed it was. More information about the severity of the regurgitant leak can be obtained by echocardiographic continuous-wave Doppler tracings or color Doppler M-mode recordings or, better yet, resorting to quantitative parameters such as ERO and regurgitant volume.[175,195,196]

Historically, it has been thought that mitral valve surgery would not benefit patients with pronounced LV dilatation and severe global LV systolic dysfunction. Satisfactory results have been reported, however, after mitral valve repair using an undersized flexible annuloplasty ring with resulting decreased LV volume and sphericity and increased ejection fraction in patients with dilated or ischemic cardiomyopathy and congestive heart failure.[270–272] In 200 patients with cardiomyopathy and severe mitral regurgitation who underwent valve repair using an undersized annuloplasty ring, Bolling and colleagues reported an operative mortality rate of 4.5% with 26 late deaths and 2 patients subsequently requiring transplantation.[272] The 1- and 5-year survival rates were 82% and 52%, respectively. A follow-up observational study suggests that although mitral valve repair may be performed safely for patients with end-stage cardiomyopathy, the long-term outcome may be limited.[273] In assessing the effects of mitral valve repair in patients with mitral regurgitation and LV dysfunction, the risk factors for death, left ventricular assist device placement, or heart transplant included the presence of coronary artery disease and decreased renal function.[273] Factors that reduced risk included use of angiotensin-converting enzyme inhibitors and beta blockers. Mitral valve repair by itself did not have an impact on long-term outcome. Therefore, no mortality benefit conferred by mitral annuloplasty for FMR or IMR with severe LV dysfunction could be demonstrated.[273] Similarly, in the Mayo Clinic experience, in which the operative mortality also was low (2.3%), mitral valve procedures in patients with nonischemic cardiomyopathy yielded less than satisfactory long-term results, with a 5-year survival rate of only 33%.[153] A randomized, prospective trial is needed to clarify further the issue of whether a mitral valve procedure in these patients is beneficial over the long term. Alternatively, evolving technology focused on catheter-based interventional methods of altering the course of FMR or IMR and cardiomyopathy are currently being investigated and may play a role in the management of these patients in the future.[153,273,274]

Ischemic mitral regurgitation

To risk stratify patients after myocardial infarction, detecting and quantifying IMR are essential.[194,275–278] In a report from the Mayo Clinic, medically managed patients who developed IMR late after myocardial infarction had a very high mortality rate (62% at 5 years) compared with those with an infarction who did not develop IMR (39% at 5 years).[194] Medium-term survival for patients with IMR and LV systolic dysfunction was inversely related to the ERO and regurgitant volume. After 5 years, the survival rate was 47% for patients with an ERO of less than 20 mm^2 and 29% for those with an ERO of 20 mm^2 or greater. Survival at 5 years was 35% when the regurgitant volume was 30 mL/beat or greater compared with 44% for those with a regurgitant volume of less than 30 mL/beat. The relative risk ratio for cardiac death for patients with IMR was 1.56 for patients with an ERO of less than 20 mm^2 versus 2.38 for those with an ERO of greater than 20 mm^2. Conversely, the ERO threshold was twice as large (40 mm^2 or greater) in patients with prolapse or flail leaflets.[195] An ERO of more than 40 mm^2 was considered to reflect severe regurgitation in either disease, but the compound injury of coexisting LV dysfunction made the prognostic impact of even a "mild" leak (ERO of about 20 mm^2) very strong in patients with IMR.[278] In patients with myocardial infarction, the incidences of congestive heart failure and congestive heart failure or cardiac death were high even in patients with no or minimal symptoms at baseline and even higher in patients with IMR.[277] Determinants of congestive heart failure were ejection fraction, sodium plasma level, and presence and degree of IMR. At 5 years, the rate of congestive heart failure was 18% without IMR compared with 53% if IMR was present. If the ERO was less than 20 mm^2, the incidence of congestive heart failure was 46% compared with 68% when the ERO was 20 mm^2 or greater. The relative risk of congestive heart failure was 3.65 if IMR was present but 4.42 if ERO was 20 mm^2 or greater. At 5 years, the rate of congestive heart failure or cardiac death was 52%; the relative risk of congestive heart failure or cardiac death was 2.97 if IMR was present and 4.4 if ERO was 20 mm^2 or greater[277] (Fig. 41-17). Moderate or severe IMR was associated with a relative risk of 3.44 for congestive heart failure and 1.55 for death among 30-day survivors independent of age, gender, ejection fraction, and Killip class.[276]

In patients with IMR and LV systolic dysfunction, quantitative assessment of exercise-induced changes in the degree of mitral regurgitation provides additional prognostic

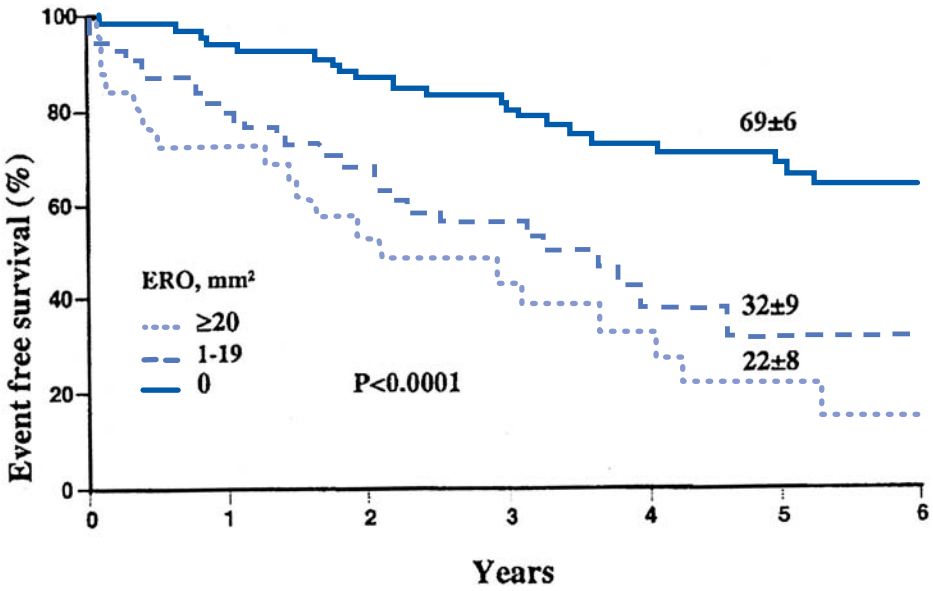
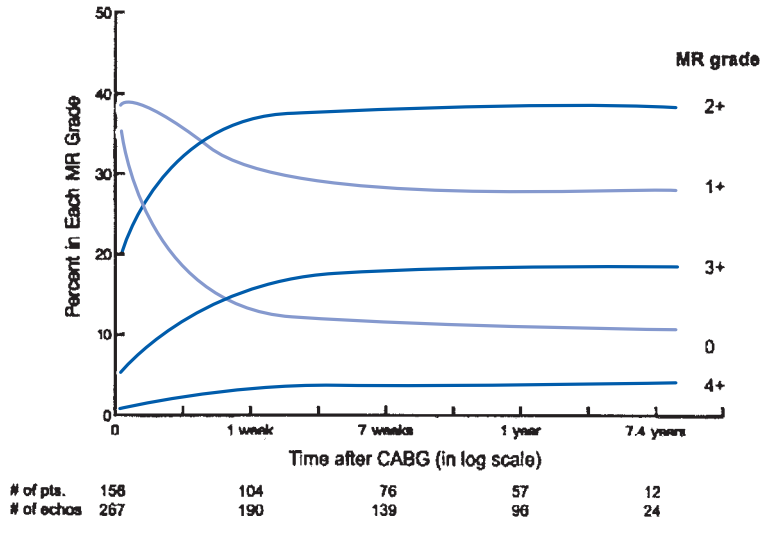


Figure 41-17. Survival free of congestive heart failure or cardiac death (event-free survival) in asymptomatic patients after myocardial infarction according to degree of mitral regurgitation measured by effective regurgitant orifice (ERO) of 20 mm^2 or more (*continuous line*), 1 to 19 mm^2 (*dashed line*), and no mitral regurgitation (ERO = 0) (*dotted line*) at diagnosis. The events at 5 years are indicated ± standard error. (*Reproduced with permission from Grigioni F et al: Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. J Am Coll Cardiol 2005; 45:260.*)

information.[279] Exercise-induced increases in mitral regurgitation unmask patients at higher risk of poor outcome. Similarly, low-dose dobutamine echocardiography may predict benefit from coronary revascularization in patients with IMR if regional LV wall motion improves.[200] Reduction of IMR has been associated with improvement in regional (inferior) systolic wall motion but not with changes in the anterior wall motion or global LV volume and function.[200] A pitfall of dobutamine stress echocardiography in assessing IMR, however, is that the ventricle becomes smaller at end-diastole and end-systole if viable myocardium is present; thus the mitral annulus is smaller at end-diastole (recall that IMR is an early-systolic leak, not holosystolic or late systolic), and increasing dobutamine dose paradoxically reduces the magnitude of the IMR. This result is predictable and should not be used as an excuse not to inspect the valve at the time of coronary bypass grafting because undersized ring annuloplasty frequently is needed.

Mitral repair or replacement for patients with IMR has been associated with higher operative risk (4 to 30%) than for patients with nonischemic chronic mitral regurgitation, which reflects the concomitant adverse consequences of previous myocardial infarction and ischemia.[280–289] The Yale group postulated that isolated coronary artery bypass grafting without valve repair is adequate in most patients with ischemic cardiomyopathy and mild to moderate mitral regurgitation, yielding survival rates of 88% at 1 year and 50% at 5 years; however, this study was small, and only a few patients had clinically important degrees of IMR.[290] Most investigators believe that coronary revascularization alone in the setting of moderate or severe IMR leaves many patients (up to 40%) with significant residual mitral regurgitation and heart failure symptoms.[149,291–293] Mitral regurgitation may be dynamic postoperatively, and it is influenced by LV afterload. Immediately postoperatively, IMR is absent or mild in 73% and severe in 6%; on the other hand, by 6 weeks, only 40% of patients have absent or mild mitral regurgitation, and 22% have severe mitral regurgitation[293] (Fig. 41-18). Postoperative residual or recurrent IMR is not associated with the preoperative extent of coronary artery disease or LV dysfunction. The 5-year survival rate of patients without IMR undergoing coronary artery bypass grafting only is 85% compared with 73% for patients with moderate IMR.[293] Because moderate IMR does not reliably resolve with coronary artery bypass grafting alone, valve repair (or even chordal-sparing valve replacement) should be considered in these patients because it potentially can reduce cardiac morbidity and may improve long-term survival.[149,291–293] Others argue that patients with moderate IMR undergoing coronary revascularization and concomitant mitral annuloplasty have less postoperative IMR but no improvement in long-term survival.[161,283,284,294] For patients with moderate or moderately severe IMR, isolated coronary artery bypass grafting and coronary revascularization combined with mitral annuloplasty provide similar long-term outcome with survival rates of 82 to 84% at 1 year, 40 to 68% at 5 years, and 37% at 10 years[282–284,295] (Fig. 41-19). Predictors of long-term mortality are older age, prior myocardial infarction, unstable angina, chronic renal failure, atrial fibrillation, absence of an internal mammary artery graft, lack of beta blocker use, lower ejection fraction, smaller left atrial size, global LV wall motion abnormalities, mitral leaflet restriction, and fewer bypass grafts.[282,284] Combined mitral valve repair and coronary revascularization does not emerge as a predictor of long-term survival. Whereas some workers report that annuloplasty can be added to coronary artery bypass grafting in high-risk patients without increasing early mortality, the potential benefit with respect to late survival and functional status may be limited owing to the underlying ischemic cardiomyopathy.[282–284,294]

In a previous Brigham and Women's Hospital experience, patients with IMR and annular dilatation or type IIIb



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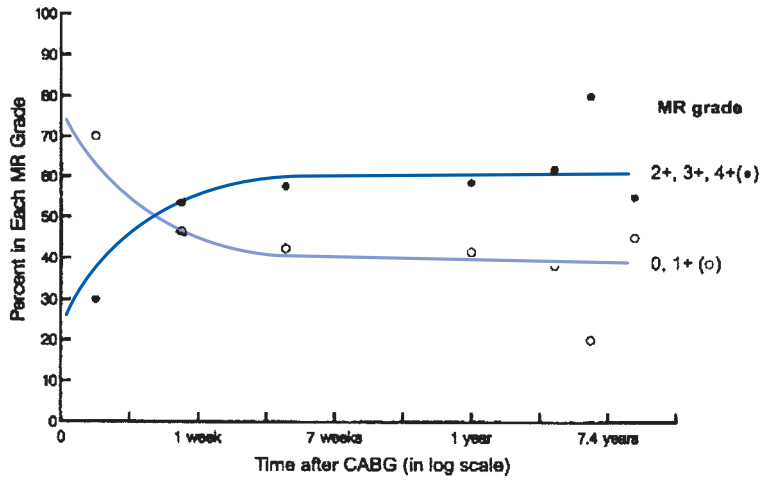

B

Figure 41-18. Course of mitral regurgitation after coronary artery bypass grafting alone. Horizontal axis is time after coronary artery bypass grafting on a logarithmic scale. 1+ is mild regurgitation, 2+ moderate, 3+ moderately severe, and 4+ severe. *A.* All grades of mitral regurgitation. *B.* Mitral regurgitation grades 0 or 1+ compared with 2+, 3+, or 4+. Symbols (*open circles, solid circles*) represent aggregated raw echocardiographic values for mitral regurgitation grade. MR = mitral regurgitation; CABG = coronary artery bypass grafting. (*Reproduced with permission from Lam BK et al: Importance of moderate ischemic mitral regurgitation. Ann Thorac Surg 2005; 79:462.*)

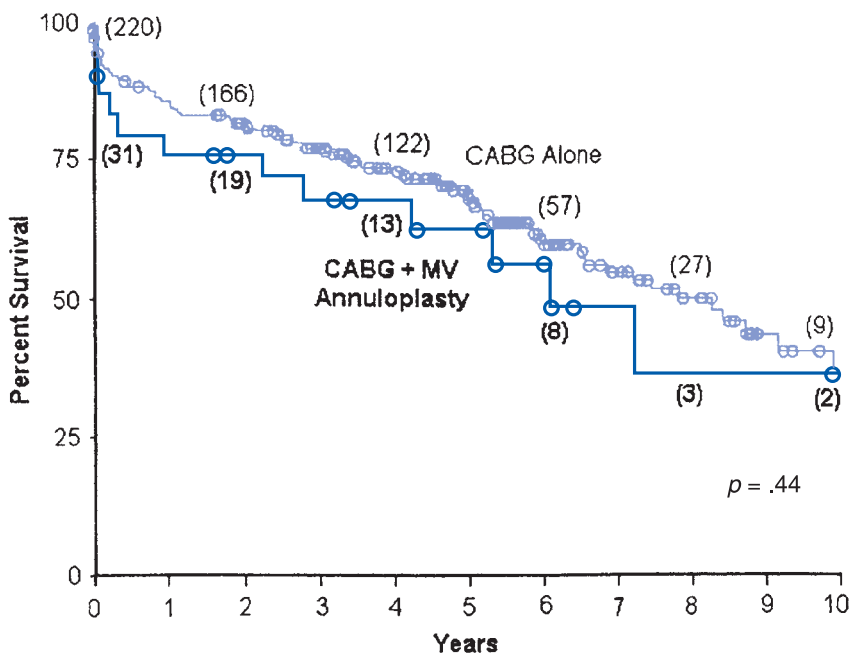

Figure 41-19. Survival estimates stratified by coronary artery bypass grafting alone versus coronary artery bypass grafting plus mitral valve annuloplasty. The numbers at risk for each group are given in parentheses. CABG = coronary artery bypass grafting; MV = mitral valve. (*Reproduced with permission from Wong DR et al: Long-term survival after surgical revascularization for moderate ischemic mitral regurgitation. Ann Thorac Surg 2005; 80:570.*)

restricted systolic leaflet motion (not chordal or papillary muscle rupture) who underwent valve repair and coronary revascularization had a worse long-term outcome than those who underwent valve replacement plus coronary revascularization.[280] These authors concluded that the pathophysiology or cause of the IMR was a stronger determinant of long-term survival than was the type of valve procedure. Conversely, the New York University group reported a higher complication-free survival rate (64% at 5 years) for patients undergoing mitral valve repair compared with 47% at 5 years for those in whom the valve had to be replaced.[296] The analysis of the early mortality risk for patients with IMR undergoing mitral valve repair versus valve replacement was confounded by many other factors, including functional disability and angina. Excluding these two variables, further analysis showed that the early mortality rate was lower for patients undergoing valve repair than for those undergoing valve replacement.[296] Based on propensity-score analysis, the Cleveland Clinic group found that in the lower-risk quintiles of patients with IMR, valve repair conferred a survival advantage (58% at 5 years) over those who underwent valve replacement (36% at 5 years); however, in the highest-risk patients, late survivals after valve repair and valve replacement were similarly poor, and valve replacement actually conferred a small survival advantage.[297] This thoughtful analysis highlights the soberingly poor prognosis of patients with IMR and how the patient's clinical condition and LV function status are more powerful determinants of outcome than operative procedure performed. Analysis of etiology of the mitral regurgitation (degenerative versus ischemic) in patients with coronary artery disease after combined mitral valve repair and coronary revascularization showed that those with IMR had more extensive coronary artery disease, worse ventricular function, more comorbidities, and more preoperative symptoms.[298] Unadjusted 5-year survival estimates were 64% and 82% for patients with IMR and degenerative mitral regurgitation, respectively; however, matched pairs had equivalent but poor 5-year survival rates (66% and 65%, respectively). Long-term survival varied widely among patients with degenerative mitral regurgitation and coronary artery disease, depending largely on ischemic burden and extent of LV dysfunction. These findings have been corroborated by a Duke study in which the large survival discrepancy between patients with IMR and those with degenerative mitral regurgitation combined with coronary artery disease was attributed to patient-related differences.[286] Only the number of preoperative comorbidities and advanced age emerged as predictors of survival, whereas ischemic etiology, gender, ejection fraction, NYHA functional class, coronary artery disease, reoperation, and year of operation did not achieve statistical significance.[286] Because survival was not different between patients with IMR and those with nonischemic mitral regurgitation after routine use of a rigid-ring annuloplasty during coronary artery bypass grafting, long-term patient survival was more influenced by baseline patient characteristics and comorbidity than by the etiology of the mitral regurgitation per se[286] (Fig. 41-20). In another

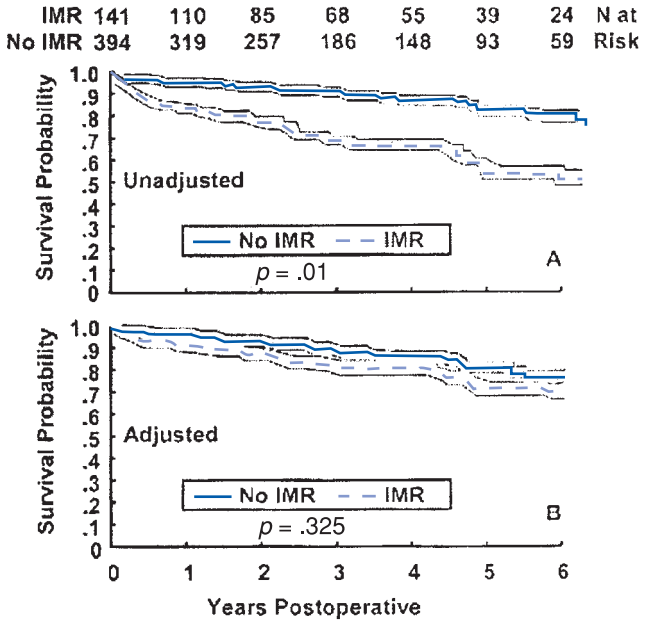

Figure 41-20. Survival of patients undergoing mitral valve repair with ischemic mitral regurgitation versus nonischemic mitral regurgitation before (*A*) and after (*B*) adjustment for differences in baseline patient characteristics. IMR = ischemic mitral regurgitation; NMR = nonischemic mitral regurgitation. (*Reproduced with permission from Glower DD et al: Patient survival characteristics after routine mitral valve repair for ischemic mitral regurgitation. J Thoracic Cardiovasc Surg 2005; 129:860.*)

Mayo Clinic analysis, the authors concluded that the decision as to whether to repair or replace the valve should be based on patient condition and should not be biased by whether mitral regurgitation is due to ischemia.[285] Older age, ejection fraction of 35% or less, three-vessel coronary artery disease, mitral valve replacement, and residual mitral regurgitation at discharge were risk factors for death. The cause of the mitral regurgitation, ischemic versus degenerative, was not a predictor of long-term survival, class III or IV congestive heart failure, or recurrent regurgitation.[285] Survival after mitral valve surgery and coronary artery bypass grafting thus is determined more by the extent of coronary artery disease and LV systolic dysfunction and the success of the valve procedure.[285,286]

A compelling explanation for the poor long-term outcome of patients who undergo mitral valve repair for IMR is the presence of residual and/or recurrent mitral regurgitation postoperatively.[299–301] Persistence of IMR after annuloplasty is due predominantly to augmented posterior leaflet apical tethering with no improvement in anterior leaflet tethering and no increase in coaptation length.[301] In a recent Cleveland Clinic report of annuloplasty (95% with concomitant coronary artery bypass grafting) for IMR, the proportion of patients with 0 or 1+ mitral regurgitation decreased from 71% preoperatively to 41% postoperatively, but the proportion with 3+ or 4+ residual or recurrent IMR increased from 13 to 28% during the first 6 months after

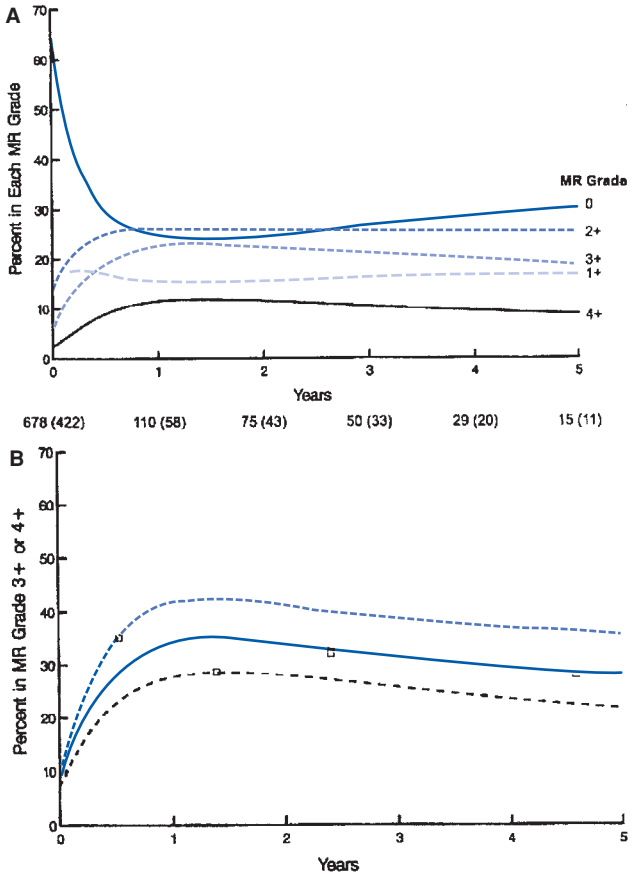

Figure 41-21. Progression of mitral regurgitation after surgical annuloplasty overall. *A.* All grades of mitral regurgitation. Curves for each regurgitation grade represent average temporal prevalence, and they sum up to 100% at each point in time. Numbers below the horizontal axis represent echocardiograms available at various time points, with the number of patients in parentheses. *B.* Prevalence of regurgitation grades 3+ or 4+. Dashed lines are 68% confidence limits of average prevalence. MR = mitral regurgitation. (*Reproduced with permission from McGee EC Jr et al: Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2004; 128:916.*)

repair[299] (Fig. 41-21). The temporal pattern of development of severe regurgitation was similar for those who received a Cosgrove partial, flexible band or a semirigid, complete Carpentier ring (25%), but it was substantially worse for those who received a strip of glutaraldehyde-preserved xenograft pericardium for annuloplasty (66%).[299] Smaller annuloplasty ring size apparently did not influence postoperative mitral regurgitation. These compelling results underscore how much additional work lies ahead in terms of developing new techniques and procedures in order to achieve a more durable valve repair.

Remodeling in ischemic mitral regurgitation

The development of IMR may not cause adverse LV remodeling, and some workers have proposed that IMR may be a manifestation rather than an important impetus for postinfarct remodeling, the extent of which may be determined by infarct size and location.[161] Anteroseptal and anteroapical infarcts lead to anterior akinesis (and in the days before thrombolysis or stenting for acute myocardial infarction, LV aneurysms); inferior and posterobasal infarcts more commonly cause progressive IMR. The extent of ventricular remodeling is a profound indicator of longevity. Mitral ring annuloplasty is fairly effective in treating IMR after inferior infarction at the time of surgical revascularization; however, annuloplasty may not induce favorable effects with respect to LV remodeling or survival.[161] Recurrence or progression of mitral regurgitation after ring annuloplasty coincides with LV volume increases (more adverse remodeling) and a more spherical ventricle; the only predictor of late postoperative mitral regurgitation was end-systolic LV sphericity index.[302] Restrictive mitral annuloplasty (undersizing by two ring sizes) may facilitate reverse remodeling, but this process is limited by the extent of preoperative LV dilatation.[289] In the study from Leiden, The Netherlands, a preoperative LV end-systolic dimension of 51 mm or less and an end-diastolic dimension of 65 mm or less predicted salutary reverse remodeling; however, the patients with IMR in this series were not typical.[289] The majority had sustained only one prior infarction relatively recently before operation, which might explain the excellent survival and favorable reverse LV remodeling observed. The gradual reductions in LA dimension and LV reverse remodeling were time-dependent processes in patients with IMR and ischemic cardiomyopathy who underwent coronary revascularization and valve repair with undersized annuloplasty. LV end-systolic dimension was smaller in 73% of patients, but LV end-diastolic dimension fell in only 56%; in those with larger LV dimensions preoperatively, no reduction in LV end-systolic or end-diastolic dimensions was seen in 27% and 42% of patients, respectively.[289] Since pronounced LV dilatation may be irreversible, it is logical to postulate that earlier mitral valve intervention to eliminate the chronic volume overload might halt the progression of LV dysfunction and mitigate the dismal prognosis.

Surgical considerations in ischemic and functional mitral regurgitation

Given the diversity of potential mechanisms contributing to the development of IMR and ischemic cardiomyopathy, current surgical therapy consisting of mitral annuloplasty with an undersized ring does not always provide a predictable or durable repair.[158,272,273,281,289,303] Because of the geometric interdependence of the entire valvular-ventricular complex, any intervention that remodels the annulus or alters LV geometry also would affect papillary muscle position and motion. Unfortunately, ring annuloplasty may not protect against recurrent IMR in patients with substantial outward (lateral) displacement of the posteromedial papillary muscle, as commonly seen after an inferior infarction. Although annuloplasty can improve both annular and subvalvular geometry in patients with IMR, leaflet apical tethering (type IIIb) often persists owing to posteromedial papillary muscle displacement, the severity of which may predict annuloplasty

failure because leaflet tenting and regional LV myocardial scarring are important contributing factors.[272,273,281,289,303] The higher incidence and greater severity of IMR in patients with inferior compared with anterior myocardial infarction is related to more severe geometric changes in the mitral subannular apparatus and greater lateral displacement of the posteromedial papillary muscle.[156] Understanding these changes has therapeutic implications in terms of infarct plication and leaflet or chordal elongation to minimize leaflet tethering. Surgical techniques that focus on LV reshaping in the segments adjacent to the papillary muscles, such as papillary muscle relocation, papillary muscle sling, and infarct restraint procedures, may have an impact on the degree and recurrence of IMR.[156,158,165]

Experimentally, a partial, flexible posterior annuloplasty ring has been shown to be just as effective as a complete semirigid ring in limiting septolateral annular dilatation during acute myocardial ischemia.[304] Another experimental procedure that may restore mitral competence during acute ischemia is the Paneth suture annuloplasty, which maintains normal annular and leaflet dynamic motion; this approach corrects ischemia-induced end-systolic distortions of the valvular-ventricular complex (i.e., interleaflet separation, mitral annular dilatation in both axes, and papillary muscle displacements) and abolishes acute IMR independent of any changes in LV end-systolic size.[305,306] In experimental chronic IMR, on the other hand, the mitral valve and subannular geometry are markedly distorted with leaflet tethering, and a complete, rigid annuloplasty ring is superior to a partial ring annuloplasty technique.[303] A novel rigid annuloplasty ring (Edwards Geoform) that radically downsizes the septolateral annular dimension and elevates the midposterior annular region has been introduced that it is claimed reduces IMR more reliably.[307]

Other experimental approaches have been proposed to treat IMR and FMR as a result of ischemic or dilated cardiomyopathy, such as infarct reduction using external plicating sutures, infarct restraint with an external mesh patch, external repositioning of the displaced posteromedial papillary muscle using an epicardial synthetic patch containing an inflatable balloon, internal papillary muscle repositioning using interpapillary sutures, or placement of subvalvular chord to reduce the annular septolateral dimension.[152,308–320] In a model of posterolateral myocardial infarction with resulting annular septolateral dilatation, posteromedial papillary muscle lateral displacement, and posterior leaflet tethering, septolateral annular cinching (SLAC, a simple transannular suture anchored to the midseptal annulus and externalized through the midlateral annulus) successfully moved the lateral annulus and the posteromedial papillary muscle closer to the septum and reduced IMR in both acute and chronic preparations[309–311,320] (Fig. 41-22). This Stanford SLAC suture concept has been developed further recently using a catheter-based device.[321] In an ovine model of rapid-pacing heart failure and FMR, the PS^3 device (Ample Medical, Foster City, CA) achieved septolateral cinching using a supra-annular

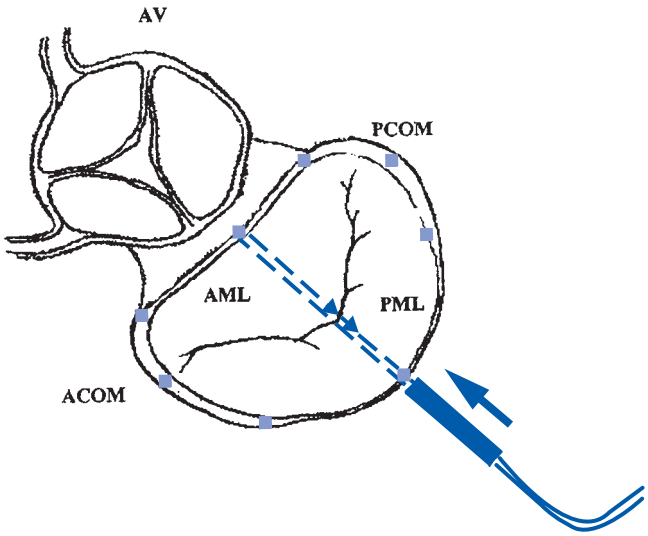

Figure 41-22. Schematic illustration of the mitral valve with annular and leaflet markers. Septolateral annular cinching suture (*dashed line*) spans the annular septolateral dimension and was externalized to an epicardial tourniquet. Arrow shows the direction of annular cinching. SLAC = septolateral annular cinching; AV = aortic valve; ACOM = anterior commissure; PCOM = posterior commissure; AML = anterior mitral leaflet; PML = posterior mitral leaflet. (*Reproduced with permission from Timek TA et al: Septal-lateral annular cinching abolishes acute ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2002; 123:881.*)

tightening member crossing the septolateral axis of the valve inside the left atrium. Based on the SLAC concept, the Coapsys device (Myocor, Inc., Maple Grove, MN), consisting of epicardial anterior and posterior pads connected by a transventricular chord, reduces septolateral annular diameter and relocates the posteromedial papillary muscle, thereby improving regurgitation in a cardiomyopathy model.[314,315] Clinically, applying the Coapsys device at the time of coronary revascularization reduced IMR and LV dimensions with no hemodynamic compromise or structural damage to the mitral apparatus. After 1 year, there was no grade 3+ to 4+ recurrent IMR, and no patient required reoperation for valve repair.[315] The Coapsys device coupled with off-pump coronary artery bypass grafting is now being compared prospectively (RESTOR-MV trial) with on-pump CABG and conventional undersized mitral ring annuloplasty.[319] Another experimental approach that corrects the end-systolic displacement of the posteromedial papillary muscle tip during acute ischemia and reduces IMR is tightening an exteriorized suture placed between the right fibrous annular trigone and posteromedial papillary muscle tip to reposition the papillary muscle.[322] A less invasive treatment in patients who have bundle-branch block (prolonged QRS > 120 ms), congestive heart failure, and functional mitral regurgitation or IMR is cardiac resynchronization therapy (CRT) with biventricular pacing. CRT can result in reverse LV remodeling, improved ejection fraction, and less IMR, but only fewer than half of patients respond favorably.[323–325] CRT may improve FMR

in some patients without any effect on LV size or systolic function by reducing LV dyssynchrony.

Because the second-order chordae tendineae anchor the valve leaflet and are more prominent on the anterior leaflet, transposition of posterior leaflet second-order chordae to the anterior leaflet has been used to correct anterior mitral valve leaflet prolapse. Recently, surgical division of the second-order chordae subtending the infarcted wall (usually those originating from the posteromedial papillary muscle) has been proposed to treat patients with chronic IMR.[326,327] If the apical systolic tethering is eliminated, the normal redundancy of the mitral leaflet area then creates better coaptation. The intact first-order or marginal chordae continue to prevent leaflet prolapse. On the other hand, division of the mitral chordae, especially the second-order or "strut" chordae, is known to impair LV systolic function.[160,328,329] Dividing the second-order chordae in an acute ovine preparation is associated with regional LV systolic dysfunction near the chordal insertion sites and neither prevents nor decreases the severity of acute IMR, septolateral annular dilatation, leaflet tenting area, or leaflet tenting volume.[160,328] Cutting the anterior mitral leaflet second-order chordae alters LV chamber long-axis and subvalvular geometry, remodels end-diastolic transmural myocardial architecture in the equatorial lateral LV region, perturbs systolic transmural LV wall-thickening mechanics (thereby decreasing subendocardial "microtorsion") and wall thickening, changes systolic temporal dynamics with delayed ejection, and impairs global LV systolic function (decreased end-systolic elastance and PRSW).[329] These findings demonstrate the importance of the chordae for LV structure and function; therefore, we believe that caution is necessary when considering procedures that cut second-order chordae to treat IMR because this may compromise LV systolic function in ventricles that are already impaired.[160,328,329]

Because IMR may be a consequence and not a cause of postinfarction LV remodeling, prevention of infarct expansion has been proposed as a more promising therapeutic target. It is possible that infarct expansion and LV stretching are the critical inciting phenomena that drive postinfarction remodeling.[161] Experimentally and clinically, prophylactic ventricular restraint or ventricular wrapping may reduce infarct expansion, attenuate adverse LV remodeling, preserve ejection fraction, and reduce the severity of IMR.[317,330,331] Prevention of IMR by prophylactic ring annuloplasty may not influence LV remodeling, but ventricular wrapping may be effective in preventing the development of IMR.[317,331]

Mitral Subvalvular Apparatus in LV Function

Originally proposed by Lillehei and colleagues in 1964, the mitral subvalvular apparatus (or valvular-ventricular complex), including chordal and papillary muscle function, is important for optimal postoperative LV geometry and systolic pump function.[137–141,204,205,332–338] After mitral valve replacement with total chordal excision, LV performance declines with depression of regional and global LV elastance, dyssynergy of contraction, and dyskinesia at the papillary muscle insertion sites; conversely, valve replacement with total or partial chordal preservation maintains LV contractile function.[137–140,224,338] Experimentally, severing either the anterior or the posterior leaflet chordae impairs global LV systolic function, as evidenced by reduced maximal elastance, but this is reversible if chordal reattachment is carried out.[139] The contributions of the chordae subtending the anterior mitral leaflet are slightly greater than the contributions of the posterior leaflet chordae, but these components are additive.[138] In a canine model of chronic mitral regurgitation, mitral valve replacement with chordal preservation (compared with chordal severing) optimized postoperative LV energetics and ventriculovascular coupling in addition to enhancing systolic performance.[205] Chordal interruption decreased global LV end-systolic elastance and depressed the end-systolic stress-volume relationship. In terms of myocardial energetics, the slopes of the LV stroke work–end-diastolic volume and pressure-volume area–end-diastolic volume relations also declined, indicating a reduction in external stroke work and mechanical energy generated at any given level of preload.

Clinically, mitral valve replacement with chordal division is associated with reduced rest and exercise LV ejection fraction owing in part to an increase in LV ESS.[337] Mitral valve repair does not perturb rest and exercise ejection indexes of LV function primarily as a consequence of reducing ESS and maintaining a more ellipsoidal chamber geometry. Mitral valve replacement with complete chordal transection results in no postoperative change in LV end-diastolic volume, an increase in LVESV, an increase in ESS, and a decrease in ejection fraction.[336] Patients who undergo chordal-sparing valve replacement, on the other hand, have a smaller LV end-diastolic volume and LVESV, decreased ESS, and unchanged ejection fraction. These findings suggest that reduced chamber size, reduced systolic afterload, and preservation of ventricular contractile function act in concert to maintain ejection performance after chordal-sparing mitral valve procedures. In contrast, increased LV chamber size, increased systolic afterload, and probable reduction in LV contractile function leading to reduced ejection performance occur in patients who undergo valve replacement with chordal transection.[336] Indeed, the 2006 ACC/AHA valve practice guidelines now stipulate that the subvalvular apparatus be preserved whenever possible when the mitral valve must be replaced, including chordae to both mitral leaflets.[246]

The loss of ventricular function after mitral valve replacement with chordal division may be due to heterogeneity of regional LV wall stress and not to local depression of regional contractile function.[339] After valve replacement with chordal transection in an experimental model, outward displacement of the ventricular wall and transverse shearing deformation were observed in the LV region papillary muscle insertion during isovolumic contraction.[339] Circumferential and radial strains during ejection were maintained at the basal LV site and enhanced in the apical LV site. Chordal

transection augmented regional myocardial loading at the papillary muscle insertion site; the resulting heterogeneity of regional systolic function might be the mechanism for reduced global LV function and slowed ventricular relaxation. Anterior chordal transection with mitral valve replacement caused impaired regional LV function and also impaired regional right ventricular function,[340] whereas radionuclide angiography before and after mitral valve repair showed that LV ejection fraction did not change and right ventricular ejection fraction improved. In the region of the anterolateral papillary muscle insertion, local LV contractile function deteriorated after valve replacement with chordal transection, and right ventricular apicoseptal region was similarly impaired.[340]

Summary

The functional competence of the mitral valve relies on the interaction of the mitral annulus and leaflets, chordae tendineae, papillary muscles, left atrium, and left ventricle. Dysfunction of any one or more components of this valvular-ventricular complex can lead to mitral regurgitation. Important causes of mitral regurgitation include ischemic heart disease with IMR, dilated cardiomyopathy leading to FMR, myomatous degeneration and prolapse, rheumatic valve disease, mitral annular calcification, and infective endocarditis. Four structural changes of the mitral valve apparatus may produce regurgitation: leaflet retraction from fibrosis and calcification, annular dilatation, chordal abnormalities, and LV systolic dysfunction with or without papillary muscle involvement. In IMR, changes in global and regional LV function and geometry, alterations in mitral annular geometry, abnormal leaflet (type IIIb) motion, leaflet malcoaptation, increased interpapillary distance, and papillary muscle lateral displacement and malalignment all may result in apical tenting of the leaflets and mitral incompetence.

With mitral regurgitation, the impedance to LV emptying is lower because the mitral orifice is in parallel with the LV outflow tract. Reduced LV impedance allows a greater proportion of contractile energy to be expended in myocardial fiber shortening than in tension development. After the initial compensatory phase, LV contractility becomes progressively more impaired with chronic mitral regurgitation owing to the chronic LV volume overload. Importantly, because of the low impedance during systole, clinical indexes of systolic function, such as ejection fraction, can be normal even if depressed LV contractility is already present. LVESV is less dependent on preload than is ejection fraction and is a better measure of LV contractile reserve. Preoperative LVESV is a good predictor of postoperative outcome. Surgical mitral valve repair (or, if repair is judged not to be durable, mitral valve replacement with total chordal preservation) for chronic mitral regurgitation can preserve LV contractility, particularly in patients with a normal preoperative ejection fraction who have minimal ventricular dilatation and those without major coronary artery disease. In patients with impaired LV contractility preoperatively, LV systolic function may not necessarily improve after operation and certainly will not if the chordae are divided during mitral valve replacement.

IMR is associated with a higher operative risk than is nonischemic chronic mitral regurgitation. In patients with ischemic cardiomyopathy and mild mitral regurgitation, isolated coronary artery bypass grafting may suffice if most of the ventricle is still viable. Other workers argue that coronary revascularization alone in the setting of moderate IMR leaves many patients with substantial residual mitral regurgitation, heart failure symptoms, and a grave prognosis. Because moderate IMR does not resolve reliably with coronary revascularization alone, valve repair (undersized mitral annuloplasty with or without other adjunctive techniques) should be considered because it can reduce complications and possibly may improve long-term survival. Survival after mitral valve surgery and coronary artery bypass grafting may be more determined by the extent of coronary artery disease and LV dysfunction than by the etiology of mitral regurgitation. IMR may be a manifestation rather than an important impetus for postinfarct LV remodeling. Surgical procedures that focus on LV reshaping and/or external cardiac constraint may have an impact on the degree and recurrence of mitral regurgitation.

The mitral subvalvular apparatus is a key component of LV ejection performance; an intact mitral subvalvular apparatus, including chordae to both leaflets, is necessary to maintain optimal postoperative LV geometry and optimize postoperative systolic pump function. After mitral valve replacement with chordal transection, LV systolic performance declines (depressed regional and global LV elastance, dyssynergy of contraction, and dyskinesia at the papillary muscle insertion sites). A large cascade of experimental and clinical findings suggests that reduced LV chamber size, reduced LV systolic afterload, and preservation of ventricular contractile function act in concert to maintain ejection performance if mitral valve repair or chordal-sparing valve replacement techniques are employed.

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CHAPTER 42

Mitral Valve Repair

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Sir Thomas Lauder Brunton, a Scottish physician, first introduced the concept of surgical repair of the mitral valve in 1902.[1] Twenty-one years later, Elliot Cutler, the future Moseley Professor of Surgery at the Peter Bent Brigham Hospital in Boston, performed the world's first successful mitral valve operation in 1923 by carrying out a transventricular commissurotomy with a neurosurgical tenotomy knife. A new era in surgery was introduced as well as the reality of mitral valve repair.[2] Cutler had worked assiduously on this problem in the Surgical Research Laboratories of Harvard Medical School before turning his attention to a critically ill, bedbound 12-year-old girl, performing mitral valvulotomy on May 20, 1923. With that seminal operation, the idea of surgically restoring normal anatomy to the pathologic mitral valve came to fruition. Subsequent attempts at transventricular valvulotomy with a cardiovalvutome to produce graded mitral regurgitation resulted in several deaths and Cutler eventually abandoned the procedure.[3] Of Cutler's contemporaries, Henry Souttar of England performed a single successful transatrial finger commissurotomy in 1925, but received no further referrals.[4] After Souttar there remained little activity in mitral valve repair until Dwight Harken, then the Chief of Cardiothoracic Surgery at the Peter Bent Brigham Hospital, published his groundbreaking series of valvuloplasty patients for mitral stenosis[5] along with Charles Bailey in Philadelphia.[6]

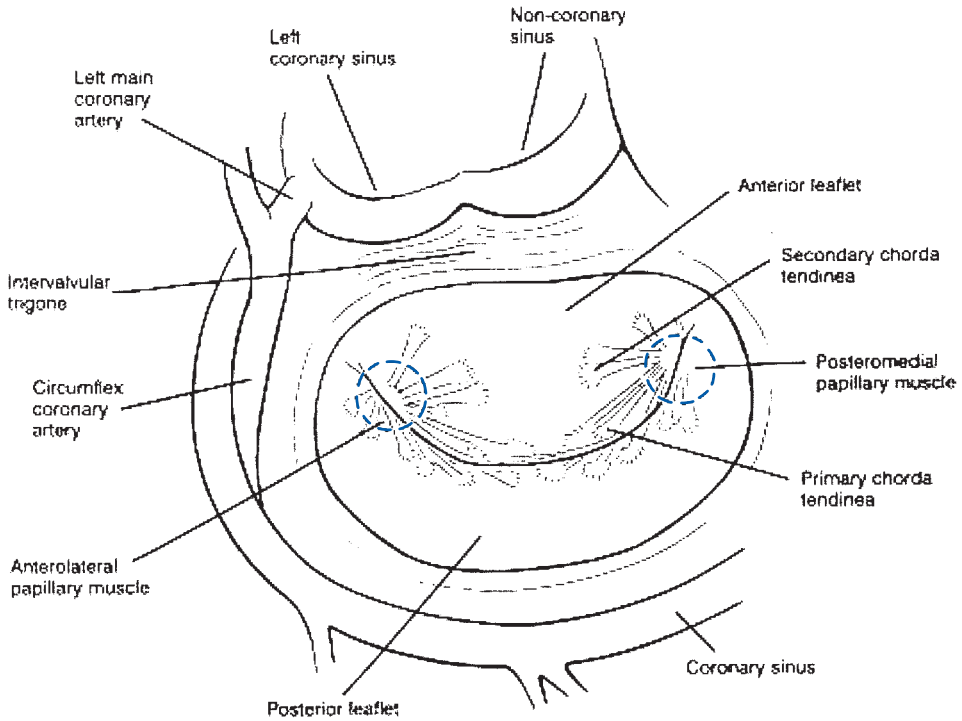
That early era focused on mitral stenosis created by rheumatic heart disease, which was extremely common at the time. Surgical treatment of mitral regurgitation for prolapse was first introduced in the 1950s[7–9] but with limited success. Later, in the '60s, '70s, and '80s, the visionary concepts and ideas first disseminated by Carpentier[10] and Duran,[11] and later promulgated by others,[12–14] stimulated the field. Initially, those ideas, like any other groundbreaking idea, were met with resistance that has gradually dissipated as long-term results by these surgeons have been validated. In particular, the idea that repair of mitral regurgitation might damage a weakened left ventricle by eliminating the left atrium as a low-resistance "pop-off" valve[15] proved a significant barrier to referral that only in the past decade has been overcome. What has now become firmly established is the significant contribution to overall left ventricular function of the papillary muscle–annular interaction.[16] As a result of these contributions, mitral valve repair, if technically possible, has now become recognized as the procedure of choice for mitral valve pathology of any etiology, even for patients with cardiomyopathy and heart failure,[17] to the extent that mitral valve repair is always considered first in virtually any clinical situation in which the mitral valve is regurgitant.

This chapter will focus on repair of the myxomatous, degenerated valve with some consideration of the repair of the rheumatic mitral valve. Repair of ischemic or infected mitral valves is presented in Chapters 30 and 44, respectively. Detailed pathophysiology of the mitral valve is presented in Chapter 41.

ANATOMY OF THE MITRAL VALVE

A surgical dictum is that form follows function and this is particularly apropos for the mitral valve. The bicuspid mitral valve is one of the most complex structures of the human heart; its complexity lies in its multifaceted anatomy. Because each part of the anatomy is intimately related to function, there are a variety of pathways whereby regurgitation may be created. If one part of the valvular apparatus fails, regurgitation results. There are five discrete components to the mitral valve complex: the annulus, the two leaflets (anterior and posterior), the chordae, the papillary muscles, and the left ventricle itself (Fig. 42-1A).

As part of the fibrous skeleton of the heart, the annulus is the circular area where the mitral valve leaflets attach to the intersection of the left atrium and ventricle. It is surrounded



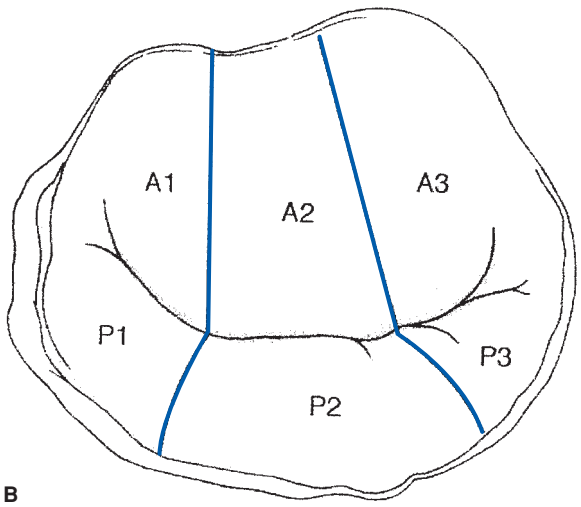


Figure 42-1. Surgical anatomy of the mitral valve. Panel A depicts critical structures that the cardiac surgeon must recognize, including the circumflex coronary artery, the coronary sinus, the atrioventricular node, and aortic root. Note that the left and right trigones are superior to the commissures. Panel B depicts the conventional terminology used to describe the pathoanatomic parts of the anterior and posterior leaflets.

by vitally important structures that the cardiac surgeon must avoid for safe surgery: the circumflex coronary artery laterally, the coronary sinus medially, the aortic root superiorly, and the atrioventricular node superior-medially. In myxomatous disease it is the posterior annulus that usually dilates.[18] Previous dictum held that the anterior annulus does not dilate, but recent data suggest that it may dilate a limited amount.[19] Of critical importance to the surgeon are the right and left fibrous trigones. These are intimately related to the anterior annulus and are contiguous with the aortic valve curtain and must be identified during surgery. The trigone points form anchoring points for ring annuloplasty.

The anterior leaflet of the mitral valve (AML) is in continuity with the left and noncoronary cusps of the aortic valve and is located directly beneath the left ventricular outflow tract (LVOT). It typically accounts for approximately 40% of the circumference of the annulus with the posterior leaflet accounting for the rest.[20] The posterior mitral valve leaflet (PML) is crescent-shaped and dilates more commonly in degenerative disease. For surgical decision making and analysis, both the anterior and posterior leaflet are divided into three parts, corresponding to the typical three scalloped areas of each leaflet (A1, A2, A3 for the anterior leaflet; P1, P2, and P3 for the posterior leaflet; 1 refers to the leftmost, or lateral scallop; 2 the middle scallop; and 3 the rightmost, or medial scallop; Fig. 42-1B).

There are two papillary muscles, the anterolateral and the posteromedial. Each muscle is attached to the leaflets by the chordae tendinae, chords of stringlike fibrous connective tissue. Primary chords are those that attach to the edge of the

leaflet. Secondary chords are those that attach to the underside of the leaflet. Tertiary chords (only the posterior leaflet has tertiary chords) are those that attach to the undersurface of the leaflet directly from the ventricular wall instead of from the papillary muscle. The papillary muscles each give off chordae to both leaflets and correspond to the anterolateral and posteromedial commissures of the mitral valve. The anterolateral papillary muscle receives blood from both the left anterior descending artery as well as the circumflex artery; the posteromedial one receives blood usually from only the posterior descending artery or a branch of the circumflex artery. Because of its single coronary blood supply, the posteromedial papillary muscle is more susceptible to infarction and rupture than the anterolateral one.

The left ventricle acts in concert with the papillary muscles via the chordae to pull in the leaflet edges during systole, thereby maintaining the line of coaptation and therefore valve competency. If the left ventricle dilates or is ischemic, the competency of the valve may be affected adversely and regurgitation created.

MYXOMATOUS MITRAL VALVE DISEASE

Etiology and Pathophysiology

The underlying etiology of myxomatous disease is a defect in the fibroelastic connective tissue of the valvular leaflets, chordae, and annulus.[21] The myxomatous defect leads to an abnormal elongation and redundancy of valve tissue and chordae. Each particular anatomic redundancy creates mitral regurgitation in its own particular manner. Annular dilatation (Fig. 42-2) obliterates the normal coaptation line between the anterior and posterior leaflet, causing regurgitation. Because of primarily posterior annular dilatation there is a separation in the middle of the valve between the two leaflets and blood leaks through during ventricular contraction. Leaflet redundancy results in a movement of the redundant leaflet into the left atrium during diastole. If severe enough, that movement leads to a compromised coaptation line and mitral regurgitation (MR) then occurs. Elongation of the chordae also causes leaflet tissue to move into the atrium during diastole, also resulting in compromised coaptation. Ruptured or flail leaflets are often the result of systolic stresses fracturing weakened chordae, causing severe regurgitation.

Mitral regurgitation represents pure volume overload for the left ventricle.[22] In myxomatous disease, MR is typically of the chronic compensated variety.[23] A vicious circle is perpetuated whereby the excess volume load over time results in ventricular failure. Ventricular failure itself implies ventricular dilatation, which results in a greater degree of MR. Thus, MR begets more MR, so a vicious downward spiral is created.[16] MR created by left ventricular failure occurs primarily by ventricular dilatation. Successful repair will result in left ventricular mass reduction.[24] By dint of the papillary muscles, ventricular dilatation "pulls" or "tethers" the leaflets open, thereby impinging on coaptation. In degenerative disease of the mitral valve, however, the left ventricle itself per se does not primarily cause MR in the early course of the disease.

Carpentier has developed a mitral valve analysis protocol and surgical philosophy for repair of all types of valves (Fig. 42-3). Myxomatous disease has become the pathology responsible for the vast majority of mitral regurgitation in the United States.[25] Currently, mitral valve prolapse, as a part of the spectrum of degenerative disease, is present in about 5% of the general population,[26] with about 10% of these patients exhibiting severe MR requiring surgery.[27] Whatever the ultimate pathologic pathway creating regurgitation, 80 to 90% of all degenerative disease should be amenable to successful repair.

Diagnostic Work-Up and Indications for Operation

Patient presentation is typically quite varied depending on the degree of MR as well as the chronicity of the disease. Patients may be floridly symptomatic or completely asymptomatic. Symptomatology is usually of two varieties. Failure symptoms are secondary to pulmonary venous hypertension as well as fluid retention. This may include shortness of breath, limited exertional capacity, fluid overload, and in the

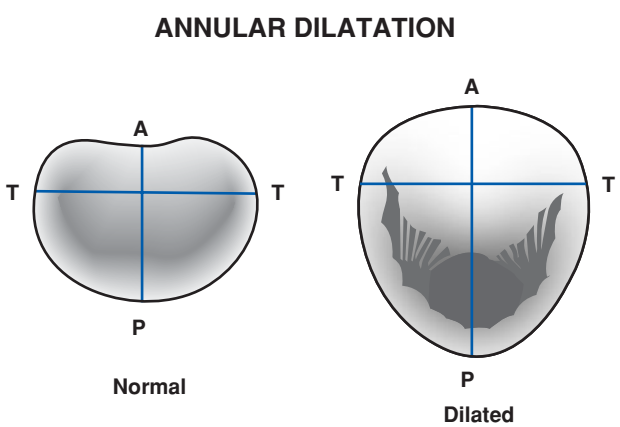


Figure 42-2. Annular dilatation. A = anterior; P = posterior; T = trigone.

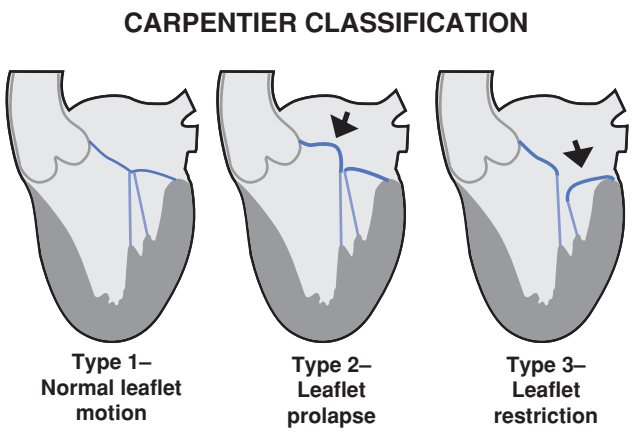


Figure 42-3. Carpentier classic mitral valve classification.

late stage of the disease, heart failure. Embolization sequelae and arrhythmias form a second set of symptoms and include atrial fibrillation and increased stroke risk;[28] regurgitation predisposes the valve to infectious endocarditis.[29] Abnormal hemodynamics create pathologic shear stresses and turbulence that generates vulnerability to infection in the valve.

The critical question for any valvular pathology is the timing of surgery. The first consideration is the MR itself. Echocardiography remains the gold standard for assessing mitral regurgitation. The key information obtained is the degree of MR, its associated pathophysiology, cardiac chamber dimensions, and left ventricular functional analysis. Transthoracic echocardiography is usually the first modality employed. However, if images from transthoracic echocardiography are of insufficient quality, then transesophageal echocardiography (TEE) is required. Mitral regurgitation is graded on a scale from mild to severe with severe typically referring to a reversal of pulmonary venous blood flow in the left atrium.[30] Methods used to determine the degree of regurgitation commonly include regurgitant volume, regurgitant fraction, and orifice area.[30] Echocardiographic analysis of the MR (e.g., flail leaflet, ruptured chordae, or anterior or posterior prolapse) is extremely helpful in planning the operative intervention. Other crucial information obtained by the preoperative echo includes left atrial size, ventricular function, ventricular dilatation, aortic valve function, and tricuspid valve function. Ventricular function is a key component in assessing operative candidacy; a left ventricular ejection fraction below the norm of 60% indicates some degree of myocardial decompensation secondary to volume overload.

What, precisely, are the indications for operation? The past decade has seen a tremendous improvement in the practice and science of cardiac surgery, such that patients who would never have been considered for surgery a decade ago are now routinely being offered repair surgery at much earlier stages of their disease. The indications for mitral valve repair have broadened as the success of repair has so dramatically improved over the last several years. Better myocardial protection and cardiopulmonary bypass technology, minimally invasive incisions, increased incidence of repair, and better intensive care unit care have all contributed to the phenomenon.[31] The biggest change has been an overall broadening of the indications for mitral valve repair and lowering of the threshold for operation because of these factors.[32]

Repair itself, as opposed to replacement, is now accepted as the superior treatment for mitral regurgitation. Out of a long laboratory and clinical experience has come the conclusions that repair is associated with better survival, enhanced preservation of ventricular function (by preserving the chordae and papillary muscles), durability of repair, and decreased late thromboembolic complications.[33–36]

Whether or not a patient is offered valve repair depends on the degree of regurgitation, the pathophysiology of the regurgitation, ventricular function, and surgeons' consistent ability to perform mitral valve repair. At Brigham and Women's Hospital, virtually any patient with severe MR is offered mitral valve repair, regardless of symptoms and ventricular function, unless other comorbidities make repair problematic. Asymptomatic patients are offered valve repair if evidence exists of myocardial decompensation by echocardiography, such as cardiac chamber enlargement or pulmonary hypertension. Such patients will usually demonstrate left ventricular or left atrial dilatation or both. For all patients with moderate to severe MR and decreased ventricular function (left ventricular ejection fraction $<60\%$) valve repair is offered, as the ventricle has exhibited signs of decompensation even with a lesser degree of MR; repair in this setting is much more urgent, as severe decompensation can occur in a matter of months as left ventricular function begins to deteriorate.

The intermediate situation of moderate mitral regurgitation and preserved ventricular function is the one in which the most judgment must be exercised. Consider the situation of a structurally normal mitral valve with moderate MR, but with concomitant critical aortic stenosis. The patient is to undergo and aortic valve replacement. Should the mitral valve be repaired? Perhaps not, as the moderate MR here is likely secondary to that patient's aortic stenosis, and correcting the aortic stenosis would likely eliminate the MR in this structurally normal valve. However, only a ring annuloplasty would be needed to correct the posterior annular dilatation. If the same situation exists, however, with a structurally abnormal valve, such as a prolapsed P2 or markedly dilated mitral annulus, then mitral repair should be undertaken, because there is a structural abnormality that aortic valve replacement will not correct. What of moderate MR secondary to myxomatous disease (and not ischemia) in a patient who is to undergo coronary bypass grafting? That patient would likely be offered concomitant valve repair, as bypass grafting would not impact on the pathophysiology of the MR in this case. What of the situation of moderate to severe, isolated MR secondary to myxomatous disease and borderline normal ventricular function? Even without symptoms of heart failure, this patient should have repair performed on an elective basis. Once left ventricular function begins to deteriorate from the normal 60 to 70% left ventricular ejection fraction, decline may be unpredictably rapid and hence intervention warranted. Increasingly, moderate ischemic, as well as degenerative, MR is thought to be detrimental for long-term survival.[37,38]

In general, no matter what the chronological age, adequate functional status before valve repair is preferred. If symptoms of heart failure exist before surgery, optimal diuresis should be undertaken before operation. If the procedure involves coronary artery bypass grafting, the conduit status should be determined. Dental clearance on all patients should be obtained before any valvular procedure. If neurologic symptoms exist or if the patient has a history of a previous cerebrovascular disease, then preoperative carotid noninvasive studies are warranted to assess carotid arterial stenosis. All patients over 40 should undergo coronary angiography. Since the late 1990s patients with MR without coronary artery disease are offered minimally invasive valve repair as the standard procedure at Brigham and Women's Hospital.[39,40]

Whatever the scenario, the decision to operate and repair the valve is a decision made preoperatively as opposed to intraoperatively. Once the patient is under anesthesia, loading conditions are not physiologic and the mitral regurgitation assessed then is inevitably underestimated. Maneuvers used to "bring out the MR," such as increasing afterload with vasoactive drugs, do not reflect true physiology, but should be used in surgical decision making and may be helpful in some situations. Recent discussions of earlier referral for the treatment of MR clearly depend on a high rate of valve repair in any center.[41,42]

Operative Philosophy

Despite the success of mitral valve repair in specialized centers, there still persists a general reluctance to perform repair, particularly in the severe Barlow variety of degenerative disease. In 2003, for example, the Society of Thoracic Surgeons database indicated that only 36% of valves that could be repaired actually were repaired,[43] although this percentage has recently improved.

Beginning in the 1990s, we have developed what we think is a simple, reproducible algorithm that can be used to repair the degenerative mitral valve in most patients. Overriding this philosophy is the belief that mitral valve repair is not an esoteric "art form" that is difficult to explain, perform, or learn. Rather, we think it is a procedure like any other that should and can be simplified, disseminated, and reproduced with success. In keeping with this philosophy, we have reduced complicated bileaflet prolapse to a competent valve with simplified and straightforward maneuvers that we have found effective with good long-term results. Our overall philosophy and technique is as follows:

1. Expose the valve well through the complete development of the Sondergaard groove, division of pericardial attachments of the superior and inferior venae cavae.
2. Assess the valve through saline injection and corroborate the intraoperative findings with transesophageal echocardiography.
3. Perform basic, obvious leaflet repair procedures first (e.g., quadrangular resections to the posterior leaflet).
4. Implant the annuloplasty ring sized by the height of the anterior leaflet (not the trigones or commissures).
5. Test the repair.
6. Perform additional reparative procedures as needed.

With the above maneuvers, we estimate that approximately 90% of all degenerative valves can be repaired. If after placing the ring some residual leak remains on passive testing, further techniques may be used.

Collaborative involvement with cardiac anesthesia colleagues is essential in utilizing the invaluable tool of transesophageal echocardiogram monitoring for pre and postrepair assessment. In our clinic, standard TEE monitoring (either two-dimensional or three-dimensional) is now utilized for every patient undergoing mitral valve repair. In addition to documenting the efficacy of repair, TEE is essential in preventing and assessing the potential or persistence of systolic anterior motion of the anterior valve.

Operative Exposure

Because the mitral valve is such a complex anatomic structure and the maneuvers involved in correcting a regurgitant valve may vary from the simple to the very complex, adequate exposure is an absolute requirement in every operative plan. This becomes more important if minimally invasive techniques are employed. The first critical aspect to the standard valve repair is the complete and thorough development of the Sondergaard plane reflecting the right atrium off the left atrium to the atrial septum, as depicted in Fig. 42-4. This was first described in the 1950s by the Danish surgeon Sondergaard[44] to expose the atrial septum for noncardiopulmonary bypass treatment of atrial septal defects. In 1990 we stressed the importance of this particular technique for exposure in mitral valve surgery.[45] Regardless of even previous procedures, it should always be possible to dissect out the groove without significant difficulty. The complete and full development of the groove is a most important aspect to obtain adequate exposure of the mitral valve. With this technique, via blunt and sharp dissection we have not needed any other incision for mitral valve repair or replacement, whether for primary surgery or reoperation. This incision brings the surgeon very close to the mitral valve even in the most difficult anatomic situations. Once the right atrium is dissected off the left atrium, a generous incision in the left atrium is made, avoiding the atrial septum.

Minimally Invasive Technique

With the development of minimally invasive incisions for adult cardiac surgery this past decade, mitral valve surgery has undergone an evolution. The standard isolated mitral valve repair incision offered at Brigham and Women's Hospital since 1996 is a minimally invasive, lower hemisternotomy

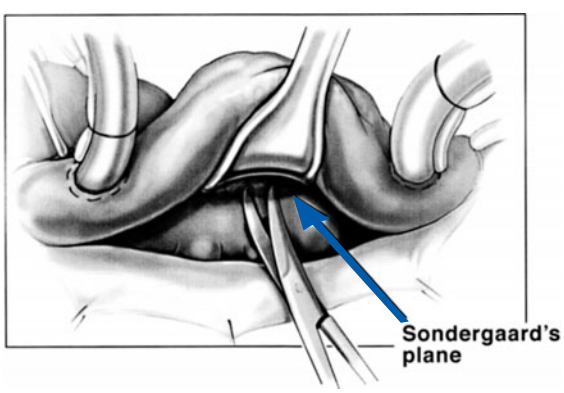


Figure 42-4. Dissection of Sondergaard's plane. Sondergaard's plane should be dissected at least 2 to 4 cm from the right superior pulmonary vein for adequate exposure of the mitral valve.

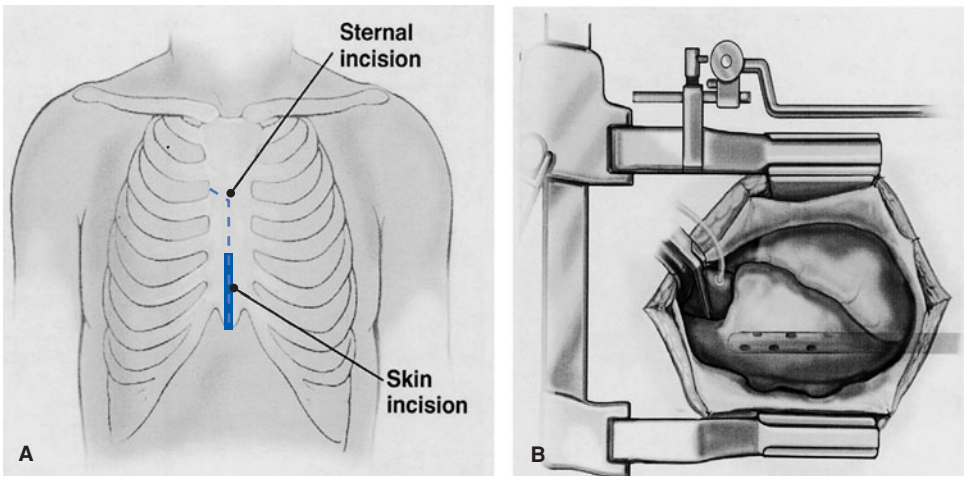


Figure 42-5. Minimally invasive mitral valve repair. (A) Via a 6- to 8-cm skin incision, a lower hemisternotomy through the right second interspace is performed. (B) Venous cannulation is percutaneous with vacuum assist. Aortic cannulation, cross-clamping, and cardioplegia administration are performed in the standard manner.

via a 6- to 8-cm skin incision[39] (Fig. 42-5A). Cannulation is typically performed with a percutaneous venous cannula via the femoral vein and vacuum-assisted drainage is employed (Fig. 42-5B). The vacuum applied never exceeds 80 mm Hg of suction. TEE guidance is used to place the venous cannula into the superior vena cava through the right atrium. The aorta is cannulated directly with a flexible 20F aortic perfusor. If venous drainage is inadequate even with vacuum assist, we cannulate the superior vena cava with an additional cannula. Details of other minimally invasive techniques are detailed in Chapter 45.

Cardiopulmonary Bypass

For cardiopulmonary bypass, we use a 22F percutaneous femoral vein venous catheter placed into the right atrium via the right femoral vein with TEE control. The cannula can even be advanced into the superior vena cava if desired. Because the cannula has multiple holes, is flexible and thus can still drain the inferior vena cava, this one cannula is sometimes all that is needed for drainage of both the superior and inferior vena cava. If performing a concomitant bypass procedure requiring a full sternotomy, then venous cannulation should be bicaval via the atria. One venous cannula should be placed in the superior vena cava above the right atrial/superior vena caval junction and the other through the lowest part of the right atrium into the mouth of the inferior vena cava. The arterial cannula should be placed directly into the distal ascending aorta.

Once on cardiopulmonary bypass, systemic temperature is allowed to drift to 34°, the ascending aorta is cross-clamped, and the heart arrested by cold blood cardioplegia. For isolated valve repair, some debate still exists regarding the use of retrograde or antegrade blood cardioplegia after cross-clamping. If there is concomitant coronary artery disease, myocardial protection in this circumstance should be antegrade and retrograde, as the coronary artery bypass graft/mitral operation presents one of the highest-risk operative settings in cardiac surgery.[34]

After the heart is arrested, the left atrium is opened well above the right superior pulmonary vein near the septum inferiorly. Retractors are placed (Fig. 42-6). The patient's bed is placed head up with a tilt to the left. A wire-reinforced suction catheter is placed in the left inferior pulmonary vein (the most dependent portion of the left atrium in this position) for drainage of collateral blood flow. Carbon dioxide is infused to minimize intracardiac air.

Alternate exposures can be obtained by the transseptal approach through the right atrium[46] or the superior septal approach.[47] The transseptal approach is a perfectly

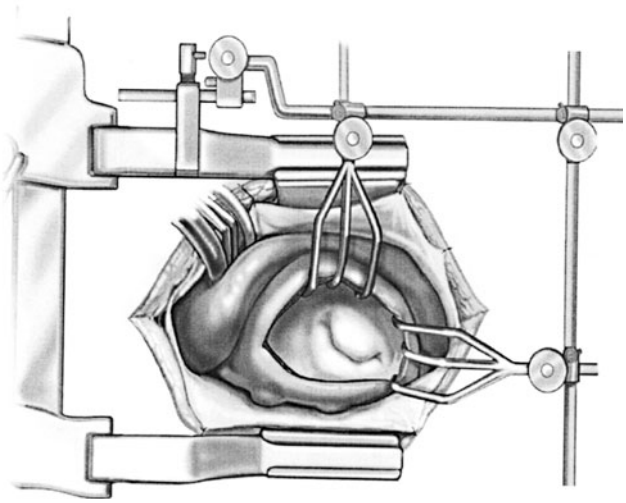


Figure 42-6. Minimally invasive operative exposure. After the retractors are placed, the patient is positioned with head up and the operative bed tilted to the left. Exposure is excellent.

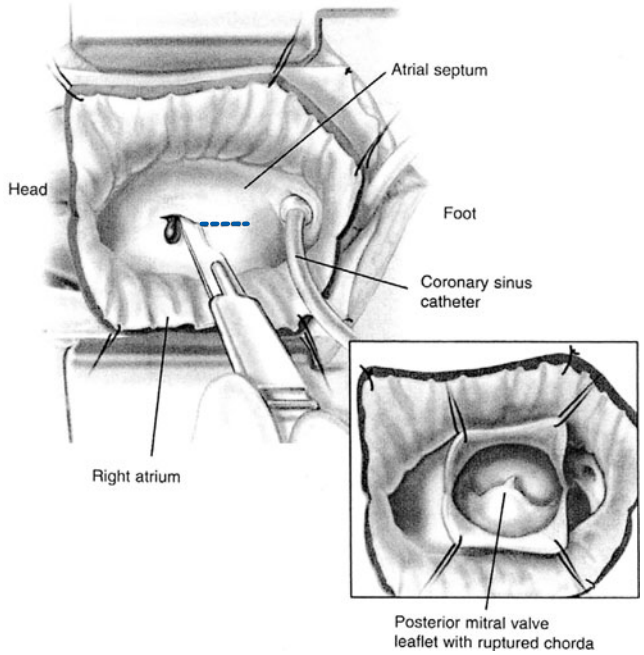


Figure 42-7. Transseptal exposure of the mitral valve. After the right atrium is incised, the septum is divided across the fossa ovalis, and stay sutures are placed. This incision allows very good access to the mitral valve and is an alternative to the Sondergaard plane.

acceptable incision that allows the cardiac surgeon to be close to the mitral valve by carrying the incision through the fossa ovalis (Fig. 42-7) and up into the superior vena cava. Retraction sutures and other types of retraction devices can be utilized to expose the mitral valve exceedingly well, particularly in these minimally invasive cases. This approach may also be helpful in patients who have had previous operations on the mitral valve or when concomitant procedures on the tricuspid valve are required.

Examination of Valve and Valve Analysis

Once exposure is obtained and a self-retaining retractor is in place, inspection of the valve is carried out. Valve analysis takes a few minutes utilizing nerve hooks, forceps, and insufflation of the ventricle with saline to determine and corroborate the pathology already diagnosed by intraoperative TEE. Valve analysis may reveal ruptured chordae or simply a prolapse of the valve with elongated chords and one or more prolapsed sections of the valve. The anterior leaflet, though frequently advertised as part of "bileaflet prolapse," often has normal-length chordae and may be without specific leaflet or subvalvular pathology. Prolapse of the commissures may be found, and calcified nodules may exist that may present difficulty in mitral valve repair and may need excision. There may be healed endocarditic vegetations on one or more parts of the valve. The annulus will almost always appear to be distorted, dilated, or deformed in long-standing cases, particularly in Barlow syndrome.

Repair Strategy

After the analysis of the valve is carried out, a detailed reparative strategy can be deduced from the pathologic analysis. In a broad generalization, degenerative disease of the mitral valve creates what amounts to a posterior mitral valve leaflet that is too large, with or without flail segments, in an annulus that is functionally too small for the anterior leaflet. In degenerative disease, most commonly the posterior leaflet is usually pathologic while the anterior leaflet usually is not. The first principle of the repair is to reduce or obliterate the enlarged posterior segments and to reduce the overall height of the posterior leaflet to prevent systolic anterior motion (SAM) of the anterior leaflet. If the height of the posterior leaflet is too high, it will push the anterior leaflet into the LVOT and create SAM. In general, the height of the posterior leaflet should be no more than 1 to 1.5 cm in average-sized patients once the repair is complete. Once the posterior leaflet reduction is performed, one must ensure that the anterior leaflet coapts with the subsequently reduced posterior leaflet within the correct plane. The resulting repair should result in a coaptation line at the level of the annulus during systole. Specific methods to lower the height of the posterior leaflet and anterior leaflet will be addressed below.

The second principle is that a remodeling annuloplasty ring is essential for all repairs. This is a fundamental concept of Carpentier[18] and Duran,[48] both of whom developed mitral valve annuloplasty rings early in the history of mitral valve regurgitation surgery and advocated remodeling of the distorted annulus as a key principle of mitral valve repair. The annulus, after many years of regurgitation, is often deformed and in myxomatous disease, it is floppy and dilated. The best approach to conceptualize the floppy and dilated annulus in myxomatous disease is to consider it functionally too small for the anterior leaflet. Why too small if it is floppy and dilated? If floppy with redundant tissue, the annulus will not provide the relatively stable skeleton necessary for the anterior leaflet to spread out completely and thus coapt at the correct line and in the correct plane with the posterior leaflet. Rather, the floppy annulus will buckle and have an effectively smaller radius, and cause the anterior leaflet to appear as though it is "prolapsing" because the leaflet cannot spread out correctly. In reality the pathology is within the annulus. That is why we believe that oversizing the ring in degenerative disease is important. The ring then re-creates the relatively rigid, broad annulus that allows the anterior leaflet to spread out and coapt in the correct plane, at the correct coaptation line, without "prolapsing." A structurally sound annulus is necessary for the correct physiologic function of the anterior leaflet. Hence, our protocol is to place the annuloplasty ring after posterior leaflet repair and then reassess for any anterior or complex leaflet pathology afterward. Our belief is that annular pathology often falsely gives the appearance of leaflet pathology, and by following the steps outlined above, many unnecessary procedures are prevented.

By utilizing the two principles outlined above, we believe that the proper and necessary attention is given to the

correct physiologic functioning of the valve in a manner that is surgically relevant. The height of the posterior leaflet is reduced to prevent SAM as well as to allow the correct coaptation plane. The two leaflets are made to coapt at the correct line by reinforcing the annulus with a remodeling ring. As outlined above, in our experience at the Brigham and that of others,[49] many times the so-called bileaflet prolapse is completely eliminated by adequate posterior leaflet resection and a large remodeling annuloplasty ring without any further anterior leaflet intervention.

There is clear evidence supporting the integral and essential necessity of the ring for a lasting repair. In an early paper on mitral valve repair, we compared a repair group that had no annuloplasty ring to another group in whom a ring was implanted at the time of valve repair.[50] All valves were competent at the time of surgery, but after several years of follow-up, the rate of mitral regurgitation in the no-ring group was five times that of the ring group. Thus, a remodeling ring is critical to a long-lasting physiologic mitral valve repair.

SPECIFIC SURGICAL TECHNIQUES

Posterior Leaflet Quadrangular Resection

The most common mitral valve pathologies (approximately 80%) encountered in the myxomatous, degenerated valve are ruptured and elongated chords from the middle section of the posterior leaflet (Fig. 42-8A). In one approach limited resection of this diseased section of leaflet is shown in Fig. 42-8B. To fill the gap produced by removing the pathologic section, leaflet advancement of the remaining leaflet sections is carried out (Fig. 42-8C and D) and the cut edges of the valve are reapproximated with running monofilament suture (Fig. 42-8E, F, and G). An annuloplasty ring is then implanted (Fig. 42-8H, I, and J). This scenario is the most common pathophysiology encountered and operative strategy employed. Interestingly, recent results by Perier[51] and Lawrie[52] have reported successful results with use of only artificial polytetrafluoroethylene (PTFE) chords to preserve the posterior leaflet instead of resecting it, a technique that has traditionally been applied only to the anterior leaflet.

For cardiac surgeons who perform a modest number of valve repairs, incising the posterior leaflet off the annulus may be somewhat daunting. In our own experience, a prolapsed leaflet without ruptured chordae at P2 may simply be obliterated by a few sutures to bring the leading edge of the prolapsed leaflet to the underside of the annular connection, thus reducing the height, preserving all the chords, and accomplishing what might be done with a resection.

If the repair includes a resection of a flail segment, then some form of the leaflet advancement technique popularized by Carpentier should be employed.[53] In this technique the two remaining sections are advanced upon each other to close the gap produced by the resected area. This includes separating each remaining segment off the annulus for a short segment. Of all the traditional techniques, this is the one that has produced some concern for surgeons who perform only moderate numbers of valve repairs because of the necessity of incising the posterior leaflet off the annulus and then reanastomosing the leaflet to the annulus.

We have evolved a simplified technique for limited PML resections in which leaflet advancement may be more easily performed, and yet still accomplish the exact same result in much less time. We have named this the "fold-over leaflet advancement." In this technique the remaining enlarged segments of P2, on either side of the elongated resected leaflet with supporting chordae, are simply folded over by a continuous polypropylene suture to the annular gap produced by the limited posterior leaflet resection, without any further incision (Fig. 42-9). The fold-over advancement accomplishes the same goals as the traditional leaflet advancement. The small gap distance, created by the small area of resected flail segment, is eliminated and the height of the posterior leaflet is reduced. We have found the fold-over advancement to be extremely effective for small resections of the posterior leaflet in any position without the necessity of incising the leaflet off the annulus.

That being stated, many situations exist with true Barlow syndrome with elongation and elevation of almost the entire posterior leaflet. In essence, the whole posterior leaflet is elongated. In these particular pathologic situations, the classic techniques are mandatory. The entire posterior leaflet on both sides of the resected area, including P1 and P3, must be incised off the annulus and a careful and detailed valve advancement carried out, beginning at each commissure, with running 4-0 polypropylene (see Fig. 42-8C and D). The height of the leaflet is lowered to avoid creation of SAM and provide a good coaptation point for the anterior leaflet. Because some of these leaflets may be as high as 3 to 4 cm, if the height of the leaflet is not shortened significantly, SAM is highly likely. While performing the leaflet advancement, imbrication of PML segment areas may also be effective if there is focal enlargement at a particular area of the leaflet. This simplifies the surgical technique, reduces operative time, and achieves the same result. Multiple interrupted mattress sutures may be used.

Commissural Prolapse

As the most straightforward example of pathologic valve prolapse, chordal rupture or elongation at the anterior-lateral or posterior-medial commissure provides the surgeon with the most obvious strategy of repair. Many surgeons still recommend resection of this area, but commissuroplasty is by far the most simple, direct, and efficient way to handle this particular problem. The prolapsed area is obliterated by one to three polypropylene mattress stitches (Fig. 42-10), eliminating the regurgitation at that point. A small obliteration of this area at A1 and P1 or A3 and P3 will not make any significant difference in the overall cross-sectional area of the mitral valve, so mitral stenosis is of no concern with this technique. Several other surgical groups[54,55] have also used this technique as an effective and long-lasting method to treat commissural prolapse.

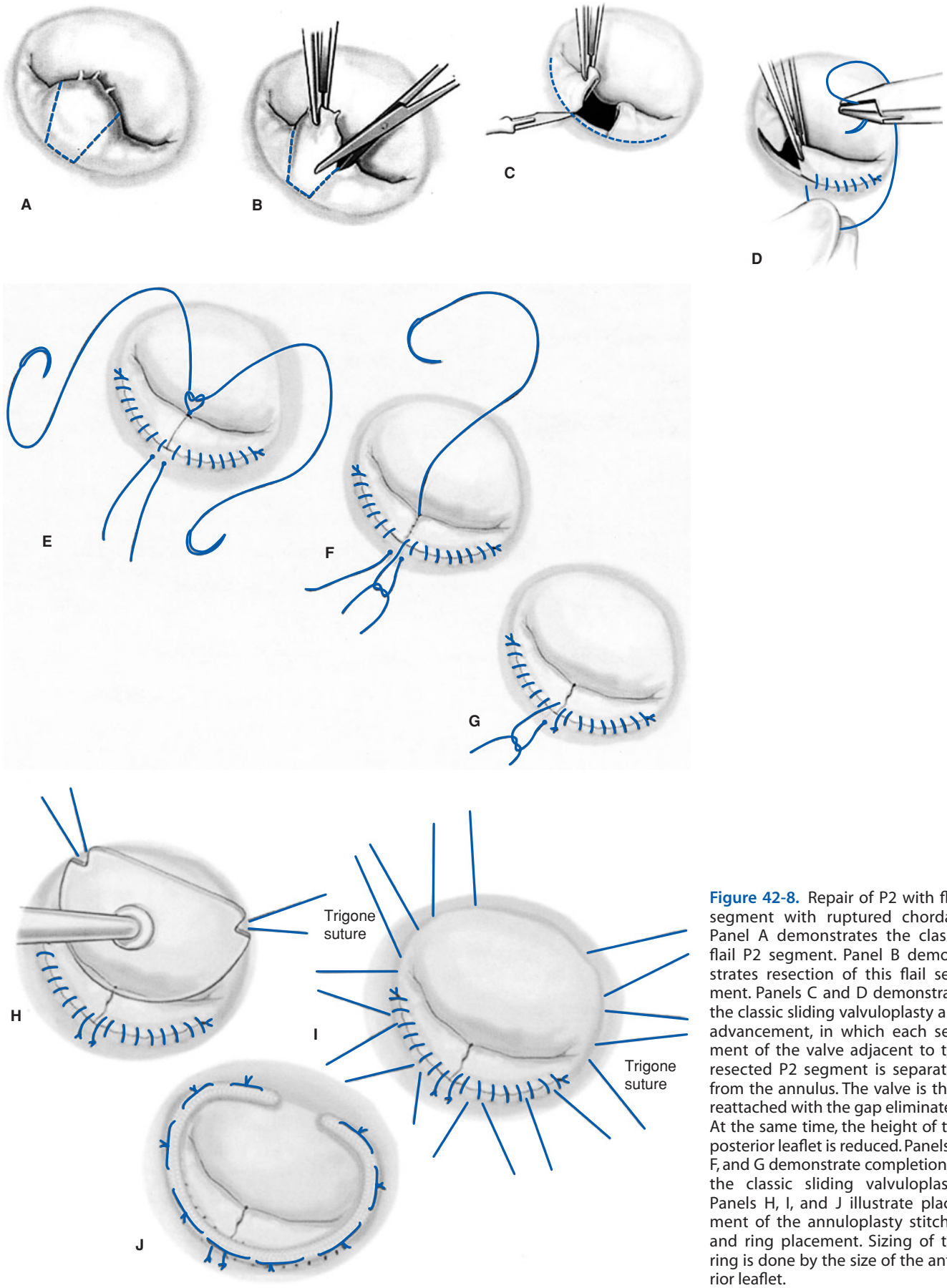


Figure 42-8. Repair of P2 with flail segment with ruptured chordae. Panel A demonstrates the classic flail P2 segment. Panel B demonstrates resection of this flail segment. Panels C and D demonstrate the classic sliding valvuloplasty and advancement, in which each segment of the valve adjacent to the resected P2 segment is separated from the annulus. The valve is then reattached with the gap eliminated. At the same time, the height of the posterior leaflet is reduced. Panels E, F, and G demonstrate completion of the classic sliding valvuloplasty. Panels H, I, and J illustrate placement of the annuloplasty stitches and ring placement. Sizing of the ring is done by the size of the anterior leaflet.

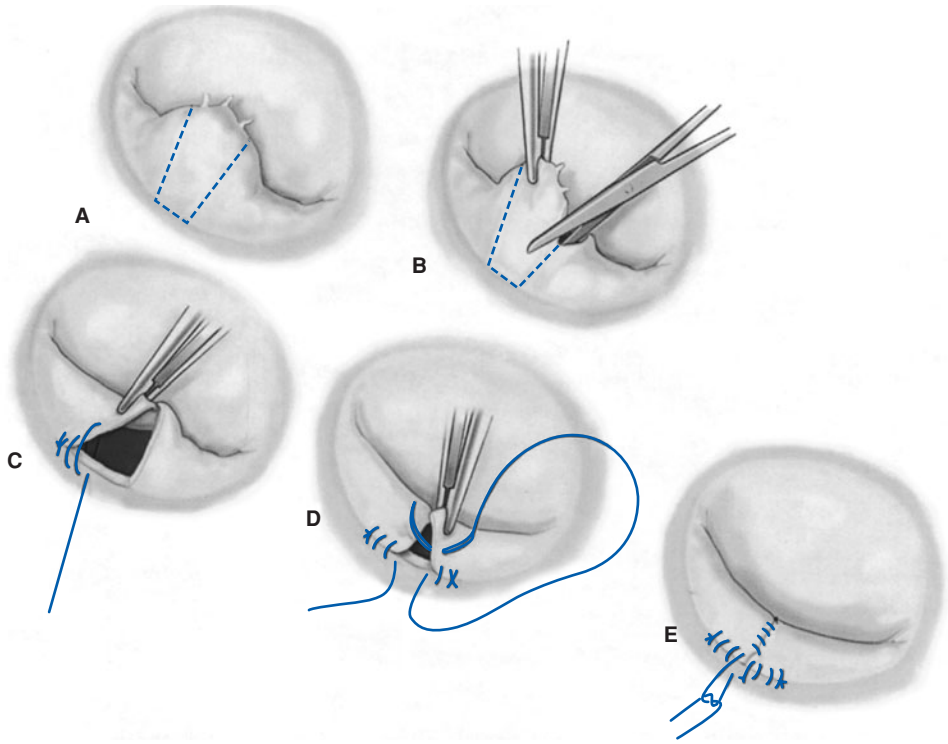


Figure 42-9. The fold-over leaflet advancement. Performed for a prolapsed and flail P2 segment here, the fold-over advancement accomplished the same goals as the classic sliding valvuloplasty, but with simpler surgical techniques. After resection of the flail P2 segment (panel B), the cut edges of each side of the resulting gap are sewn to the annulus as they are "folded down." This is done for each side of the gap for half of the original height of each side. The top halves are then sewn together (panel E). The result is that the leaflet gap is eliminated and the height of the leaflet reduced.

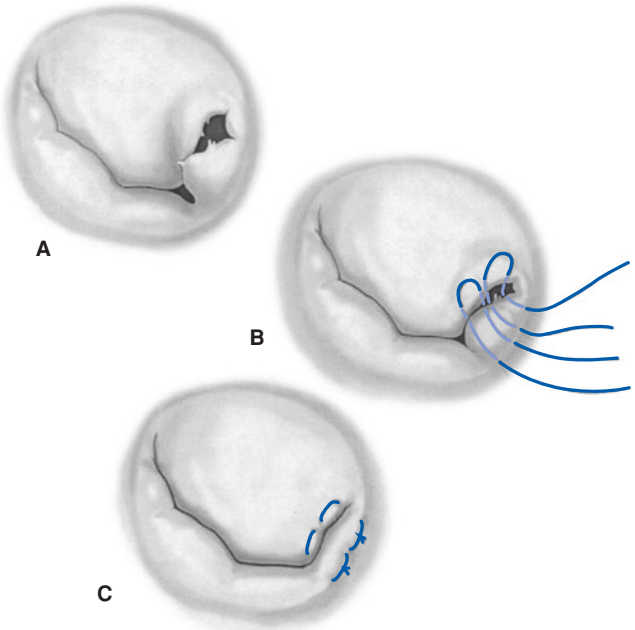


Figure 42-10. Commissuroplasty. Simple horizontal mattress stitches placed in the ruptured commissure eliminate regurgitation without need for further leaflet resection, even with ruptured chordae.

Anterior Leaflet Prolapse

Though uncommon, true prolapse of the anterior leaflet engenders significant concern to surgeons because such pathology is associated with less successful long-term repair results than posterior leaflet pathology. A recent report by David[56] substantiates this finding again. The height of the chordae underlying the anterior leaflet must be assessed and chords may be grossly elongated or ruptured and make the AML flail. This problem may be addressed by a variety of techniques and the long-term follow-up on many of these techniques has been quite promising. There are four basic techniques to repair true prolapse of the anterior leaflet. They are: (1) reduction of the chordal height by implantation techniques; (2) artificial PTFE chordae; (3) chordal transfer from the posterior to anterior leaflet; and (4) the edge-to-edge technique.

Chordal shortening by implantation into papillary muscles

One of the first techniques developed by Carpentier[10] of chordal shortening involves incising the papillary muscle, placing the redundant anterior leaflet chords within the muscle, and then sewing the papillary muscle over the chord, thus entrapping the chordae and shortening it (Fig. 42-11). This is

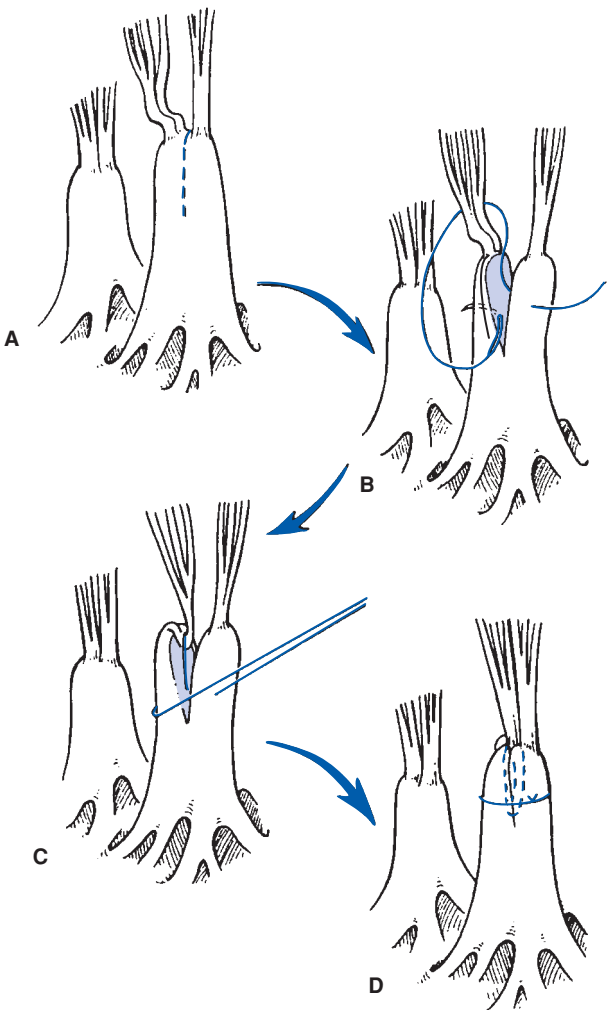


Figure 42-11. Anterior leaflet chordal shortening. The papillary muscle is incised and the redundant chord folded into it. The excess chord is held in place with pledgeted sutures.

a simple technique, but it has gone out of favor, as reports by Cosgrove and coworkers[57] have demonstrated that additional chordal ruptures may occur after use of this technique. They postulate that the potential sawing action of the papillary muscle on the buried chord is the cause. Other techniques of this type include papillary muscle repositioning[58] and chordal plication and free edge (AML) remodeling.[59]

Artificial chordae

Artificial chordae with PTFE is the technique that is perhaps the most popular current technique for AML pathology. Originally described by Frater and Zussa,[60,61] this technique has grown in popularity over the past several years.[56,62] Lawrie[52] has also recently reported excellent results in applying PTFE neochords for the anterior and posterior leaflet repair. Furthermore, Duran has devised a method for more precise measurement of the correct height for these new chordal structures.[62] This technique (Fig. 42-12) involves placing a mattress suture with a pledget on the papillary muscle to which the redundant or ruptured chord has been attached. The two ends of the double-armed PTFE are then brought up through the edge of the leaflet that needs to be lowered. The critical part of this technique is determining the degree to which the leaflet is lowered and hence how tightly the stitch is tied down. This is determined by ascertaining the optimal position of the two leaflets in systole. Both the anterior and posterior leaflets should be in apposition at this point, and thus the leaflet's height in systole should be the level to which the chords are adjusted. We have used tenting of the posterior leaflet as our guide while carefully tying down the chord (Fig. 42-12B). Whatever the technique employed, the end result should be that the anterior leaflet now coapts at the same level as the posterior leaflet with left ventricular contraction.

Chordal transfer

The third technique for true anterior prolapse is chordal transfer from the posterior leaflet to the anterior leaflet. This was originally described by Carpentier[10] and has been popularized by the Cleveland Clinic[57] and Duran and coworkers.[63] Figure 42-13 illustrates the operative steps. A resection of the flail chordae of the anterior leaflet is carried out, and an adjacent segment of the posterior leaflet is then resected from the posterior leaflet and then transferred to the gap produced by the anterior leaflet resection. This technique has had good long-term results, but may involve both leaflets when only single-leaflet pathology exists.[64]

Edge-to-edge technique

The edge-to-edge repair is a technique in which the anterior leaflet and posterior leaflet are sewn together at the coaptation line, producing a double-orifice mitral valve.[65] This has gained considerable popularity and even percutaneous interventional attempts to emulate this surgical maneuver are being pursued.[66] Developed by Alfieri and coworkers,[67] their theory is that with Barlow syndrome or truly redundant anterior leaflets, apposition of the mid-portion of the anterior leaflet to the mid-portion of the posterior leaflet will prevent the elevation of the anterior leaflet above the level of the posterior leaflet, thus eliminating mitral regurgitation. This technique greatly simplifies the repair of the true bileaflet prolapse and has been adopted as standard therapy for AML pathology by several groups. In particular, with anterior leaflet chordal rupture or marked elongation of the chordae to the anterior leaflet, repair consists of a single stitch carefully placed.

Figure 42-14 illustrates our technique. A figure-of-eight braided polyester suture is placed at the apposition points of the anterior and the posterior leaflet. We use this stronger suture, as there have been reports of the more commonly used polypropylene sutures rupturing. An important point of the surgical technique is our strong belief that the stitch should be placed only with myxomatous valves, so as to avoid producing mitral stenosis as has been the case with ischemic MR.[68] To ensure the adequacy of each orifice created by the edge-to-edge technique, we also measure the diameter of each orifice and confirm that it is at least 2 cm

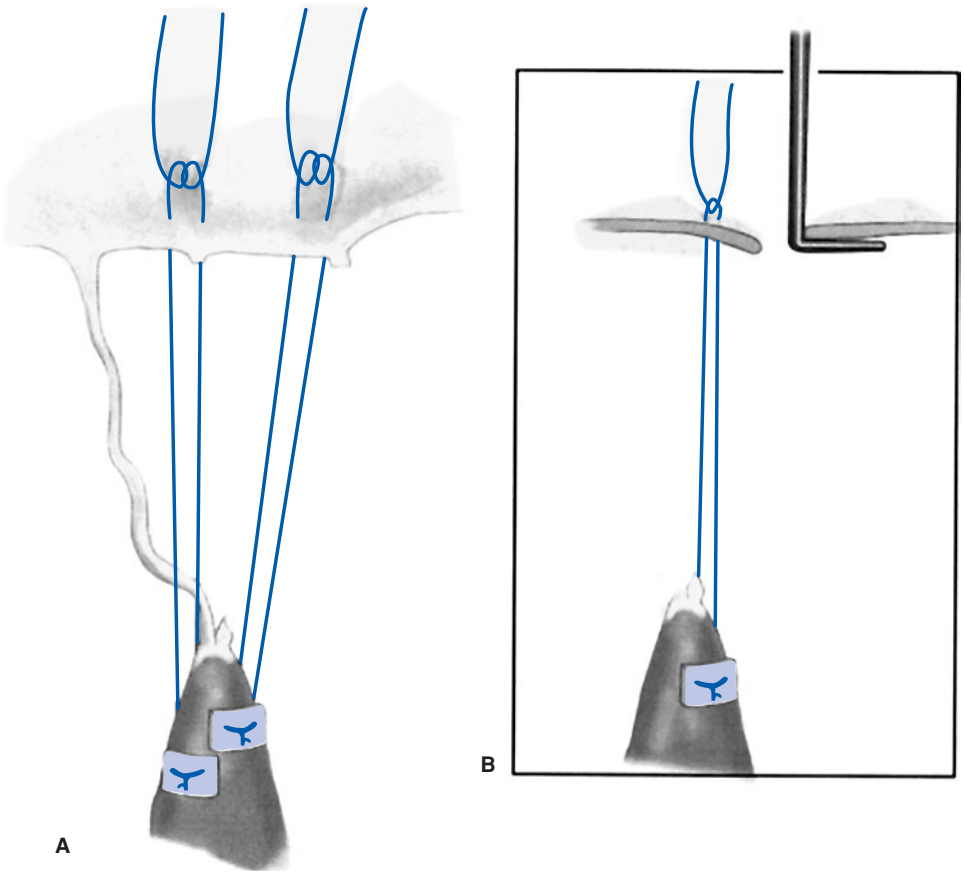


Figure 42-12. Artificial PTFE chords for the anterior leaflet. (A) Pledgeted PTFE stitches are placed through a papillary muscle and brought through the leading edge of the anterior leaflet. Using the tented-up posterior leaflet (B), the correct length of artificial chord is created.

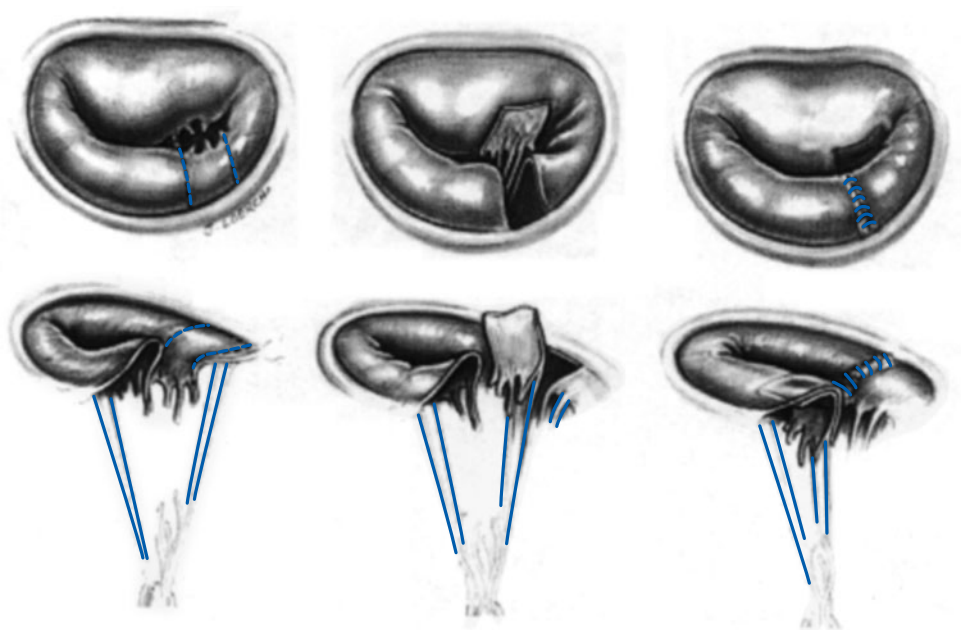


FIGURE 42-13. Chordal transfer. For an isolated flail anterior leaflet segment, first the prolapsed section of anterior leaflet is resected. An adjoining section of posterior leaflet is then resected and transposed over to the gap created by the anterior resection.

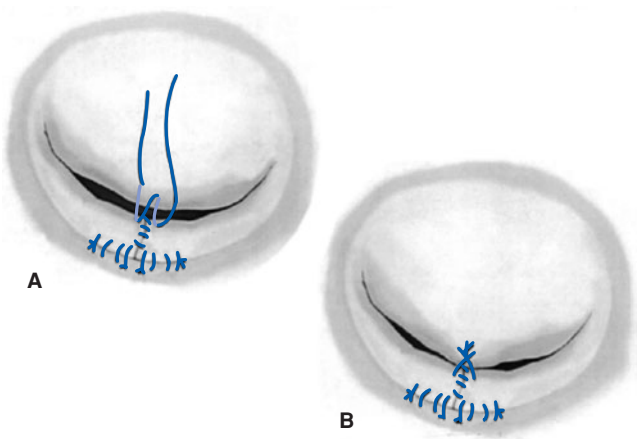


Figure 42-14. Edge-to-edge technique. The technique involves a braided polyester figure-of-eight stitch at apposition of A2 and P2.

in diameter. If the orifices are less than 2 cm in diameter, the technique is abandoned. This technique is a very valuable adjunct in patients who have the potential for systolic anterior motion of the mitral valve.[69,70] In fact, prevention of SAM may be the best utilization of this technique at present. In our small series of 20 patients with SAM potential, all were treated and SAM was prevented in all patients. A competent mitral valve was maintained in all at 8 years at postoperative follow-up.[69]

Medium-term results of this surgical maneuver are satisfactory and compatible with all other commonly used repair techniques, according to studies by Alfieri and coworkers,[67,71] but there have been no comparative, prospective, randomized studies comparing the classic repair techniques to this approach in the long term.

Resection of the anterior leaflet

It has been well established that the body of the anterior leaflet should be treated with great respect, and preservation of AML tissue is important. Resections can be carried out, but only as a small triangular resection for ruptured chords to reduce the bulk of a large anterior leaflet.[72] For anterior mitral valve prolapse associated with idiopathic hypertrophic subaortic stenosis, or as an alternative technique for reduction of the AML height, creation of a longitudinal perianular anterior leaflet resection with reconstruction of the leaflet has also been advocated to reduce the height of the anterior leaflet with some success.[73,74]

SPECIAL PROBLEMS AND CONSIDERATIONS

The Calcified Annulus

Calcification, particularly of the posterior annulus, is a complicating aspect of mitral valve repair. Calcification makes repair more difficult, as stitches are more difficult to place and the risk of paravalvular leak is increased. Severe calcification, however, does not necessarily rule out an effective mitral valve repair. Partial or total removal of the calcified bar may be done safely. Carpentier has promulgated removal of the entire calcified bar in radical fashion, which in essence partially detaches the left ventricle from the left atrium.[75] Partial and selective calcification removal may also be quite effective and potentially safer.[76] Partial removal of calcium with leaflet advancement can be performed without the need for a radical débridement in many patients. Only the amount of calcium should be removed that allows adequate stitch placement and leaflet and annular flexibility. Obviously, calcification of the chordae or a substantial part of the leaflet tissue is a poor prognostic factor for long-term freedom from valve repair, and an extensively calcified valve usually indicates valve replacement.

Systolic Anterior Motion of the Mitral Valve

As mentioned above, persistent systolic anterior motion of the anterior leaflet is an adverse outcome after valve repair. In this condition, the anterior leaflet obstructs the LVOT. Clearly, increased redundancy of leaflet tissue is a risk factor with a small annuloplasty ring. After repair, if the line of leaflet coaptation is displaced anteriorly, then the anterior leaflet will be displaced into the LVOT and cause LVOT obstruction.[77,78] The etiology is usually inadequate reduction of the height of the posterior leaflet, which then pushes the anterior leaflet into the LVOT. SAM is particularly prevalent in patients with bileaflet prolapse or those with extremely enlarged anterior leaflets. Thus, the PML height reduction has to be meticulously carried out, and in myxomatous valve disease, an upsizing rather than a downsizing of the mitral valve annuloplasty ring should be done. As indicated above, if the anterior leaflet is supported by a relatively small annulus, the anterior leaflet will not spread out and instead will appear to have redundant tissue above the correct plane of coaptation, predisposing to SAM.[69]

Several investigators have looked at the potential echocardiographic risk factors for systolic anterior motion. Echocardiographic details that are associated with a high risk of systolic anterior motion include proximity of the mitral valve coaptation point to the interventricular septum, as well as asymmetry between the anterior and posterior leaflets. If the posterior leaflet is relatively large with respect to the anterior leaflet, then SAM is potentiated. We look for this information pre-repair and take such data into account as the repair strategy is finalized in the operating room.[69,70]

If the probability is high that SAM will occur, our practice is to use the Alfieri edge-to-edge technique to reduce such a risk.[69] By forcing the coaptation line to be correct with a single stitch in the situation of high SAM probability, the probability of SAM is reduced. Another strategy to consider in this circumstance is implantation of PTFE anterior chordae to lower the AML. That will reduce the height of the anterior leaflet, and thus further reduce the potential of

SAM. In our own experience long-term competency is maintained in this group.

If SAM appears by TEE following what appears to be an excellent repair, filling the left ventricle with fluid volume post–cardiopulmonary bypass will relieve systolic anterior motion in approximately 90% of patients. In rare circumstances, if an adequate reduction of the posterior leaflet has not been carried out, more posterior leaflet may have to be resected or the ring size increased. The most common alternative in our clinic is the edge-to-edge technique, as mentioned above, for situations where post-repair SAM still exists despite all techniques to reduce it.[69]

Remodeling Ring Annuloplasty

Remodeling the annulus by ring annuloplasty after mitral valve repair is essential to a complete and long-lasting repair. The remodeling concept, promulgated by Carpentier[17] and Duran[43] is that the distorted mitral annulus requires restorative structural support. There is debate on which type of ring should be used for remodeling: rigid or soft, full circle or C-ring. Our thought is that it is not critical which type of ring is utilized for myxomatous valve degeneration as long as there is a relative upsizing of the ring and a secure attachment to the trigone area of the anterior mitral leaflet. There is some evidence to suggest that flexible rings may incur less possibility of SAM and that open-ended rings, such as a C-ring, are safer with respect to SAM.[79] As none of this has been studied in a prospective randomized fashion, these opinions will continue to exist. Though we prefer the Cosgrove ring for mitral valve prolapse, our belief based on over 2000 mitral valve repairs is that the existing evidence is not compelling for any particular ring, and that the type of ring implanted is far less important than a correctly performed operation and appropriate sizing of the ring.

The technical aspects of ring implantation are important to avoid circumflex artery compromise, atrioventricular dissociation, or dehiscence of the ring. Implantation of currently available annuloplasty rings requires the placement of mattress sutures, parallel to the annulus, at the conjunction of the posterior leaflet and the annulus. Radially oriented bites are to be avoided because by definition they exert radial stresses and thus will pull to some extent on the circumflex artery. Bites should be deep with the needle entering the annulus, then into the left ventricular cavity, and then coming out on the atrial side again. Of paramount importance is the requirement that the plane of the needle bite should be orthogonal to the annular plane. If this is done, it is impossible for the stitch to impinge or distort the circumflex artery. That is why such bites may be made deep. Wide bites are taken such that there is not an excess number of sutures. A mitral C-ring should require approximately 9 to 12 sutures depending on the size of the annulus. The sutures are not pledgeted unless there is extreme fragility of the annular structures. Annular integrity will of course depend on the pathology. Sutures are then passed through the fabric part of the ring. The mandrill of the ring is kept in place to maintain the ring shape while the sutures are tied down, thus preventing crimping of the cloth rings in the nonrigid or semi-rigid rings.

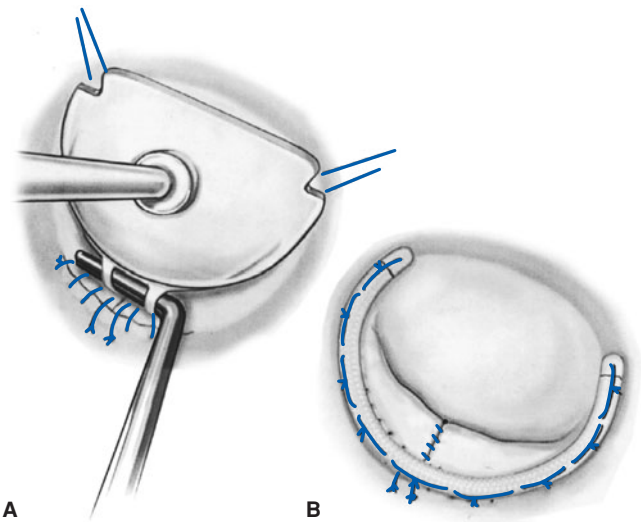


Figure 42-15. Ring annuloplasty sizing and insertion. The ring for degenerative disease should be slightly oversized. Sizing should be done to match the height of the anterior leaflet, not the distance between the trigones or commissures. Nine to eleven mattress sutures are usually needed.

Sizing is the most important aspect of ring placement. We believe that slight oversizing of the ring in myxomatous degenerated disease is appropriate. This corrects for the degenerative annulus that is functionally too small. Sizing is typically done by two techniques. Placement of aortic trigonal stitches (Fig. 42-15) allows for measurement of the intertrigonal distance. Many ring-sizing devices have notches on the rings to facilitate this. Except in rheumatic disease, we do not rely on this measurement. In myxomatous disease, our belief is that the height of the anterior leaflet from the annulus to the highest point on the leaflet when it is stretched is the most important criterion for sizing, a concept originally espoused by Carpentier.[10] This height of the leaflet is the critical dimension that must be carefully measured so that during systole there is minimal redundancy that may lead to SAM. Using trigonal sizing may, in fact, downsize the ring and cause either systolic anterior motion or ring dehiscence because of the huge disparity between ring size and annulus size. In our re-repair series, either improved sizing or placing the ring below the commissures were the most common remedies.[80] Therefore, using the sizer to evaluate anterior leaflet size is the most critical maneuver. Echocardiographic dimensions of the anterior leaflet correlate well with in vivo sizing, and calculating the anterior leaflet size by standard echocardiogram techniques is performed in every case. Deployment of a ring matching the anterior leaflet size in our experience has been most efficacious and has rarely led to systolic anterior motion.[69]

Results

Based on long-term studies the probability of mitral valve repair being intact at 10 years is greater than 90%.[36,42,50,56,81] Thromboembolic incidence is also exceedingly low; long-term anticoagulation is not required unless patients are in atrial fibrillation.

RHEUMATIC MITRAL VALVE DISEASE

The incidence of rheumatic fever and its valvular sequelae have dropped precipitously in North America and Europe during the last few decades. This has resulted in far fewer rheumatic valves requiring surgery. The disease is still seen, however, in individuals from undeveloped countries where rheumatic valve disease is still quite prevalent.[82] The primary lesion of rheumatic mitral valve disease is mitral stenosis caused by a fibrotic restriction at both commissures of the mitral valve. Open commissurotomy evolved from the early efforts in the 1940 and 1950s with closed mitral valvotomy and commissurotomy (Harken)[83,84] and was carried out successfully with a very low rate of recurrence and with a high probability of symptom relief.

Over the last several years, balloon mitral valvuloplasty has been the treatment of choice for noncalcified rheumatic mitral stenosis.[85] This technique has been widely used and has proven to be extremely efficacious in the noncalcified, nonregurgitant mitral valve. Nonetheless, there are still a number of patients with rheumatic valve disease who present primarily with severe mitral regurgitation secondary to varying degrees of restricted leaflet motion, thickening of the subvalvular apparatus, and commissural fusion. In most instances, if the valve is severely calcified and there is obliteration of the subvalvular chordal structure by fibrosis, repair will be fruitless and replacement carried out. In younger patients, with preservation of the chordal apparatus and minimal calcification, a satisfactory repair for mitral regurgitation can be carried out. Thickening of the valve may require, however, some thinning of the valve by removal of some of the rheumatic scarification process.

Techniques of rheumatic repair should always employ commissural incisions of the stenosis leaving a 2- to 3-mm edge to the annulus. Débridement of calcium and scar and incising the papillary muscles and chordae may improve mobility. Several European surgeons, particularly Duran and colleagues,[86] have devised techniques that include lengthening the anterior leaflet of the mitral valve, and even in some instances the use of PTFE chords to improve the flexibility of the posterior leaflet and retraction due to the chordal scarring and fibrosis.

Particularly in patients with severe mitral regurgitation related to rheumatic mitral disease, a remodeling annuloplasty ring will be necessary. Repair is possible with combined mitral stenosis and regurgitation since alleviation of stenosis may improve the mobility of the anterior leaflet, which then allows for a corrective operation rather than replacement. Finally, the absence or presence of fibrosis of the subannular chordal structure may often determine mitral valve replacement versus mitral valve repair. In young patients, however, every effort should be made to repair these valves by the techniques outlined above, as repair results are better in the long term than valve replacement.[87]

SUMMARY

Mitral valve repair for degenerative disease has undergone a virtual revolution in the previous 30 years. What was once viewed skeptically is now well accepted as the ideal treatment for mitral regurgitation based on improved physiology and lower valve-related morbidity than valve replacement. In major valve referral centers, repair is commonplace and routine. However, for many cardiac surgeons mitral valve repair is still surrounded by mystical references to such surgery as "a special art," one that is difficult to understand and one that requires special esoteric skills to master. Repair should be part of every cardiac surgeon's standard toolbox and should be considered as simply another procedure to be mastered.

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CHAPTER 43

Mitral Valve Replacement

Tomas Gudbjartsson · Tarek Absi · Sary Aranki

HISTORICAL BACKGROUND

Mitral valve surgery in the twentieth century began with Elliot Cutler's first operation at the Peter Bent Brigham Hospital in 1923.[1] This was a mitral valvulotomy that he had worked on for two years in the laboratory with Samuel Levine, a Boston cardiologist. Two years later, Dr. Suttar, an English surgeon, performed a mitral valvulotomy using his fingers to open up the commissures.[2] The patient made an uneventful recovery, but Dr. Suttar did not perform any more mitral valvulotomies. It took two more decades until Dwight Harken and Charles Bailey independently continued the development of digital valvulotomy for rheumatic mitral stenosis.[3,4] The results were dramatic, and the operation gained popularity. This launched the modern area of cardiac surgery. But recurrence of the stenosis still was a major problem, even after the development of cardiopulmonary bypass in the early 1950s, which enabled more complete open valvulotomy.

The next major step in the development of mitral valve surgery was the development of reliable, quality-controlled prosthetic heart valve devices in the late 1950s and early 1960s. For the first time, devices were available that could effectively replace a diseased, nonreparable mitral valve with relative ease of implantation and assurance that the hemodynamic abnormalities from either mitral stenosis or mitral regurgitation were corrected and maintained indefinitely.

The first successful prosthetic mitral valve was a device implanted by Nina Braunwald at the National Institutes of Health in 1959.[5] This was a homemade device with artificial chordae made of polyurethane. Two years later, the first reliable device for replacement of the mitral valve was produced on a commercial basis. This was the Starr-Edwards ball-and-cage mitral valve that resulted from the collaboration of Albert Starr, a cardiac surgeon in Portland, and Lowell Edwards, a mechanical engineer in southern California.[6] This prosthesis was a great success and became the "gold standard" for many years, until the late 1960s, when second- and third-generation prosthetic valves began to appear. Although reliable hemodynamically, it was soon found that the Starr-Edwards valve had significant thromboembolic potential, particularly in the small ventricle, and aggressive anticoagulation was required to control thromboembolic events.[7] The Silastic ball in the original prosthesis also had to be replaced because of inadequate durability.

During the next decade, a large number of different ball-and-disk valves were developed, and their profile was considerably reduced by alterations in both the height of the valve and the type of occluder (Fig. 43-1).

After a number of experimental valves were evaluated [without Food and Drug Administration (FDA) supervision], one valve emerged as the leading prototype for the 1970s: the Björk-Shiley tilting-disk valve, which was developed by Viking Björk in Stockholm and Earl Shiley in California.[8] This valve had better hemodynamics (larger cross-sectional area and less hemolysis) than the Starr-Edwards valve and consequently had a lower thromboembolic potential.[9,10] However, problems with thrombosis occurred when the anticoagulation was altered. When an engineering change was made to correct this problem in a later model (a concave-convex disk), a fracture in the strut ensued, and the Björk-Shiley prosthesis was taken off the market.[11]

A third-generation prosthetic valve was developed in the late 1970s that became the valve of the 1980s: the bileaflet St. Jude Medical valve, which had improved hemodynamics compared with older valves with less stagnation of blood, more complete opening of the leaflets, and reduced incidence of thromboembolism.[12–17] Several other disk prostheses are available currently (see Fig. 43-1), all with flow characteristics similar to the St. Jude valve but still with a small but definite risk of hemorrhage related to anticoagulant therapy and thromboembolism.

As the first, second, and third generations of prosthetic valves were developed, biologic or tissue replacement devices

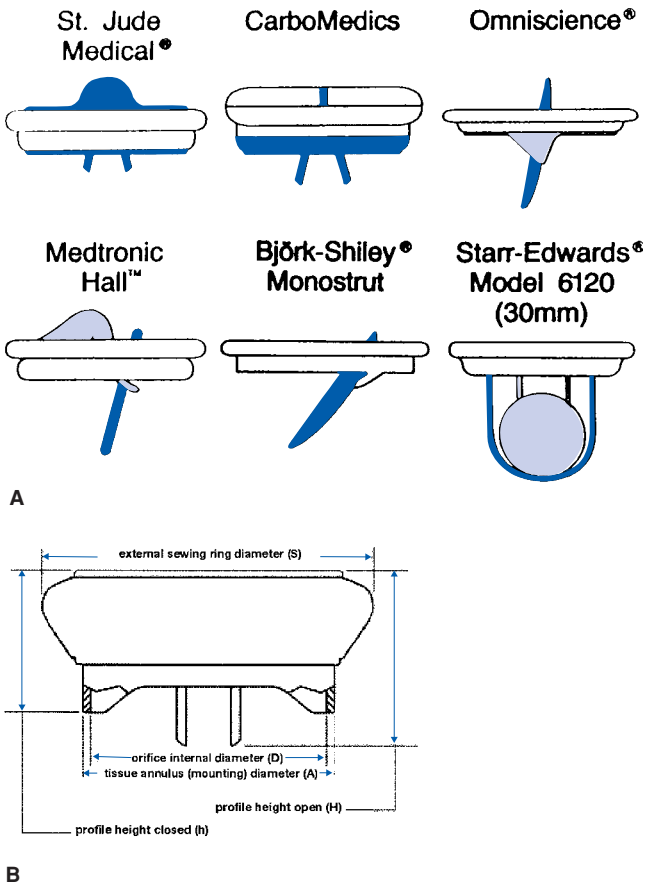


Figure 43-1. *A.* Profiles of mechanical mitral valve prostheses. *B.* Profile of the On-X mitral valve.

were developed concomitantly. The biologic valves showed a much lower frequency of thromboembolism, and long-term anticoagulation seemed to be unnecessary.

In the 1960s, investigators began to use formalin fixation to sterilize and fix fresh heterograft tissue.[18] However, when it became apparent that this fixation was unreliable because of collagen breakdown in valve cusps resulting in fibrosis and calcifications, glutaraldehyde fixation of porcine tissue began.[19] This fixative stabilized collagen bonding in the valve cusps and led to increased durability. The glutaraldehyde-fixed porcine aortic valve, principally developed by Hancock in the United States (1970) and Carpentier in Paris (1976), was the first commercially available bioprosthetic valve.[20,21] These valves revolutionized mitral valve surgery by providing a biologic alternative that allowed long-term use without the need for lifelong warfarin anticoagulation. Both the Hancock and the Carpentier-Edwards valves became enormously popular in the 1970s, and studies showed excellent 5-year durability (95%). In the early 1980s, however, structural valve dysfunction (SVD) became more apparent, with 15 to 20% of the prostheses failing within 10 years. The rate of deterioration seemed to accelerate in younger patients, with the valve gradually wearing down as a result of different biologically mediated dysfunctional processes.[22–26]

The first- and second-generation biologic valves were constructed from porcine aortic valves. Because of limited durability, these valves mostly have been replaced by the third generation of biologic valves, which still include porcine valves in addition to biomechanically engineered bovine pericardial valves. For this third generation of valves, new technology has been incorporated aimed at improving valve longevity and hemodynamic function This has resulted in better midterm and long-term results.[27–33] These techniques include low-pressure or no-pressure fixation, antimineralization processes of the tissues, and low-profile, semiflexible stents that better define the biomechanical properties of the leaflets.

This chapter discusses the surgical indications, operative techniques, and early and late follow-up after implantation of mechanical and bioprosthetic mitral valve devices. The valves that are discussed are those that are currently (2006) approved by the FDA. Figure 43-2 shows the current FDA-approved prosthetic mitral valve devices, including the Starr-Edwards ball-and-cage valve, the Omnicarbon tilting-disk valve, the Medtronic Hall tilting-disk valve, the St. Jude Medical bileaflet valve, the Carbomedics bileaflet valve, the ATS bileaflet valve, and the On-X bileaflet valve. The FDA-approved bioprosthetic valve devices are shown in Fig. 43-3 and include the Hancock II porcine valve, the Carpentier-Edwards porcine valve, the Carpentier-Edwards pericardial valve, the Mosaic porcine valve, and the Biocor porcine valve.

INDICATIONS FOR MITRAL VALVE REPLACEMENT

The indications for mitral valve replacement are variable and undergoing evolution. Because of increasing use of reparative techniques, particularly for mitral regurgitation, replacement or repair of a mitral valve often depends on the experience of the operating surgeon. Current indications for valve replacement pertain to those types of valve problems that are unlikely to be repaired by most surgeons or which have been shown to have poor long-term success after reconstruction. Indications are discussed according to (1) pathophysiologic states for needing operation and (2) type of valve required (i.e., mechanical or bioprosthetic).

Mitral Stenosis

Mitral stenosis is almost exclusively caused by rheumatic fever, even though a definite clinical history can be obtained in only about 50% of patients. The incidence of mitral stenosis has decreased substantially in the United States in the last several decades because of effective prophylaxis of rheumatic fever. In some African and Asian countries, especially India, mitral stenosis is still very common. Two-thirds of patients with rheumatic mitral stenosis are female.

The pathologic changes in rheumatic valvulitis are mainly fusion of the valve leaflets at the commissures, shortening and fusion of the cordae tendinae, and thickening of

the leaflets owing to fibrosis with subsequent stiffening, contraction, and calcification. Approximately 25% of patients have pure mitral stenosis, but an additional 40% have combined mitral stenosis and mitral regurgitation.[34]

Stenosis usually develops one or two decades after the acute illness of rheumatic fever with no or slow onset of symptoms until the stenosis becomes more severe. Limitation of exercise tolerance usually is the first symptom, followed by dyspnea that can progress to pulmonary edema. New-onset atrial fibrillation and the risk for thromboembolism, hemoptysis, and pulmonary hypertension are other common symptoms in patients with mitral stenosis.

The diagnostic workup of the symptomatic patient with mitral stenosis should include a complete cardiac catheterization, including coronary angiography in any patient over the age of 40. Under age 40, echocardiographic findings of the mitral valve suffice in most symptomatic patients for the definition of mitral valve pathology unless there is a history of chest pain or coronary artery disease. Cardiac catheterization establishes the extent of mitral valve stenosis by determining valve gradients and valve area. Pulmonary artery pressure, which may be extremely high in long-standing cases of mitral stenosis, is also documented. In general, operation is prescribed

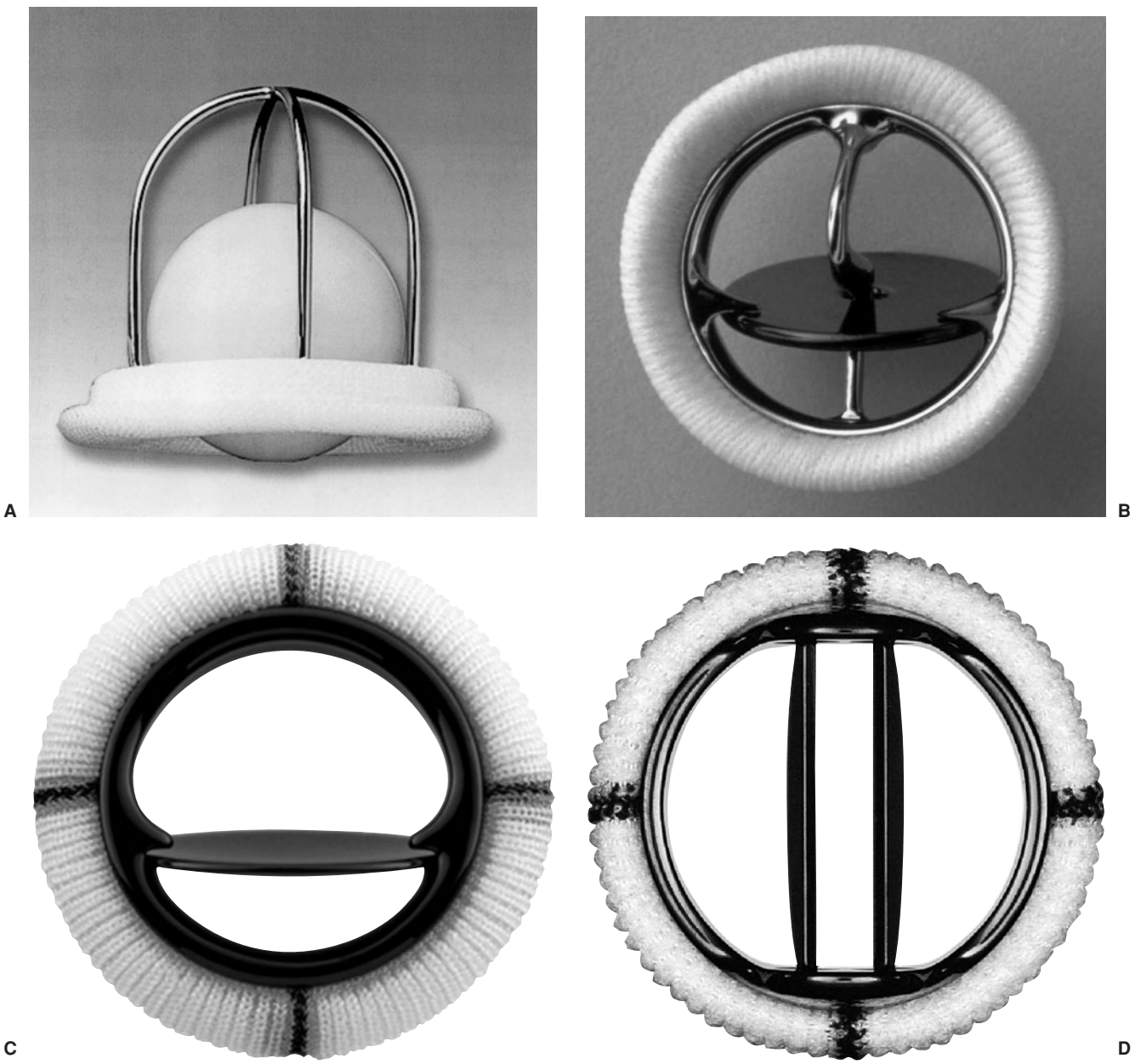
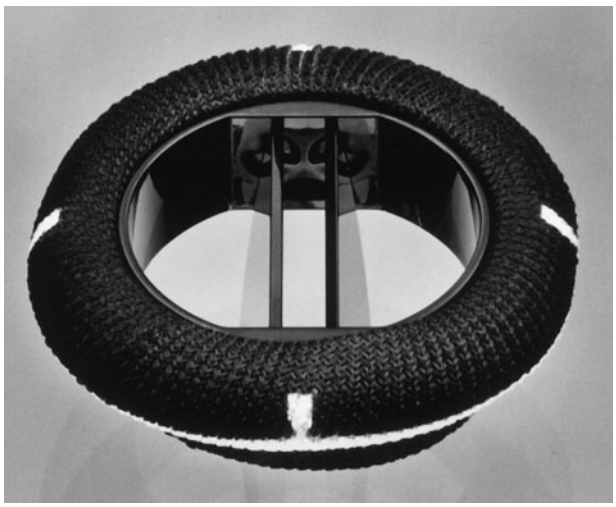


Figure 43-2. FDA-approved mechanical mitral valves. *A.* Starr-Edwards ball-and-cage. *B.* Medtronic-Hall tilting-disk. *C.* Omnicarbon tilting-disk. *D.* St. Jude Medical bifleaflet.



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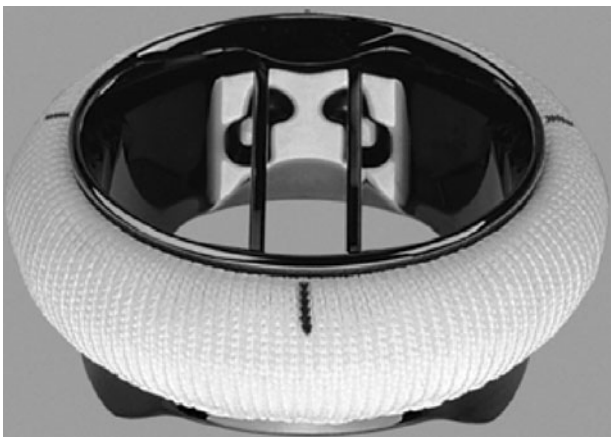

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Figure 43-2. *(continued)* E. Carbomedics bileaflet. F. ATS bileaflet. G. On-X bileaflet.

when the mean valve area is 1.0 cm^2 or less[35] (normal mitral valve area is 4 to 6 cm^2); however, with a "mixed" lesion of mitral stenosis and mitral regurgitation, the valve area in symptomatic patients occasionally may be as large as 1.5 cm^2. Asymptomatic patients generally are not considered for surgery,[36] but some authors recommend operation in asymptomatic patients with significant hemodynamic mitral stensosis[37] (see Chap. 36). The degree of pulmonary artery pressure elevation secondary to mitral stenosis continues to be an area of concern for the mitral valve surgeon. Is there any level of pulmonary hypertension that is too high for mitral valve replacement in the current surgical era of improved intraoperative and postoperative care? There is still no definitive answer to this question, but most surgeons operate on patients with severe pulmonary hypertension (suprasystemic) with the knowledge that intensive postoperative respiratory and diuretic therapy is necessary to maintain relatively dry lungs and to reduce the risk of severe right ventricular failure. It has been known for over 40 years that after mitral valve replacement for mitral stenosis, pulmonary artery pressure decreases within hours in most patients and decreases more gradually over weeks to months in others.[41–43]

The reason for this is not known. However, recently it has been suggested that valve prosthesis-patient mismatch (defined as indexed effective orifice area of 1.2 cm^2/m^2 or less and pulmonary artery hypertension of 40 mm Hg) might be important in preventing the regression of pulmonary artery hypertension after mitral valve replacement.[42]

The success with closed commissurectomies after World War II and the development of the Starr-Edwards valve in the early 1960s led to an enormous increase in operations for rheumatic mitral valve disease; this pattern began a decrease as rheumatic disease declined. In recent years, a small resurgence in rheumatic valve disease has been observed in emigrés from Southeast Asia and Latin America. In the 1990s, balloon dilation of fibrotic, stenotic mitral valves became increasingly common.[43,44] At the present time, percutaneous mitral balloon valve dilation is used in most cases of symptomatic noncalcified, fibrotic mitral stenosis. But even though this technique has been shown to be equivalent in the short run to closed mitral commissurectomy, especially in young patients, it is only indicated in a minority of patients, i.e., those with optimal valvular characteristiscs.[36,45] Open mitral commissurotomy and valvuloplasty for such patients can be a successful operation,[46,47] but

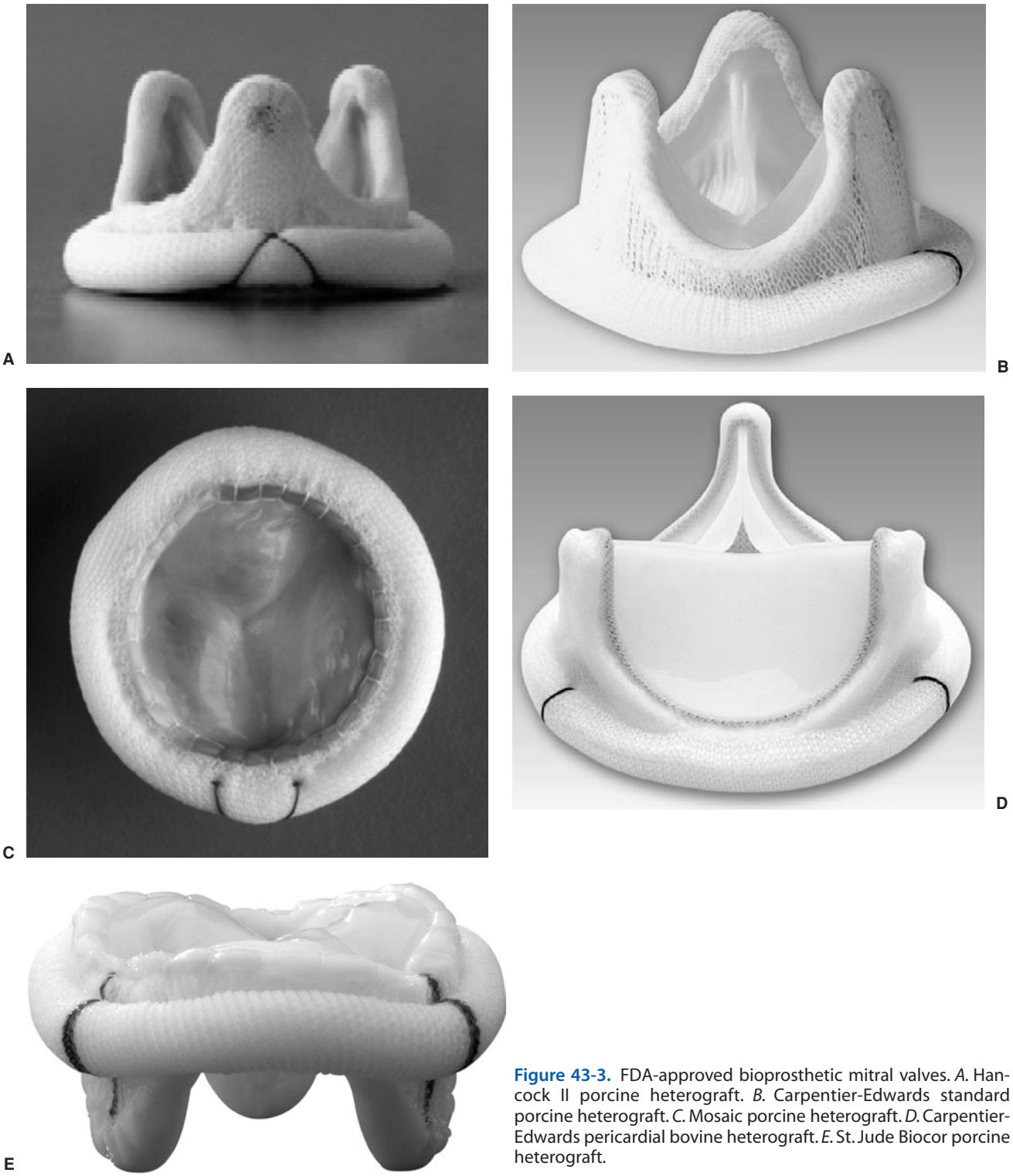

Figure 43-3. FDA-approved bioprosthetic mitral valves. *A.* Hancock II porcine heterograft. *B.* Carpentier-Edwards standard porcine heterograft. *C.* Mosaic porcine heterograft. *D.* Carpentier-Edwards pericardial bovine heterograft. *E.* St. Jude Biocor porcine heterograft.

other studies have shown better long-term results with mitral valve replacement using a mechanical valve.[48] Many patients with chronic mitral stenosis now require valve replacement because the valve has developed significant dystrophic changes, including marked thickening and shortening of all chordae, obliteration of the subvalvular space, agglutination of the papillary muscles, and calcification in both annular and leaflet tissue. Aggressive decalcification and heroic reconstructive techniques for these extremely advanced pathologic valves generally have produced poor long-term results; nevertheless, some surgeons still advocate aggressive repairs in this subset of patients.[49]

Mitral Regurgitation

The etiology of mitral regurgitation is very diverse, and the decision to recommend operation for patients with mitral regurgitation is more complex than for patients with mitral stenosis, except in cases of acute ischemic mitral regurgitation and endocarditis, where indications are more straightforward. The pathologic subsets that produce mitral regurgitation are related to a number of metabolic, functional, and anatomic abnormalities.[36] These can be categorized into degenerative (e.g., mitral prolapse and ruptured/elongated chordae), rheumatic, infectious, and ischemic diseases of the mitral valve. Most of these entities are now amenable to mitral valve repair and reconstruction with or without the use of annuloplasty rings, as mentioned in Chap. 37.

For any of the preceding major pathologic subsets, indications for surgery in patients with mitral regurgitation vary from the asymptomatic patient with an enlarging but well-functioning left ventricle and atrium to severely depressed left ventricular function. Any symptomatic patient with significant mitral regurgitation (3+ to 4+) should be operated on, and operation should be considered in any relatively symptom-free individual if there is objective evidence of left ventricular deterioration and documented and significant increases in left ventricular end-systolic and end-diastolic volumes.[50–55]

Regurgitation through the valve usually is measured with Doppler echocardiography, but magnetic resonance imaging (MRI) is another noninvasive technology for measuring the regurgitant flow and can provide measurements of ventricular end-diastolic/systolic volumes and ventricular mass.[56,57] Left ventricular angiography can be helpful but is otherwise indicated for evaluating the coronary arteries preoperatively in patients older than 40 years.

It is important to stress that depressed ejection fraction is a poor indicator of left ventricular function in patients with mitral regurgitation. Ejection fraction can be preserved in patients with irreversible left ventricular failure because of regurgitant flow through the valve.[58,59] Depressed cardiac output (<40%) therefore usually indicates severe left ventricular dysfunction, and results of surgery are not as favorable in these patients as they are in patients with normal ventricles.[60,61] Compared with ejection fraction, measurements of end-systolic volume and diameter are more reliable noninvasive parameters to evaluate the status of the left ventricle and determine the optimal time for operation[62,63] (see Chap. 36).

Once the valve is exposed, indications for mitral valve replacement in patients with mitral regurgitation depend on the extent of the pathology in each patient and the reparative experience of the operating surgeon. Thus, in regurgitation from degenerative prolapsing myxomatous valves that have a high probability of reconstruction, mitral valve repair is indicated if the prolapse is generalized, and local findings that decrease the probability of a successful repair are absent.[64–68] Similarly, if rheumatic mitral regurgitation, calcific deposits throughout the leaflet substance, and shortened chordae and papillary muscles are encountered, mitral valve replacement is often the most prudent operation because the probability of successful repair is low.[69] However, good results with reconstructive surgery in this patient group have been reported.[70] In ischemic mitral regurgitation, pathology that precludes satisfactory repair includes restrictive valve motion from shortened, scarred papillary muscles, an acutely infarcted papillary muscle, and rupture of chordae associated with extensive calcification of valve leaflets.[71–73] In endocarditis, mitral valve replacement may be required because of destruction of the valve leaflets and subvalvular mechanisms and annular abscess formation. Although repair of the valve and avoidance of prosthetic material are very desirable in septic situations, the extent of the destruction may preclude repair. Therefore, mitral valve replacement is required after careful débridement of the infectious tissue and reconstruction of the valve annulus.[74–76]

CHOICE OF VALVE TYPE

Indications for Mechanical Valve Replacement

Currently available prosthetic valves in the United States, in descending order of popularity, are the bileaflet, the tilting-disk, and the ball-and-cage valve. For young patients, patients in chronic atrial fibrillation who require long-term anticoagulation, and any patient who wants to minimize the chance of reoperation, a prosthetic valve should be chosen if valve replacement is required. The St. Jude Medical bileaflet valve is the most widely used prosthetic mitral valve at present because it has good hemodynamic characteristics and is easy to insert. Indications to choose one prosthetic or another vary primarily by surgeon preference and occasionally depending on the state of the annulus and whether or not there have been multiple previous operations. For example, infrequently, the mitral annulus provides poor anchorage with subsequent perivalvular leak with the bileaflet or tilting-disk valve, which requires an everting-suture technique. In this instance, a valve with a bulky sewing ring may be chosen to reduce the probability of subsequent perivalvular leak. A low-profile mechanical valve is preferable in a patient with a small left ventricular cavity to prevent obstruction of left ventricular outflow and impingement of the myocardium.

Indications for Bioprosthetic Valve Replacement

Patients in any age group in sinus rhythm who wish to avoid anticoagulation may prefer a bioprosthetic valve. This is especially true for patients in whom anticoagulation is contraindicated, e.g., patients with a history of gastrointestinal bleeding or those who have a high-risk occupation or lifestyle.[36] A bioprosthetic valve is preferred in patients over age 70 and in sinus rhythm because these valves deteriorate

more slowly in older patients.[77] In addition, some 60-year-olds may not outlive their prosthetic valves because of comorbid disease.[78,79] Specifically, patients who require combined mitral valve replacement and coronary bypass grafting for ischemic mitral regurgitation and coronary artery disease have significantly reduced long-term survival as compared with patients who do not have concomitant coronary artery disease.[80–85] These individuals may avoid anticoagulation with little risk of reoperation.

As 20-year results have become available for various bioprostheses, it is clear that structural valve degeneration (SVD) is the most prominent drawback of these valves.[24,27,86–91] The durability of porcine valves is less with mitral bioprostheses than with aortic bioprostheses. The more rapid deterioration of mitral bioprostheses may be due to higher ventricular systolic pressures against the mitral cusps compared with the diastolic pressures resisted by aortic bioprosthetic leaflets.[23] Durability of bioprosthetic valves is directly proportional to age[87]; deterioration occurs within months or a few years in children and young adults and only gradually over years in septuagenarians and octogenarians.[23,27,29,30,33,86,92] Essentially all valves implanted into patients younger than 60 years of age have to be replaced ultimately, and valve failure is prohibitively rapid in children and adults younger than 35 to 40 years of age; therefore, bioprostheses are not advisable in these age groups.[36,93] Nevertheless, there are still indications for mitral porcine bioprosthetic valves in young patients. In a woman who desires to become pregnant, a bioprosthesis may be used to avoid warfarin anticoagulation and fetal damage during pregnancy.[94–97] In patients with chronic renal failure and hypercalcemia related to hyperparathyroidism, bioprostheses have extremely limited durability and therefore should be avoided.

Over the last decade, there were several reports, mainly from European centers, on the use of unstented cryopreserved homografts[98–101] and stentless heterografts[102–105] for mitral valve replacements, particularly in patients with endocarditis. The prosthetic valve is transplanted, donor papillary muscles are reattached to recipient papillary muscles, and the annulus is sutured circumferentially. This technique has been shown to be safe and reproducible, but it does not always provide durable results and therefore should not be used in young patients.[102] Other reports suggest that these operations may be a feasible alternative to stented valve replacement in patients with endocarditis. Pulmonary autografts also have been used for replacing the mitral valve (Ross II procedure), but these series are small, and follow-up is relatively short.[106–108]

HEMODYNAMICS OF MITRAL VALVE DEVICES

Mechanical Prostheses

The designs of mechanical and bioprosthetic heart valves have evolved over the last five decades in an effort to develop the ideal replacement for the pathologic mitral valve. Biochemical and engineering advances have produced hemodynamic improvements and reduced morbidity from valve-related complications. The ideal valve, however, is not available, and the positive and negative characteristics of current valves must be considered when choosing the most appropriate valve for an individual patient. The optimal heart valve exerts minimal resistance to forward blood flow and allows only trivial regurgitant backflow as the occluder closes. The design must cause minimal turbulence and stasis in vivo during physiologic flow conditions. The valve must be durable enough to last a lifetime and must be constructed of biomaterials that are nonantigenic, nontoxic, nonimmunogenic, nondegradable, and noncarcinogenic. The valve also must have a low incidence of thromboembolism.

The opening resistance to blood flow is determined by the orifice diameter; the size, shape, and weight of the occluder; the opening angle; and the orientation of leaflet or disk occluders with respect to the plane of the mitral annular orifice for any given annular size. Least resistance to transvalvular blood flow during diastole for valves in the mitral position is provided by a large ratio of orifice to total annular area. A wide opening angle also improves the effective orifice area and results in decreased diastolic pressure gradients. With an increasing orifice diameter, however, more energy is lost across the valve as more backflow passes through the valve at end diastole and early systole. Table 43-1 shows hemodynamic assessments of each of the FDA-approved mitral valve prostheses for the most commonly used mitral valve sizes.[12,15,17,109–141] The results of in vivo assessments at rest by invasive (catheterization) or noninvasive (Doppler echocardiography) techniques are tabulated.

Blood turbulence flowing across mitral valve devices results from impedance to forward or reverse flow. This impedance can be minimized by occluder design and orientation, central flow through the orifice, and limited struts or pivots extending into flow areas (Fig. 43-4). Hemolysis is the product of red blood cell destruction that is caused by cavitation and shearing stresses of turbulence, high-velocity flow, regurgitation, and mechanical damage during valve closure.[142] Areas of perivalvular blood stagnation and turbulence increase platelet aggregation, activation of the coagulation proteins, and thrombus formation.

Dynamic regurgitation is a feature of all prosthetic valves and is the sum of the closing volume during occluder closure and the leakage volume that passes through the valve while it is closed. The closing volume is a function of the effective orifice area and the time needed for closure. Closure time is influenced by the difference between the opening and closing angles of the occluder and valve ring. Leakage volume is inherent to the design of the valve and depends on the amount of time the valve remains in the closed position.[143] A small amount of regurgitant volume can be beneficial by minimizing stasis and reducing platelet aggregation; this decreases the incidence of valve thrombosis and valve-related thromboembolism.[123]

Table 43–1.

Hemodynamics of Mitral Valve Prostheses

		EOA (cm^2)					Mean diastolic gradient (mm Hg)				
Valve	**Reference (year)**	**25 mm**	**27 mm**	**29 mm**	**31 mm**	**33 mm**	**25 mm**	**27 mm**	**29 mm**	**31 mm**	**33 mm**
Starr-Edwards	Pyle[133] (1978)		1.4	1.4	1.9			8.0	10.0	5.0	
	Sala[135] (1982)							7.9	6.7	5.0	
	Horskotte[123] (1987)			1.8				6.3			
Omniscience/ Omnicarbon	Mikhail[131] (1989)							6.1		5.4	
	Messner-Pellenc[130] (1993)		1.9	2.2	2.0	2.0	4.3	3.6	3.5	2.0	
	Fehske[119] (1994)						6	6	5	6	4
	di Summa[117] (2002)	1.7	1.9	1.6	1.9		9	4.1	5.1	5.6	
Medtronic Hall	Hall[121] (1985)							3.0	2.7	2.0	
	Fiore[15] (1998)						4.0	4.3	3.1	2.9	2.7
St. Jude	Chaux[12] (1981)			2.1	2.8	3.1			1.9	1.8	1.6
	Horskotte[123] (1987)			3.1					2.3		
	Fiore[15] (1998)						3.0	3.3	3.8	1.5	2.5
	Hasegawa[122] (2000)	2.6	2.5	2.4							
Carbomedics	Johnston[126] (1992)			3.3					3.8		
	Chambers[114] (1993)		2.1	2.1	1.8			3.9	3.3	3.3	
	Carbomedics[110] (1993)		2.9	3.0	3.0			3.9	4.6	4.6	
	Carrier[112] (2006)						5.3	4.9	4.6	4.4	4.9
ATS	Westaby[141] (1996)		3	2	2	2					
	Shiono[136] (1996)						5	6	4.5		
	Hasegawa[122] (2000)	2.3	2.6	2.7							
	Emery[188] (2001)						7.8	5	6	4	3
Hancock standard	Johnson[125] (1975)		1.0	2.5	1.8			12.0	5.0	5.0	
	Ubago[139] (1982)		1.3	1.0	1.0			7.0	7.6	7.4	
	Khuri[127] (1988)		1.5	2.0	1.8			7.0	7.0	7.0	

Carpentier-Edwards porcine	Chaitman[113] (1979)		1.7	2.2	2.8			7.0	6.7	5.0		
	Levine[129] (1981)			3.0	3.2				2.0	2.6		
	Pelletier[132] (1982)		1.7	2.4	2.5			6.5	7.4	5.3		
Carpentier-Edwards pericardial	Aupart[111] (1997)	2.6	2.7	2.6	3.1		4.1	3.0	3.0	3.0	???	
Mosaic	Thomson[138] (2001)			1.7 (all sizes)								
	Eichinger[168] (2002)	2.6	1.5	1.8	2.1		4.6	3.8	4.4	2.7		
	Fradet[120] (2004)	1.1	0.9	1.0	0.9		4.2	5.8	4.8	4.0		
Biocor	Rizzoli[134] (2005)			3.1	3.3	3.6			6.7	6.2	5.4	
Normal				4.6					0			
Severe stenosis				>1.0					>12			
Desired postoperative				>1.5					>10			

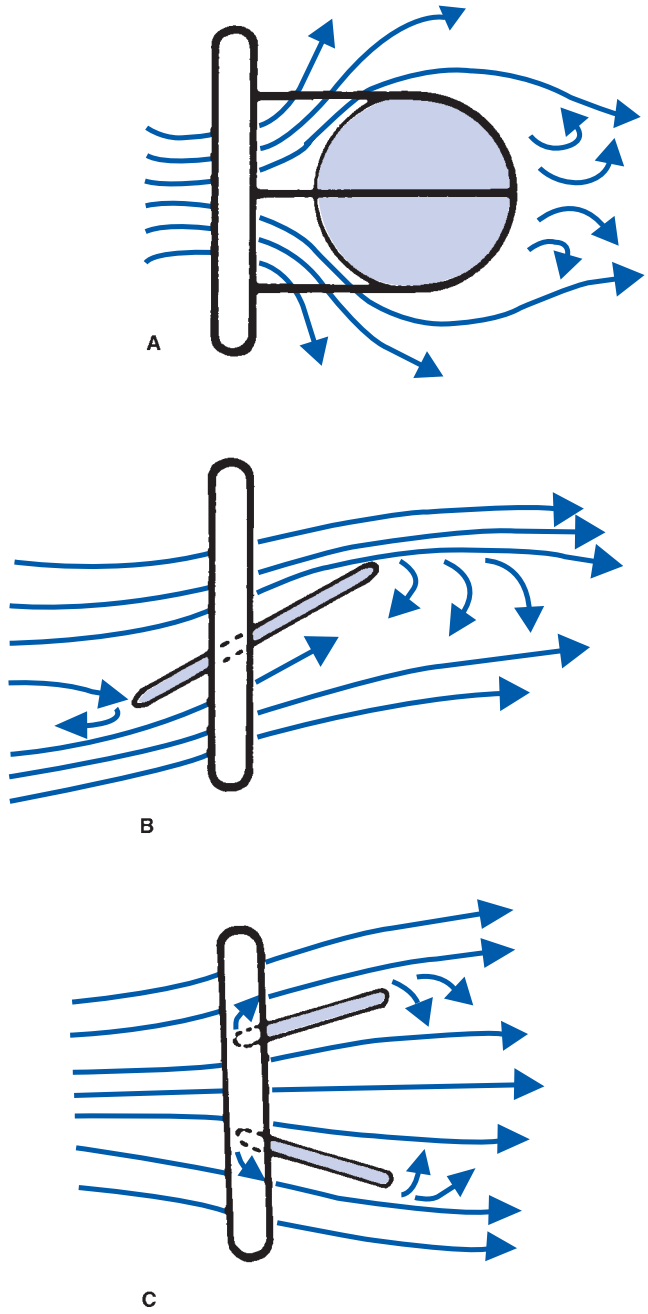

Figure 43-4. Flow characteristics of different mechanical valve designs. *A.* Ball-and-cage. *B.* Tilting-disk. *C.* Bileaflet.

The Starr-Edwards Model 6120 is the only ball-and-cage mitral valve prosthesis currently approved for use in the United States by the FDA. It was introduced with its current design in 1965 after undergoing several engineering modifications and has been in use longer than any other type of mechanical valve (see Fig. 43-2*A*). The occluder is a barium-impregnated Silastic ball in a Stellite alloy cage that projects into the left ventricle. This valve has a large Teflon/polypropylene sewing ring that produces a relatively smaller effective orifice and larger diastolic pressure gradients than other prosthetic valves of similar annular sizes. Leakage volumes are not inherent in the ball-and-cage design, and in contrast to other mechanical valves, the presence of regurgitation may indicate a pathologic process. The central ball occluder causes lateralization of forward flow and results in turbulence and cavitation that increase the risk of hemolysis and thromboembolic complications (see Fig. 43-4*A*). The incidence of thromboembolism has been shown to be higher with the Starr-Edwards valve than with bileaflet valves in some studies[144,145] but not in others.[146] Because the cage projects into the left ventricle, it is unwise to implant this valve in small left ventricles, where the cage may contact the ventricular wall or cause ventricular outflow obstruction.

Tilting-disk mitral valve prostheses have better hemodynamic characteristics than ball-and-cage valves (see Fig.43-4*B*). The Medtronic Hall central pivoting-disk valve was introduced in 1977 and is based on engineering design modifications of the earlier Hall-Kaster valve[147] (see Fig. 43-2*B*). The axis of the tilting disk was moved more centrally to allow greater blood flow through the minor orifice and to reduce stagnation in areas of low flow. The opening angle originally was increased to 78 degrees to decrease resistance to forward flow and later narrowed to 70 degrees when in vitro studies revealed an unacceptable regurgitant volume. The opening angle of 70 degrees produced regurgitation volumes of less than 5% of left ventricular stroke volume without significantly compromising forward flow. The disk occluder was allowed to slide out of the housing at the end of the closing cycle to provide a gap through which blood could flow to minimize stasis at the contact surfaces.[147] The large opening angle and slim disk occluder, along with a thinner sewing ring, provide improved hemodynamics with comparably larger effective orifice areas and lower mean diastolic pressure gradients for each valve size. During implantation, the larger orifice should be oriented posteriorly when using the larger valve sizes to minimize the potential for disk impingement. Smaller valves (27 mm or less) should be oriented with the larger orifice anteriorly to optimize in vivo hemodynamics.[116,148]

The Omniscience tilting-disk valve is a second-generation device derived from improvements to the design of the Lillehei-Kaster pivoting-disk valve.[149] This low-profile device has a pyrolytic disk located eccentrically in a one-piece titanium housing attached to a seamless Teflon sewing ring. Introduced in 1978, the Omniscience prosthesis includes several engineering modifications from prior devices in an effort to improve its hemodynamic function. The orifice-to-annular-area ratio was increased to minimize resistance to forward flow. The opening angle of 80 degrees is relatively large to allow flow reserve in patients with high cardiac outputs and during exercise. Resulting increases in regurgitant volumes are minimized by the disk design. Turbulence is reduced by the curvature of the disk, and areas of stasis and shear stress are reduced by the eccentric location of the pivot axis in an effort to decrease the risk of thrombosis, thromboembolism, and hemolysis. Retaining prongs are not used, and the lower profile reduces the risk of impingement.[131] A potential hemodynamic disadvantage that has been the subject of debate is the possibility of incomplete disk opening in vivo. Clinical studies

report postoperative mean opening angles of between 44.8 degrees[116] and 75.9 degrees.[150] Implicated factors causing this variation include valve sizing, orientation during implantation, and anticoagulation status.[150,151] A subsequent generation of the Omniscience valve is the all-carbon Omnicarbon monoleaflet valve that was released in 2001 in the United States but has been in clinical use in Europe since 1984 (see Fig. 43-2*C*). The housing material is made of pyrolytic carbon instead of titanium. As a result of this change, the incidence of thromboembolism, valvular thrombosis, and reoperations was decreased significantly compared with the Omniscience valve protheses.[152] For all the tilting-disk valves, meticulous surgical technique is important because retained leaflets or chordae can cause subvalvular interference and leakage.

The unique design of the bileaflet St. Jude Medical valve was introduced in 1977, and it is currently the prosthesis used most commonly worldwide (see Fig. 43-2*D*). Two separate pyrolytic carbon semidisks in a pyrolytic carbon housing are attached to a Dacron sewing ring. The housing has two pivot guards that project into the left atrium. The bileaflet design produces three different flow areas through the valve orifice that provide overall a more uniform, central, and laminar flow than in the caged-ball and monleaflet tilting-disk designs. The improved flow results in less turbulence and decreased transmitral diastolic pressure gradients[143,153] (see Fig. 43-4*C*) at any annulus diameter size and cardiac output compared with the caged-ball and single-leaflet tilting valves.[154] The favorable hemodynamics in smaller sizes makes it especially useful in children.[36] The central opening angle is 85 degrees, with a closing angle of 30 to 35 degrees, which, along with a thin sewing ring, provides a large effective orifice area for each valve size at the expense of greater regurgitant volumes, especially at low heart rates. Asynchronous closure of the valve leaflets in vivo also contributes to the regurgitant volume.[155] The design of this prosthesis provides excellent hemodynamic function even in small sizes in any rotational plane.[156] The antianatomic plane, however, with the central slit between the leaflets oriented perpendicular to the opening axis of the native valve leaflets decreases the potential risk of leaflet impingement by the posterior left ventricular wall.[157]

The Carbomedics bileaflet valve was approved by the FDA in 1986 (see Fig. 43-2*E*). This low-profile device is constructed of pyrolytic carbon and has no pivot guards, struts, or orifice projections to decrease blood flow impedance and turbulence through the valve.[143] It has a rotatable sewing cuff design and is available with a more generous and flexible sewing cuff (the OptiForm variant) that confirms more easily to different patient anatomies and allows sub-, intra-, or supra-annular suture placement. The leaflet opening angle is 78 degrees, which, with the bileaflet design, provides a relatively large effective orifice area and transvalvular diastolic pressure differences only slightly greater than the St. Jude Medical bileaflet valve. Rapid synchronous leaflet closure reduces closing regurgitant volumes to less than that of the Björk-Shiley pivoting-disk prosthesis, which has an opening angle of 60 degrees. Leakage volume, however, is greater with Carbomedics valves because of backflow through gaps around pivots. Because of its narrow closing angle and large leakage volume, the Carbomedics valve does not reduce the relatively large regurgitant volume associated with the bileaflet design. Although this valve has good hemodynamic function overall, in the mitral position, the 25-mm Carbomedics valve has a relatively high diastolic pressure gradient and large regurgitant energy loss across the valve, especially at high flows. Hemodynamic studies suggest that the Carbomedics valve should be avoided in patients with a small mitral valve orifice.[143]

The ATS (Advancing The Standard) mechanical prosthesis has been in clinical use in the United States since 2000. Similar to the Carbomedics valve, the ATS valve is a low-profile bileaflet prosthesis with a pyrolytic housing and pyrolytic carbon leaflets containing graphite substrate (see Fig. 43-2*F*). The pivot areas are located entirely within the orifice ring, and the valve leaflets hinge on convex pivot guides on the carbon orifice ring. This design minimizes the overall height of the valve and provides a wider orifice area, and the absence of cavities in the valve ring theoretically reduces stasis or eddy currents that may develop. Valve noise, a bothersome problem for some patients, also is reduced by this design.[158] The opening angle is up to 85 degrees, and the sewing cuff is constructed of double velour polyester fabric that is mounted to a titanium stiffening ring, which enables the surgeon to rotate the valve orifice during and after implantation.

The On-X prosthesis was approved by the FDA in 2002. It has a bileaflet design similar to the St. Jude Medical, Carbomedics, and ATS prostheses with comparable hemodynamic performance, i.e., a relatively large orifice diameter and a wide opening angle (90 degrees) (see Fig. 43-2*G*). Instead of silicon-alloyed pyrolytic carbon, as used in the other mechanical prostheses, the On-X valve is made of pure pyrolytic carbon. This material is stronger and tougher than silicon-alloyed carbon[159] and allows incorporation of hydrodynamically efficient features into the valve orifice, such as increased orifice length and a flared inlet that reduces transvalvular gradient.[115] Early clinical results are promising,[160,161] and the valve produces very little hemolysis with postoperative levels of serum lactate dehydrogenase in the normal range.[161,162]

Bioprostheses

Porcine valves

The porcine bioprosthetic mitral valves are designed to mimic the flow characteristics of the in situ aortic valve. The Hancock I mitral valve bioprosthesis was introduced in 1970. It has three glutaraldehyde-preserved porcine aortic valve leaflets on a polypropylene stent attached to a Dacron-covered silicone sewing ring. The design allows for central laminar flow through the valve, which tends to decrease diastolic pressure gradients and minimize turbulence.[153] The stent, however, impedes forward flow and results in relatively large diastolic pressure gradients across the bioprosthesis. The stent and the large sewing ring contribute to effective orifice areas that are smaller than those of size-matched mechanical valves (see Table 43-1).

The Hancock II porcine bioprosthesis (see Fig. 43-3*A*) is the more modern version of the Hancock I prosthesis. The stent is made of Delrin with a scalloped sewing ring and reduced stent profile. The leaflets are fixed in glutaraldehyde at low pressure and subsequently for a prolonged period at high pressure. To retard calcification, the leaflets are treated with sodium dodecyl sulfate.

The Carpentier-Edwards porcine valve uses a flexible stent to decrease the stress of leaflet flexion while maintaining its overall configuration (see Fig. 43-3*B*). The effective orifice-to-total-annulus-area ratio for the Carpentier-Edwards valve is relatively small, but exercise studies show that the effective orifice area increases significantly with increased blood flow across the valve; diastolic gradients also increase, although to a lesser degree.[127,132,163] Porcine bioprostheses in the mitral position should be avoided in patients with small left ventricles because of the possibility of ventricular rupture or left ventricular outflow obstruction caused by the large struts.[163]

The Mosaic porcine bioprosthesis is a third-generation bioprosthesis using the Hancock II stent (see Fig. 43-3*C*). It was introduced in the United States in 2000 and has a Delrin stent, scalloped sewing ring, and reduced stent profile. The valve tissue is pressure-free fixed with glutaraldehyde, and the prosthesis is treated with alpha-oleic acid (AOA) to retard calcification.

The prosthesis approved most recently by the FDA in 2005 is the Biocor porcine bioprosthesis (St Jude Medical); however, it has been used and investigated for almost two decades in Europe.[30] It belongs to the third generation of bioprostheses, and the valve tissue is pretreated in glutaraldehyde at very low pressure (<1 mm Hg), making the valve cusps less stiff with less tendency to tissue fatigue.

Pericardial valves

Previous studies indicated poor durability of pericardial valves, namely, the Ionescu-Shiley valve, caused by leaflet tearing. This led to significant changes in design, including mounting of the pericardium completely within the stent, causing less leaflet abrasion and increased durability. The Carpentier-Edwards pericardial valve uses bovine pericardium as material to fabricate a trileaflet valve that is cut, fitted, and sewn onto a flexible Elgiloy wire frame for stress reduction (see Fig. 43-3*D*). The tissue is preserved with glutaraldehyde with no applied pressure, and the leaflets are treated with the calcium mitigation agent XenoLogiX. Compared with the Carpentier-Edwards porcine bioprosthesis, the stent profile is reduced. Long-term durability for the Carpentier-Edwards pericardial valve is strong, and compared with third-generation porcine valves, valve-related complications are similar (see discussion later in this chapter).

Hemodynamically, pericardial valves provide the best solution to flow problems. The design maximizes use of the flow area, which results in minimal flow resistance.[164] Figure 43-5*A* shows how the cone shape of the open valve and circular valve orifice minimize flow disturbance compared with the more irregular cone shape of the porcine valves that allow for central unimpeded flow (see Fig. 43-5*B*).

Structural valve deterioration is seen after long-term follow-up of patients with both porcine and pericardial bioprostheses and results in mitral stenosis or regurgitation or both. Hemodynamic studies early after operation and at 5 years reveal higher average diastolic pressure gradients and smaller effective orifice areas when compared in the same patients at the follow-up study. In some patients, these changes are sufficiently severe to require reoperation as soon as 4 to 5 years postoperatively, and by 10 years, the rate of primary tissue failure averages 30%. It then accelerates, and by 15 years postoperatively, the actuarial freedom from bioprosthetic primary tissue failure has ranged from 35 to 71%[28,29,31–33,86,88,90,91,111,120,124,134,138,165–176] (Table 43-2). Most of these patients show hemodynamic evidence of valvular deterioration prior to any clinical signs or symptoms.[132] Bioprosthetic valves have the advantage of low thrombogenicity, which must be weighed against poor long-term durability and subsequent hemodynamic deterioration and the risk of reoperation.

OPERATIVE TECHNIQUES

Preoperative Management and Anesthetic Preparation

Congestive heart failure secondary to mitral stenosis usually can be treated with aggressive diuretic therapy and sodium restriction preoperatively. If the patient is in rapid atrial

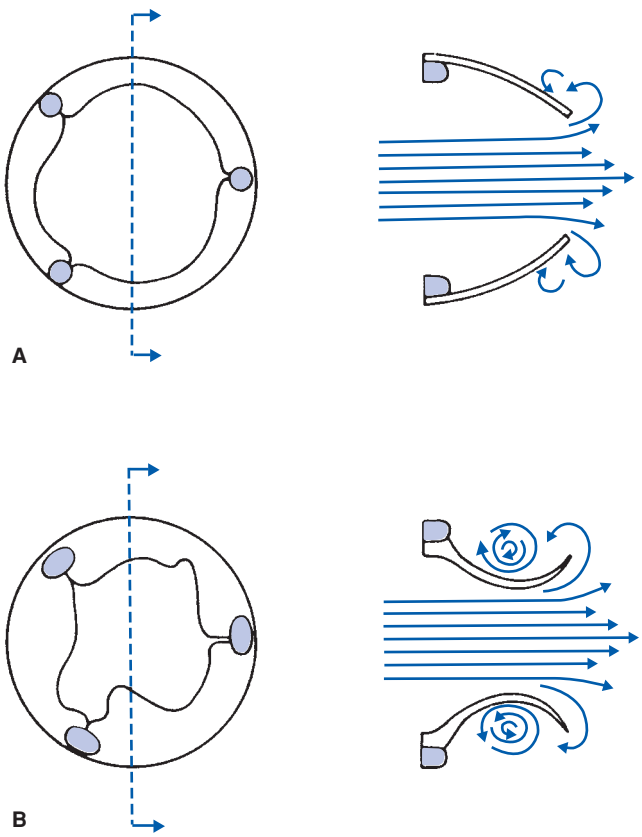

Figure 43-5. Flow patterns for bioprosthetic valves. *A.* Pericardial bioprosthesis. *B.* Porcine bioprosthesis.

Table 43–2.

Freedom (Actuarial) from Structural Valve Deterioration After Mitral Valve Replacement with Bioprotheses

Valve	Reference (year)	5 y	10 y	15 y	20 y
Hancock Standard	Cohn[166] (1989)	98%	75%	45%	
	Burdon[86] (1992)	98%	80%	44%	
	Bortolotti[165] (1995)	94%	73%	35%	
	Khan[90] (1998)				65%
Hancock II	Legarra[170] (1999)		65%		33% (18 y)
	David[167] (2001)	100%	86%	66%	
	Rizzoli[174] (2003)	99%	86%	60%	
	Masters[171] (2004)		98% (8 y)		
Carpentier-Edwards porcine	Perier[173] (1989)	89%	65%		
	Sarris[175] (1993)	97%	60%		
	Jamieson[169] (1995)	98%	72%	49%	
	Van Doorn[91] (1995)	97%	71%		
	Corbineau[88] (2001)	98%	83%	48%	
Carpentier-Edwards pericardial	Pelletier[32] (1995)	100%	79% (8 y)		
	Takahara[176] (1995)		84% (9 y)		
	Aupart[111] (1997)	100%	76%		
	Marchand[29] (1998)	98%	85% (11 y)		
	Neville[31] (1998)	100%	78% (12 y)		
	Poirer[33] (1998)	100%	81%		
Mosaic	Jasinski[124] (2000)	100% (2 y)			
	Thomson[138] (2001)	100% (4 y)			
	Eichinger[168] (2002)	100%			
	Fradet[120] (2004)	100% (7 y)			
	Jamieson[28] (2005)	98% (6 y)			
Biocor	Myken[172] (2000)			92%	
	Rizzoli[134] (2005)		100% (8 y)		

fibrillation, digoxin, beta blockers, and calcium channel antagonists can be used to slow down the ventricular rate. Patients with acute mitral regurgitation often are in cardiogenic shock, and they can be stabilized preoperatively with inotropes and arterial vasodilators to reduce systemic afterload. Intra-aortic balloon counterpulsation also can be used for this purpose. Symptoms of congestive heart failure in patients with chronic mitral regurgitation are treated with diuretics and oral vasodilators. The vasodilators lower the peripheral vascular resistance, and forward cardiac output is increased by reducing the regurgitant volume into the left atrium.

Preferred anesthesia for mitral valve replacement typically involves a combination of narcotic and inhalational agents. Ultimately, anesthetic management is dictated by the wide range of functional disabilities and hemodynamic abnormalities of patients who present for mitral valve replacement. For example, a cachectic patient with functional class IV mitral stenosis and severe pulmonary hypertension may require postoperative positive-pressure mechanical ventilation for 1 or 2 days to remove excess pulmonary fluid by diuresis, facilitate bronchial toileting, and provide optimal conditions for adequate gas exchange. Alternatively, young patients who require mitral valve surgery and present with less preoperative comorbidity may benefit from a short-acting, balanced anesthetic that can facilitate extubation within 6 hours of surgery.[177]

Monitoring should include arterial and venous lines, a urinary catheter, and a pulmonary artery catheter placed before bypass to measure pulmonary pressures and cardiac output. Following valve replacement, occasionally a left atrial catheter directly inserted through the left atrial incision can be helpful to allow measurement of pulmonary vascular resistance, but we do not use it routinely. Preoperative intravenous prophylactic antibiotics are administered to all patients and are continued for 2 postoperative days until lines are removed.

Temporary ventricular pacing wires are placed, and in many instances, temporary atrial pacing wires are placed for possible pacing or diagnosis of various atrial arrhythmias.

Management of Cardiopulmonary Bypass for Mitral Valve Replacement

Cardiopulmonary bypass is instituted by placing two right-angle cannulas into the superior and inferior venae cavae. We place a small (22F) plastic or metal cannula directly into the superior vena cava, above the sinoatrial node. The inferior caval cannula is placed at the entrance of the inferior vena cava, low in the right atrium. These insertion sites keep the caval catheters out of the operative field and yet maintain excellent bicaval drainage. An arterial cannula is placed in the distal ascending aorta. Bypass flows are approximately 1.5 L/m^2 per minute, and moderate hypothermia 28 to 32°C is used with vacuum-assisted suction. Myocardial protection includes antegrade and retrograde blood cardioplegia and profound myocardial hypothermia.[178] Retrograde cardioplegia is useful for all valve surgery to protect the ischemic left ventricle and to help remove ascending aorta bubbles. Antegrade cardioplegia, used as an initial loading dose, is augmented by intermittent retrograde cardioplegia every 20 minutes. This provides safer delivery of cardioplegia because when the atrium is retracted during valve replacement, the aortic valve is distorted, and antegrade cardioplegia tends to fill the ventricle.

Exposure of the Mitral Valve

Evolution of meticulous and complicated methods of mitral valve repair and reconstruction has required optimal exposure of the mitral valve. In primary operations, median sternotomy, development of Sondergaard's plane, and incision of the left atrium close to the atrial septum provide excellent exposure[179,180] (Fig. 43-6). This incision is a ubiquitous one, and we have rarely seen indications for use of other incisions, such as the superior approach through the dome of the left atrium,[181,182] the so-called biatrial incision popularized by Guiraudon and colleagues,[183] division of the superior vena cava,[184,185] and the less common but occasionally useful trans–right atrial septal incision.[139,186] The trans–right atrial incision has in some studies been related to higher incidence of junctional and nonsinus rhythm postoperatively,[187] although this has not been confirmed by other studies.[188]

Minimally Invasive Mitral Valve Replacement

Following advances in videoscopic and other minimally invasive techniques in many areas of surgery in the 1990s, similar techniques are now being used increasingly in cardiac surgery, especially in mitral valve surgery. In 1996, we began minimally invasive valve surgery for patients who have isolated valvular pathology without concomitant coronary artery disease. Our experience at Brigham and Women's Hospital now totals over 1000 patients, including mitral valve repairs and aortic and mitral valve replacements.[189]

The minimally invasive approach for mitral valve surgery usually is accomplished with a 5- to 7-cm midline skin incision. The superior margin of the incision is 2 cm distal to the angle of Louis, and the incision then extends caudally to a point that is 2 cm proximal to the sternoxyphoid junction. Partial lower sternotomy is performed with an oscillitating saw from the xyphoid process up to the manubrium with an angled incision made into the right second intercostal space. The pericardium is incised vertically, and pericardial stay sutures are placed at the right side of the pericardial edge. Suspension of the right side of the pericardial cradle to the sternal edges allows better exposure of the base of the heart. This approach allows excellent exposure of the left and right atrium and proximal ascending aorta. A slightly different approach is to access the right atrium through a right parasternal incision, excising the third and fourth costal cartilage. This approach, which was used in some of the early cases of minimally invasive mitral surgery, was associated with significant incidence of lung herniation and has been abandoned.

Cardiopulmonary bypass can be established in several different ways depending on the exposure of the ascending aorta and superior vena cava. The exposure depends on the habitus of the patient, as well as on the relative sizes of the right atrium and ascending aorta. If easily accessible, the ascending aorta can be cannulated directly using a Seldinger technique with a flexible aortic cannula. Both femoral and internal jugular veins are cannulated percutaneously. Percutaneous venous cannulation allows better visualization of the operative field because none of the cannulas exit the sternotomy incision. We routinely use vacuum-assisted venous drainage, which allows the use of smaller-diameter cannulas (i.e., 21F femoral venous cannula and 14F right internal jugular cannula). Tips of the cannulas are positioned in the distal parts of the superior and inferior venae cavae, respectively. The positioning of the cannulas is done under transesophageal echocardiographic guidance. After fibrillating the heart, the aortic cross-clamp is applied, and antegrade blood cardioplegia is administered through the aortic root. Systemic temperature is lowered to 28°C. The valve is approached through the left atrium as described earlier or more often the right atrium with a transseptal incision. After the valve has been replaced with a standard technique, the atrium and septum (if opened) are closed with running 4-0 Prolene. Intracardiac air is always monitored by transesophageal echocardiography, and alternate filling is used to evacuate the air by manipulating the volume of the heart on bypass. Figure 43-7 demonstrates minimally invasive reoperative mitral valve replacement.

Safety and efficacy of minimally invasive mitral valve surgery have been confirmed in several reports.[68,188–190] Trauma seems to be less with the minimally invasive incisions, which is beneficial in regard to infections (including mediastinitis) and bleeding from the incision and the operative field, leading to lesser usage of homologous blood.[190] There is also improved cosmesis with these incisions, and postoperative pain seems to be considerably less than in

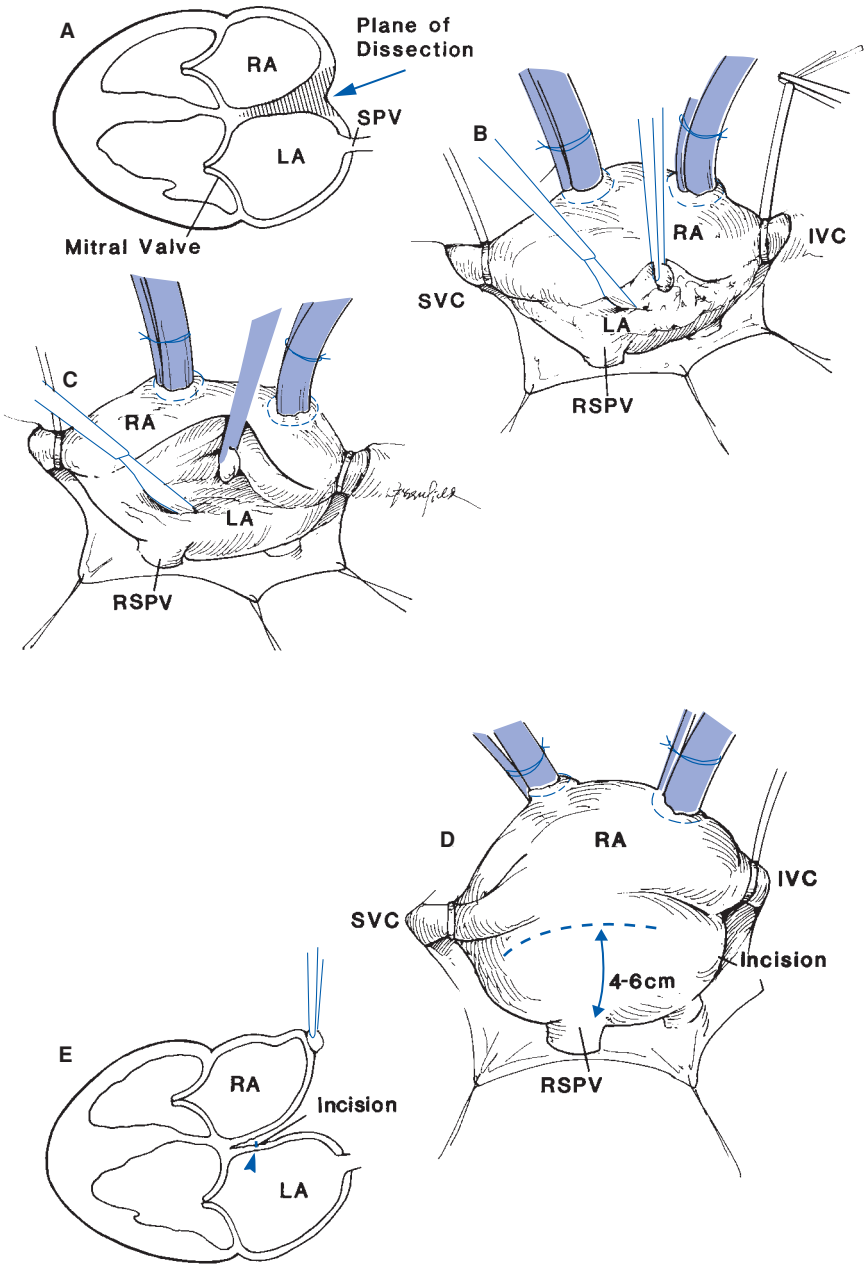

Figure 43-6. Exposure of the mitral valve. *A.* Location of Sondergaard's plane. *B,C.* Development of the interatrial plane. *D.* Location of the left atrial incision. *E.* Cross-sectional view.

patients with the median sternotomy. This can result in less requirement for pain medication and faster return to normal activity with less dependence on after-hospital stay and after-hospital care without compromising results.

Femoral arterial and venous cannulation are tolerated well in the vast majority of patients and are associated with minimal morbidity. One of the important technical aspects of cannulation is the use of a limited (2 to 3 cm) oblique suprainguinal incision just above femoral vessels. This incision, in contrast to the standard vertical incision, has been associated with minimal discomfort and a low wound infection rate because it does not transverse the inguinal skin crease and is not exposed to stretching during hip flexion and ambulation. One of the rare potential risks of femoral arterial cannulation is the development of retrograde aortic dissection or retrograde plaque embolization in patients with severe atherosclerotic disease of the descending aorta. We perform routine assessment of the descending aorta with transesophageal echocardiography prior to cannulation. If concomitant coronary artery bypass grafting is needed, a full sternotomy is necessary.

Intracardiac Technique

Operation entails secure fixation of a valve prosthesis to the annulus by reliable suture techniques without damage to adjacent structures or myocardium and without tissue interference with valve function. Implantation should prevent

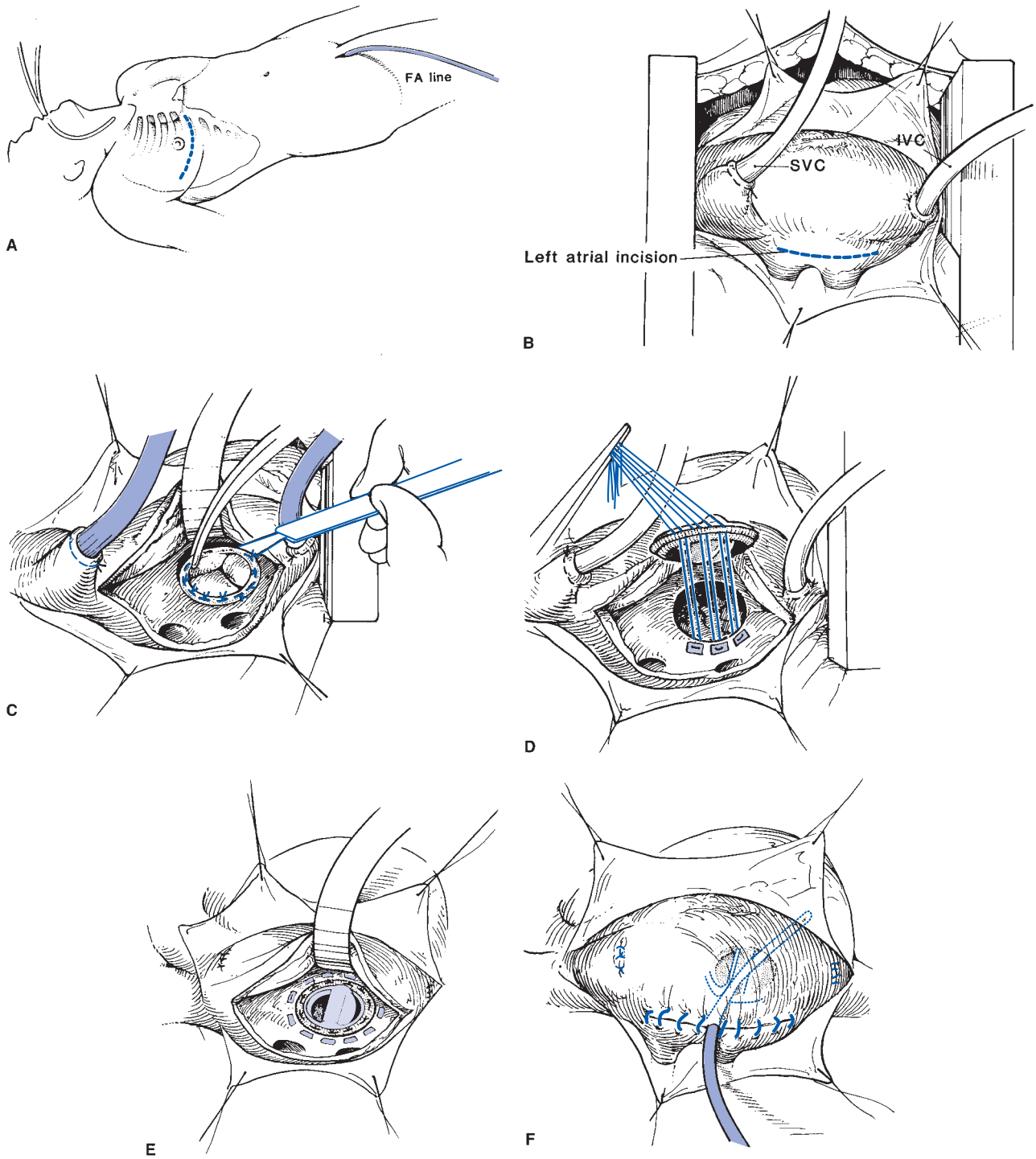

Figure 43-7. Right anterior thoracotomy for exposure of the left atrium and removal of a previously implanted mitral prosthesis. *A.* Skin incision. *B.* View of the heart and location of the left atrial incision. *C.* Excision of the previously placed bioprosthesis. *D.* Insertion of a new mechanical prosthesis with everting interrupted mattress sutures. *E.* View of new prosthesis in place. *F.* Closure of the left atrium with a catheter left across the valve to prevent left ventricular distension.

injury to anatomic structures surrounding the mitral valve annulus. Figure 43-8 shows the proximity of important cardiac structures near the mitral valve annulus. These include the circumflex coronary artery within the atrioventricular (AV) groove, the left atrial appendage, the aortic valve in continuity with the anterior mitral curtain, and the AV node.

An accumulation of laboratory and clinical evidence indicates that preservation of papillary muscle–chordal attachments to the annulus is important for

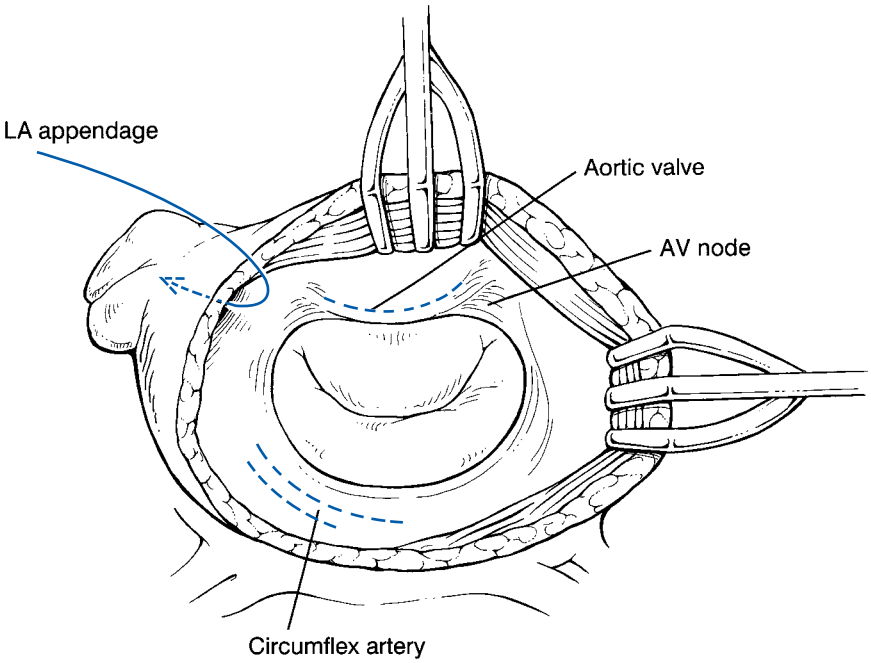

Figure 43-8. Location of important structures surrounding the mitral annulus. (*Courtesy of David Bichell, M.D.*)

maintenance of left ventricular function. In patients with mitral stenosis with agglutinated, fibrotic chordae and papillary muscles, preservation of these structures probably has little effect on left ventricular dysfunction but does protect the AV groove from rupture by preserving the posterior leaflet. However, preservation of the posterior mitral leaflet may preclude use of an adequately sized prosthesis. If fibrotic, agglutinated chordae and the posterior leaflet are excised, placement of artificial Gore-Tex chordae to reattach the papillary muscles to the annulus may improve early and late preservation of cardiac output.[191] In patients with mitral regurgitation, however, it is important to preserve as much of the papillary muscle and annular interaction as possible. This can be achieved by a variety of techniques, as shown in Fig. 43-9. The anterior leaflet may be partially excised and brought to the posterior leaflet[192] (see Fig. 43-9*A*) or can be partially excised and "furled" to the anterior annulus by a running Prolene suture[193,194] (see Fig. 43-9*B*).

Experimental and clinical evidence suggest that preservation of the conical shape of the ventricle is important to maintain normal cardiac output[195–198] and that assumption of a globular shape from cutting papillary muscles is deleterious to left ventricular function. Furthermore, preservation of the posterior leaflet and chordae has reduced the incidence of perforation of the left ventricle and atrioventricular separation dramatically during mitral valve replacement.[48,199,200]

Suturing techniques vary according to the type of valve that is implanted. The bioprosthetic valve is inserted preferentially with the sutures placed from ventricle to atrium (noneverting or subannular). This has been shown to be the strongest type of suturing technique to the mitral annulus and is used with this valve and with the central-flow Starr-Edwards ball-and-cage valve[201] (Fig. 43-10*A*).

To ensure adequate function of bileaflet or tilting-disk valves, everting sutures (atrium to ventricle to sewing ring) should be used (see Fig. 43-10*B*). This technique pushes the prosthetic valve out into the center of the orifice and minimizes any tissue interference of the prosthetic valve leaflets. This is particularly important if annular-chordal attachments are preserved. Teflon pledgeted sutures, particularly with the thin sewing rings of the currently available bileaflet and tilting-disk valves, should be used. If a bioprosthetic valve is inserted, a dental mirror is used to ensure that no annular suture is wrapped around a stent strut. A running Prolene suture for implantation of mitral valves has been advocated by some surgeons.[202,203] This technique makes a very clean suture line with minimal knots but runs the risk of valve dehiscence if an infection occurs.[204]

Prior to closure, the left atrial appendage is ligated by suture or stapled to prevent clot formation in patients with chronic atrial fibrillation, enlarged left atrium, or left atrial thrombus.[205] The atrium is closed by a running Prolene suture, making sure that endocardial surfaces are approximated. If needed, a left atrial catheter can be inserted through the suture line.

Associated Operations/Procedures

Coronary bypass is the most common procedure performed with mitral valve replacement and should be performed first. This reduces lifting of the heart after the rigid mitral valve prosthesis is in place, which can cause rupture of the myocardium or the atrioventricular

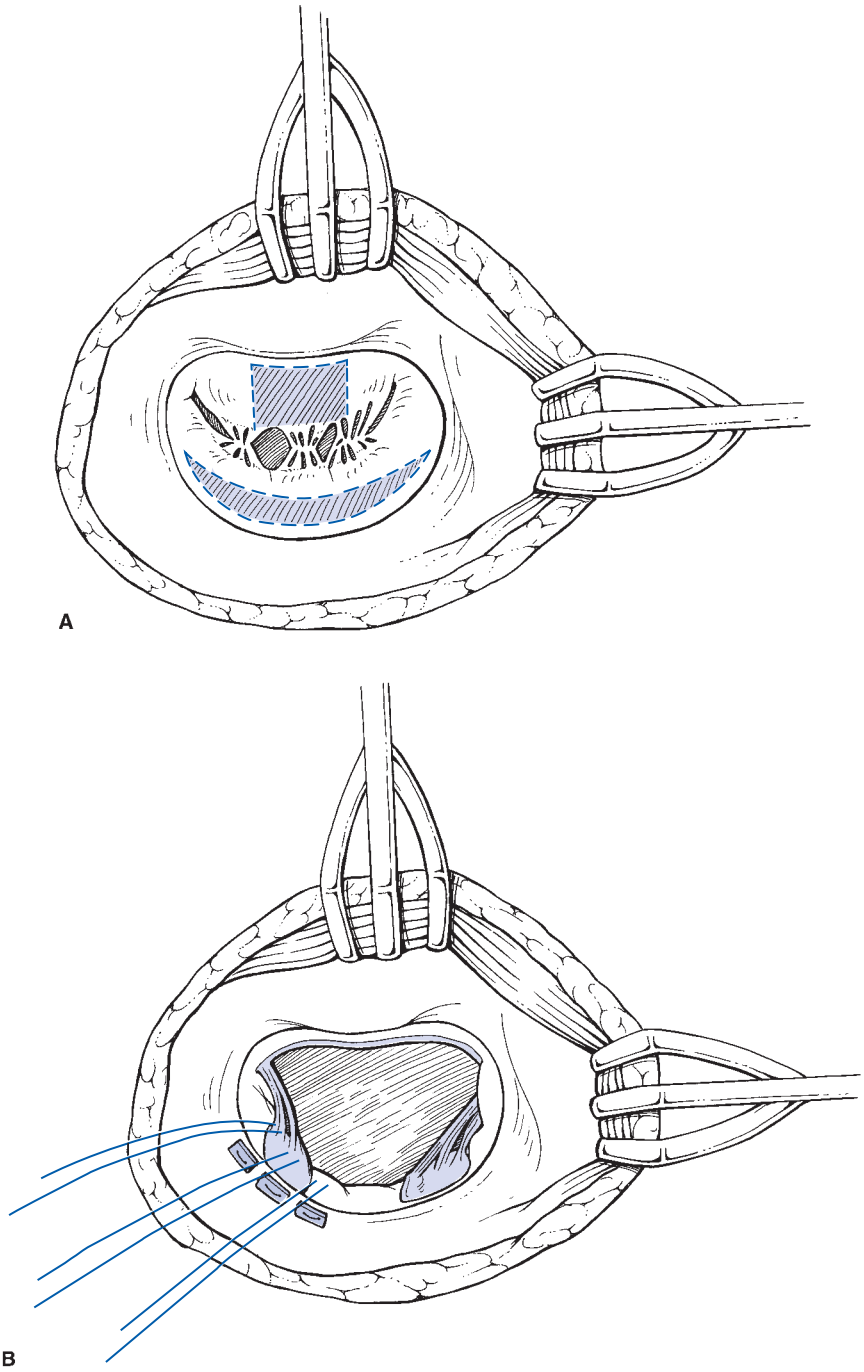

Figure 43-9. Techniques to maintain annular–papillary muscle continuity. *A.* An ellipse is removed from the posterior leaflet, and a flap is cut from the central portion of the anterior leaflet. The anterior flap is flipped to the posterior annulus and tacked to the caudad edge of the posterior leaflet and the posterior annulus. Sutures anchoring the prosthesis include the annulus and anterior and posterior leaflet remnants to which chordae are attached. *B.* The anterior leaflet is partially excised, and remnants are "furled" to the annulus by sutures used to insert the prosthesis.

groove. This also allows cardioplegia to be delivered through the bypass grafts.

Tricuspid valve repair or replacements usually are performed after replacing the mitral valve. In these cases, the mitral valve often is approached through the right atrium and a transseptal incision. After the mitral valve prosthesis is in place, the septum is closed, and the aortic cross-clamp is removed before proceeding with the tricuspid valve procedure.[206]

When both the aortic and mitral valves are replaced at the same operation, most surgeons begin with excising the aortic valve before proceeding with the mitral valve procedure. When excising the anterior mitral valve leaflet, care must be taken not to injure the aortic annulus and the intra-annular region. The aortic valve then is sewn in after the mitral valve is in place.

Weaning Off Cardiopulmonary Bypass

We use transesophageal echocardiography for every valve operation and particularly for mitral valves, where excellent images can be obtained. If transesophageal echocardiography is contraindicated (e.g., because of esophageal disease), direct epicardial echocardiography can be used. The echocardiograms

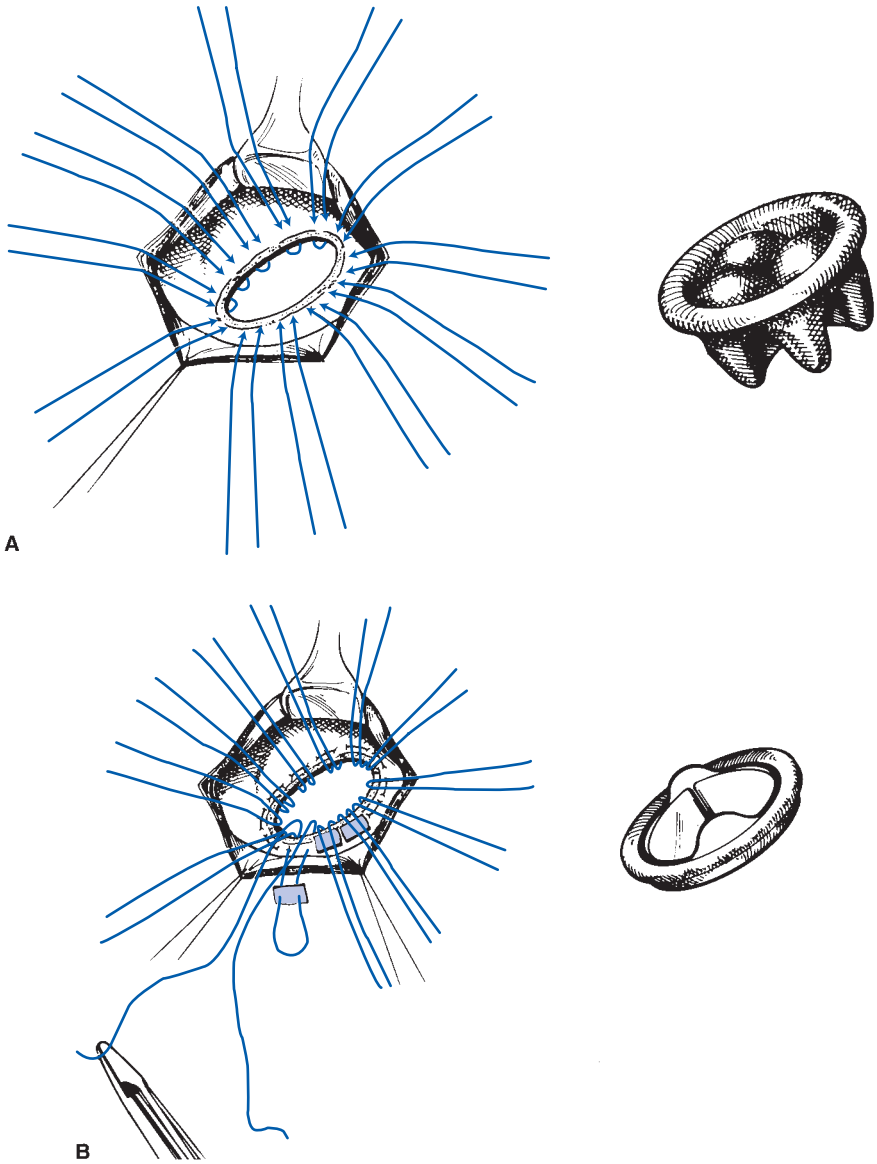

Figure 43-10. Suturing techniques for prosthetic mitral valve implantation. Noneverting (subannular) sutures placed from ventricle to atrium for bioprosthetic or Starr-Edwards valves. Everting (supra-annular) sutures placed from atrium to ventricle for bileaflet or tilting-disk valves.

provide information about valve and left ventricular function, possible retained material in the left atrium including thrombus, and removal of intracardiac air.

A careful deairing at the end of the operation is essential. The heart is vented through the left atrium and the ascending aorta and sometimes the left ventricle. Before the aortic cross-clamp is removed, the patient's head is lowered and the lungs inflated carefully to dislodge any air bubbles in the pulmonary vein. The operating table then is tilted from side to side, the left atrial appendage is inverted, and the cardiac chambers are aspirated if necessary. Once deairing maneuvers are completed, and after the patient is completely rewarmed, venous return is partially occluded, and the heart is gradually volume loaded. Pulmonary artery pressures are monitored carefully. Pharmacologic agents, such as amrinone or dobutamine, particularly for right ventricular overload, are used frequently.

Deairing the heart after a minimally invasive approach is more complex because the heart is only partially visible through the 5- to 7-cm sternal incision, and the apex of the heart is not accessible. Flooding the operative field with continuous CO_2 can be beneficial in reducing intracardial air.[207] In addition, by filling the left ventricle with cardioplegia through the left atriotomy suture line, and by manipulating the volume of the heart on bypass and alternating the position of the patient, air can be evacuated effectively.

POSTOPERATIVE CARE

Postoperative care is directed toward the resumption of normal cardiac output, respiratory function, temperature

control, electrolyte management, adequate renal flow, and prophylaxis against bleeding. Patients with low cardiac output are managed with a variety of pharmacologic agents after providing adequate volume loading. Left atrial and especially pulmonary arterial catheters are particularly helpful in determining optimal balancing of volume loading and myocardial function in the first hours following operation.

Reduction of pulmonary interstitial fluid is pursued aggressively by diuresis in the intensive-care unit in patients with severe pulmonary hypertension. Most patients with severe pulmonary hypertension can be extubated within 48 hours of surgery. Nutritional, respiratory, and general metabolic support is provided. Many patients with severe, long-standing mitral valve disease are cachectic and, despite preoperative nutritional support, are severely catabolic at the time of operation. These patients generally require longer periods of ventilatory support owing to lack of respiratory muscle strength. They need aggressive nutritional support with nasogastric hyperalimentation to increase respiratory muscle strength. In patients with severe pulmonary hypertension and cardiac cachexia who require prolonged intubation, tracheostomy may be necessary to reduce ventilatory dead space and facilitate faster weaning and better pulmonary toilet. Tracheostomy usually is performed by the end of the first postoperative week.

Postoperative atrial arrhythmias are so common that their absence is unusual. Arrhythmias vary from rapid supraventricular tachycardias, usually atrial fibrillation, to junctional rhythm and heart block. These arrhythmias are treated by pharmacologic agents, pacemakers, or both. If rapid atrial fibrillation cannot be controlled pharmacologically and is destabilizing hemodynamically, emergency cardioversion is done to improve cardiac output. Pharmacologic management of supraventricular tachycardia usually is required but may precipitate the need for a prophylactic transvenous pacemaker if severe slowing of the heart rate occurs.

Anticoagulation is prescribed for all patients undergoing mitral valve replacement with either a mechanical or a bioprosthetic valve. In the first 6 weeks following operation, the incidence of atrial and other arrhythmias is high; thus these fluctuating rhythms mandate anticoagulation even if the basic rhythm is sinus. In addition to rhythm concerns, the left atrial incisions and the possibility of stasis in the left atrial appendage justify full anticoagulation with warfarin for all patients. Some surgeons advocate immediate intravenous heparin until therapeutic warfarin doses can be reached.[208,209] Low-molecular-weight heparin (LMWH) also can be used.[210,211]

The therapeutic international normalized ratio (INR) after mitral valve replacement is 2.5 to 3.5 depending on the type of valve, cardiac rhythm, and presence or absence of the aforementioned intraoperative risk factors for thromboembolism.[35,205,209,210] Anticoagulation levels are in the low range for patients in sinus rhythm who received tissue valves. Patients who have mechanical valves need lifelong anticoagulation. Patients who have bioprosthetic valves are evaluated at 6 to 12 weeks for cardiac rhythm abnormalities. If they are in predominantly sinus rhythm, warfarin is stopped, and one aspirin tablet is given daily indefinitely. If the patient has continuous atrial fibrillation or fluctuating rhythms, anticoagulation with warfarin is continued. This is also true for patients with a history of previous embolism or in whom thrombus is found in the left atrium at operation.

Warfarin usually is started on the second postoperative day. Addition of aspirin, 80 to 150 mg daily, to the warfarin may reduce the risk of thromboembolism[212,213] and may have a role in patients with prosthetic valves.[214]

RESULTS

Early Results

The hospital mortality for mitral valve replacement with and without coronary bypass grafting has decreased significantly since the inception of mitral valve surgery. The current risk (2006) of elective primary mitral valve replacement with and without coronary bypass grafting is 5 to 9% in most studies (range 3.3 to 13.1%).[15,17,27–29,90,91,111,138,172,195,215–223] Operative (30-day) mortality is related to myocardial failure, multisystem organ failure, bleeding, respiratory failure in the chronically ill, debilitated individual, diabetes, infection, stroke, and very rarely, technical problems.[65,82] Mortality is correlated with preoperative functional class, age, and preexisting coronary artery disease.[216,224,225]

Published results on mitral valve surgery have improved in recent years,[226] probably because of preservation of papillary muscles, preventing midventricular rupture,[199,200] and preservation of the normal geometry of the left ventricle, which aids in the maintenance of early postoperative cardiac output.[195,196,227] Mitral valve replacement and coronary artery bypass surgery 20 to 25 years ago had an associated mortality of about 10 to 20%.[81,228] This mortality risk also has decreased as myocardial protection has improved with the use of blood cardioplegia and retrograde methods of administration.[178,229] Some studies have indicated that the risk of combined mitral valve replacement–coronary artery bypass grafting is now no greater than that of mitral valve repair with an annuloplasty ring or mitral valve replacement without coronary artery bypass grafting.[195,230] Other studies have shown significantly increased morbidity and mortality with the addition of coronary artery bypass grafting.[85,231] Figures from the database of the Society of Thoracic Surgeons indicate that both reoperation and emergency operation increase operative mortality[232] (Fig. 43-11).

Late Results

Functional improvement

In over 90% of patients following mitral valve replacement, functional class improves to at least class II. A small group of

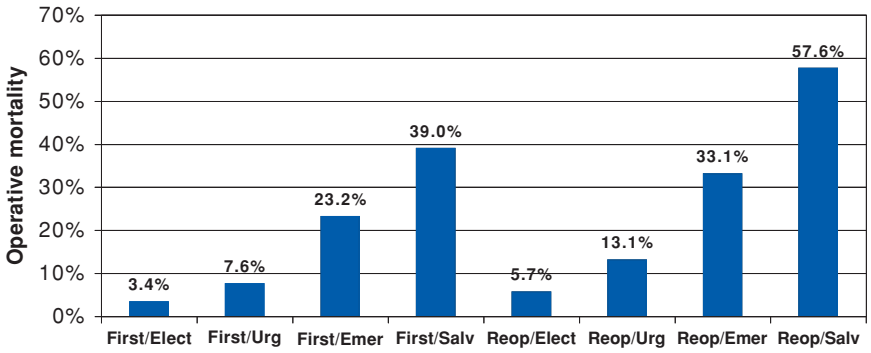

Figure 43-11. Operative mortality for elective, urgent, emergency, and salvage procedures for primary operations and reoperations for mitral valvular replacements. (*Data used with permission from Society of Thoracic Surgeons.*)

patients remains in class III or IV depending on left ventricular function prior to surgery or other coexisting morbidity.

Survival

The causes of late death in patients following mitral valve replacement are primarily chronic myocardial dysfunction, thromboemboli and stroke, endocarditis, anticoagulant-related hemorrhage, and coronary artery disease. The extent of left ventricular dysfunction and patient age, particularly if myocardial and coronary diseases are combined, also correlate with late mortality. The probability of survival after mitral valve replacement at 10 years is usually around 50 to 60% (range 42 to 81%)[15,17,22,23,27–29,31–33,86,90,91,111,112,117,120,134,135,138,145,146,166,170–172,174–176,215,216,218–220,222,223,233–259] (Table 43-3). Long-term patient survival seems to be similar for patients with biologic and mechanical mitral valves.[260–263] Unlike patients with severe aortic regurgitation or aortic stenosis, arrhythmias seldom cause sudden death in patients following mitral valve replacement; however, a few patients die from thromboembolic stroke owing to chronic atrial fibrillation.[244] The fact that more than 50% of patients following mitral valve replacement are in chronic atrial fibrillation increases the propensity for thromboembolic stroke despite anticoagulation and for mechanical valve thrombosis if the anticoagulation protocol is altered. In addition, patients with older types of prosthetic valves who receive higher-intensity anticoagulation may develop severe anticoagulant hemorrhage.[264]

In patients with bioprosthetic valves, one of the important determinants of mortality is reoperation secondary to structural valve degeneration[27,29,31–33,90,91,111,120,124,134,166–168,170,173–175,256,265–268] (Table 43-4). Reoperative mitral valve replacement mortality has decreased significantly in the last 15 years to under 10%, even in patients who have required multiple mitral valve reoperations.[229,269] At the Brigham and Women's Hospital, operative mortality was less than 6% for reoperative mitral valve operations from 1990 to 1995.[229] Improved myocardial protection, earlier selection of patients for reoperation, and better perfusion techniques, including frequent femorofemoral bypass to protect the right ventricle during incision and dissection of the heart, are factors contributing to decreased mortality.[195,229,270–272]

Late morbidity

The major morbidity in patients following mitral valve replacement is structural valve deterioration of a bioprosthetic valve and thromboembolism and anticoagulant hemorrhage with a mechanical prosthesis. Both valve types develop perivalvular leak and infection.

THROMBOEMBOLISM: Thromboembolism is perhaps the most common complication of both biologic and mechanical mitral prostheses but is more frequent in patients with mechanical valves. Chronic atrial fibrillation and local atrial factors, discussed earlier, increase the risk of thromboembolism in patients with mitral prostheses.[13,22,24,240,273] A number of recent studies have summarized the thromboembolic potential of various valves[13,17,22,27,29,31–33,91,111,112,117,134,136,138,141,144,145,150,160,162,165,166,168,172–174,209,215–217,222,223,234–237,239,240,245,246,248,250,252–256,257–259,266,274–286] (Table 43-5), and it appears that the better the valve hemodynamics, the lower is the probability of thromboemboli. The incidence of thromboemboli in currently available bileaflet and tilting-disk valves is similar to that in bioprosthetic valves—about 1.5 to 2.0% per patient-year. Thromboembolism in patients with mitral valve replacement is lower in those with a small left atrium, sinus rhythm, and normal cardiac output. It is much higher in patients with a large left atrium, chronic atrial fibrillation, and the presence of intra-atrial clot.[205,287] Thrombosis of a mechanical valve, once a feared complication of tilting-disk valves,[288,289] is now relatively rare unless anticoagulation is stopped for any period of time. Valve thrombosis can be treated with thrombolytic agents if the patient is not in cardiogenic shock but requires surgery if the circulation is inadequate.[290,291]

ANTICOAGULANT HEMORRHAGE: Bleeding related to anticoagulation is seen most commonly in the gastrointestinal, urogenital, and central nervous systems and usually is proportionate to the INR. The incidence of anticoagulant-related hemorrhage has decreased markedly with hemodynamic improvements in mitral valve prostheses. New valves do not require the intensity of anticoagulation of older prostheses. For example, the distinctive Starr-Edwards ball-and-cage valve requires an INR of 3.5 to 4.5.[264] Patients with streamlined bileaflet or tilting-disk valves require an

Table 43–3.

Actuarial Survival Following Mitral Valve Replacement

Valve	Reference (year)	Actuarial survival				
		5 y	10 y	15 y	20 y	30 y
Starr-Edwards	Teply[249] (1981)	78%	56%			
	Sala[135] (1982)	78%	72%			
	Miller[145] (1983)	71%	47%			
	Godje[239] (1997)	85%	75%	56%	37%	23%
	Murday[146] (2003)		57% (8 y)			
	Gao[218] (2004)		51%		23%	8%
Omniscience/Omnicarbon	Damle[236] (1987)	91% (4 y)				
	Peter[246] (1993)	77% (4 y)				
	Otaki[257] (1993)	82% (6 y)				
	Misawa[255] (1993)	94% (3 y)				
	Thevenet[258] (1995)		88% (9 y)			
	Iguro[254] (1999)	88%				
	Torregrosa[259] (1999)		81%			
	di Summa[117] (2002)		61%			
Medtronic Hall	Vallejo[251] (1990)	79%				
	Masters[244] (1995)	70%	67%			
	Fiore[15] (1998)	70%	58%			
	Butchart[216] (2001)		58%	36%		
	Masters[243] (2001)	75%	63%			
St. Jude	DiSesa[238] (1989)	65% (4 y)				
	Kratz[240] (1993)	80%	63%			
	Aoyagi[215] (1994)	88%	81%			
	Fiore[15] (1998)	65%	53%			
	Camilleri[234] (2001)	89% (4 y)				
	Remadi[17] (2001)	88%	76%	61%		
	Masters[243] (2001)	75%	52%			
	Lim[241] (2003)	72%				
	Murday[146] (2003)		44% (8 y)			
Carbomedics	Bortolotti[233] (1991)	90%				
	Rabelo[247] (1991)	75% (4 y)				
	De Luca[237] (1993)	93% (3 y)				
	Copeland[235] (1995)	81%				
	Nistal[245] (1996)	83%				
	Yamauchi[253] (1996)	92%				
	Masters[243] (2001)	76%				
	Santini[222] (2002)	86%	86%			
	Lim[241] (2002)	72%				
	Soga[248] (2002)	88%				
	Ikonamidis[219] (2003)		61%		39%	
	Tominaga[250] (2005)	95%	94%			
	Kang[220] (2005)		89%			
	Carrier[112] (2006)	76%	59%	40%		
	Wu[223] (2006)	74%	54%			
ON-X	Williams[252] (2006)	87% (4 y)				

Table 43–3.

Actuarial Survival Following Mitral Valve Replacement *(Continued)*

Valve	Reference (year)	Actuarial survival 5 y	10 y	15 y	20 y	30 y
Hancock standard	Cohn[166] (1989)	82%	60%			
	Burdon[86] (1992)	74%	55%			
	Sarris[175] (1993)	79%	58%			
	Khan[90] (1998)		50%	29%	14%	
Hancock II	Legarra[170] (1999)		65%		33% (18 y)	
	Rizzoli[174] (2003)	72%	49%	37%		
	Masters[171] (2004)		57% (8 y)			
	Borger[27] (2006)		50%		6%	
Carpentier-Edwards standard	Akins[22] (1990)	53%	45%			
	Louagie[242] (1992)	61%	46%			
	Bernal[23] (1995)	89%	80%			
	Pelletier[32] (1995)	83%	62% (8 y)			
	van Doorn[91] (1995)	75%	53%			
	Murakami[256] (1996)		75%			
	Marchand[29] (1998)		53% (11 y)			
Carpentier-Edwards pericardial	Takahara[176] (1995)		59% (9 y)			
	Aupart[111] (1997)	78%	71%			
	Marchand[29] (1998)		53% (11 y)			
	Neville[31] (1998)		54% (12 y)			
	Porier[33] (1998)	84%	58%			
Mosaic	Jasinski[124] (2000)	100% (3 y)				
	Thomson[138] (2001)	79% (4 y)				
	Fradet[120] (2004)	83 (7 y)				
	Jamieson[28] (2005)	74% (6 y)				
Biocor	Myken[172] (2000)		55%	25%		
	Rizzoli[134] (2005)	55%	51%			

INR of between 2.5 and 3.5; thus the incidence of anticoagulant hemorrhage is reduced significantly in the newer, hemodynamically improved prostheses.[238,292] Table 43-5 lists the incidence of anticoagulant hemorrhage with various bioprostheses and mechanical valves.[13,17,22,27,29,31–33,91,111,112,117,134,136,138,141,144,145,150,160,162,165,166,168,172–174,209,215–217,222,223,234–237,239,240,245,246,248,250,252–256,257–259,266,274–286]

Structural valve degeneration

Structural valve degeneration (SVD) is the most important complication of the bioprosthetic valve. The probability of structural failure with currently available porcine valves (Hancock or Carpentier-Edwards) begins to increase 8 years after operation and reaches over 60% at 15 years.[27,88,90,170,267] This finite durability is a major impediment to long-term success of these biologic prostheses, even though the failure rate in a patient 70 years of age or older is significantly less than in younger age groups[22,27,29,31–33,88,111,166,167,169,172,174] (Table 43-6). Structural valve degeneration presents as either mitral regurgitation from leaflet tear or calcific mitral stenosis owing to calcification of valve leaflets or as both. The appearance of a new murmur with new congestive symptoms should prompt a noninvasive investigation of the prosthesis and elective re-replacement if dysfunction is documented. Structural valve degeneration leading to reoperation is the cause for at least two-thirds of the reoperations in patients with bioprostheses.[22,270,271] The probabilities of structural

Table 43–4.

Freedom from Reoperation

Valve	Reference (year)	Actuarial freedom from reoperation		
		5 y	10 y	15 y
Hancock	Cohn[166] (1989)	96%	79%	41%
	Perier[173] (1989)	88%	59%	
	Bernal[265] (1991)	92%	69%	25%
	Sarris[175] (1993)	93%	69%	
	Khan[90] (1998)		44%	
Hancock II	Legarra[170] (1999)		77%	37% (18 y)
	David[167] (2001)	98%	85%	69%
	Rizzoli[174] (2003)	97%	88%	70%
	Borger[27] (2006)		88%	44 (20 y)
Carpentier-Edwards standard	Perier[173] (1989)	91%	64%	
	Jamieson[93] (1991)	94%	64%	39%
	Sarris[175] (1993)	91%	57% (8 y)	
	Van Doorn[91] (1995)	95%	69%	
	Glower[266] (1998)	94%	65%	30%
Carpentier-Edwards pericardial	Pelletier[32] (1995)	98%	67% (8 y)	
	Murakami[256] (1996)	100%	77%	
	Aupart[111] (1997)		90%	
	Marchand[29] (1998)		83% (11 y)	
	Neville[31] (1998)		76% (12 y)	
	Poirer[33] (1998)	99%	76%	
Mosaic	Jasinski[124] (2000)	100% (3 y)		
	Eichinger[168] (2002)	95%		
	Fradet[120] (2004)	97% (7 y)		
Biocor	Myken[273] (1995)			79%
	Rizzoli[134] (2005)	95%	91%	

valve degeneration at 5, 10, and 15 years of the six most commonly used biologic prostheses are shown in Table 43-2. With current quality controls, the incidence of structural valve degeneration is virtually zero for bileaflet, tilting-disk, and ball-and-cage valves.

Perivalvular leak

Perivalvular leak is an uncommon complication that usually depends on technical factors. Patient-related factors such as endocarditis and calcifications involving the annulus are also important. Perivalvular leak usually causes refractory hemolytic anemia in contrast to the milder chronic hemolysis seen after implantation of some of the mechanical valves, especially the tilting-disk valves.[293]

Because of improved surgical techniques and the use of Teflon pledgets, the incidence of perivalvular leak has fallen and is about 0 to 1.5% per patient-year for both mechanical and biologic valves.[13,247,259,276,286,294] Perivalvular leak is slightly more common with the bileaflet valve than with the porcine valve because of the need for the everting suture technique and less bulky sewing ring.[295,296] Surgery should be offered to all symptomatic patients and even patients with mild symptoms who require blood transfusions.[294]

Endocarditis

Endocarditis is a feared complication after valve replacement, and prosthetic mitral valve endocarditis often presents difficult management problems related to timing of opera-

Table 43–5.

Incidence of Thromboembolism and Anticoagulant-Related Hemorrhage

Valve	Reference (year)	Incidence of thromboembolism (%/pt-y)	Incidence of anticoagulant-related bleeding (%/pt-y)
Starr-Edwards	Miller[145] (1983)	5.7	3.7
	Akins[274] (1987)	3.9	2.4
	Agathos[144] (1993)	6.6	2.2
	Godje[239] (1997)	1.3	0.6
Omniscience/Omnicarbon	Cortina[278] (1986)		2.7
	Damle[236] (1987)	2.5	
	Akalin[150] (1992)	1.0	2.7
	Peter[246] (1993)	1.7	0.9
	Otaki[257] (1993)	0.7	0.0
	Misawa[255] (1993)	1.8	0.0
	Ohta[283] (1995)	1.1	0.8
	Thevenet[258] (1995)	0.9	1.1
	Iguro[254] (1999)	1.0	0.6
	Torregrosa[259] (1999)	0.6	0.8
	di Summa[117] (2002)	0.4	0.2
Medtronic Hall	Antunes[276] (1988)	4.2	1.5
	Beaudet[277] (1988)	2.1	3.2
	Akins[275] (1991)	1.8	3.2
	Butchar[216] (2001)	4.0	1.4
St. Jude	Czer[13] (1990)	1.9	2.1
	Kratz[240] (1993)	2.9	2.2
	Jegaden[209] (1994)	1.5	0.9
	Aoyagi[215] (1994)	1.1	0.3
	Nistal[245] (1996)	3.7	2.8
	Camilleri[234] (2001)	1.9	1.5
	Khan[281] (2001)	3.0	1.9
	Ramadi[17] (2001)	0.7	0.9
	Emery[217] (2005)	2.8	2.7
Carbomedics	De Luca[237] (1993)	0.8	0.0
	Copeland[235] (1995)	0.6	1.5
	Nistal[245] (1996)	0.9	2.8
	Yamauchi[253] (1996)	1.6	1.5
	Jamieson[280] (2000)	4.6	2.7
	Soga[248] (2002)	0.8	1.3
	Santini[222] (2002)	2.2	
	Tominaga[250] (2005)	1.8	0.9
	Carrier[112] (2006)	0.7	0.7
	Wu[223] (2006)	0.5	0.4
ATS	Shiono[136] (1996)		0.0
	Westaby[141] (1996)	0.0	
	Emery[279] (2004)	3.0	2.3
	Stefanitis[284] (2005)	0.5	0.0
ON-X	Laczkovics[160] (2001)	1.8	0.0
	Moidl[282] (2002)	1.7	1.4
	McNicholas[162] (2006)	1.6	3.1
	Williams[252] (2006)	1.5	1.0

Table 43–5.

Incidence of Thromboembolism and Anticoagulant-Related Hemorrhage *(Continued)*

Valve	Reference (year)	Incidence of thromboembolism (%/pt-y)	Incidence of anticoagulant-related bleeding (%/pt-y)
Hancock standard	Cohn[166] (1989)	2.4	0.4
	Perier[173] (1989)	1.1	1.0
	Bortolotti[165] (1995)	1.4	0.7
Hancock II	Rizzoli[174] (2003)	1.7	1.1
	Borger[27] (2006)		
Carpentier-Edwards Porcine	Perier[173] (1989)	0.8	1.0
	Akins[22] (1990)	1.4	1.2
	Jamieson[286] (1987)	2.4	0.7
	van Doorn[91] (1995)	1.9	
	Glower[266] (1998)	1.7	0.7
Carpentier-Edwards Pericardial	Pelletier[32] (1995)	1.5	0.3
	Murakami[256] (1996)	0.6	0.0
	Aupart[111] (1997)	0.7	1.2
	Marchand[29] (1998)	1.2	1.0
	Neville[31] (1998)	0.6	1.1
	Poirer[33] (1998)	1.7	0.3
Mosaic	Fradet[285] (2001)	1.4	1.1
	Thomson[138] (2001)	0.2	0.9
	Eichinger[168] (2002)	0.8	2.0
Biocor	Myken[172] (2000)	2.1	1.1
	Rizzoli[134] (2005)	2.0	1.1

tion, type of operation, ability to fix the prosthesis securely, and operative and late survival. Mitral valve endocarditis is considerably less common than aortic prosthetic valve endocarditis,[297] but when it does appear, it may present as septicemia, malignant burrowing infections, abscess formation, and septic emboli. With better antibiotic prophylaxis at the time of mitral surgery and improved prophylaxis for all patients having dental or other surgical procedures, the incidence of endocarditis is relatively low.

The incidence of prosthetic endocarditis is usually higher during the initial 6 months after surgery and thereafter declines to a lower but persistent risk.[36] The probability of freedom from this morbid event is shown in Table 43-7 for both mechanical and bioprosthetic valves.[15,22,27,29,31–33,91,111,112,117,120,124,134,138,144,145,160,162,165–168,170–172,174,175,215–217,219,222,223,234–237,239,240,242–246,248,250,252,253,255–259,265,274–276,279–284,298–301]

Biologic and mechanical valves seem to have a similar incidence of endocarditis, except for the initial months after valve implantation, when mechanical prostheses carry a greater risk of infection.[302]

The diagnosis and treatment of mitral perivalvular endocarditis are related to the infecting organism. The diagnosis is made by symptoms or the appearance of a new murmur, a septic embolus, or a large vegetation on echocardiogram. Blood cultures usually are positive, although a small percentage of patients have culture-negative endocarditis. Echocardiograms may show a rocking motion of the prosthesis and the presence of vegetations. The most frequent organisms are still *Streptococcus* and *Staphylococcus;* the latter is usually hospital-acquired. Antibiotic therapy depends on the sensitivity of the organisms, but immediate high-dose intravenous therapy must begin as soon as possible. Experience indicates that a number of patients with bioprosthetic valvular endocarditis can be "cured" of low-potency organisms such as *Streptococcus.* However, it is unlikely that antibiotics alone can sterilize more virulent mitral valve infections, particularly *Staphylococcus.* These infections usually require urgent and sometimes emergent surgery because of invasion of the cardiac exoskeleton.

Table 43–6.

Freedom (Actuarial) from SVD by Age

Valve	Reference (year)	Age	Freedom from SVD 5 y	10 y	15 y
Hancock	Cohn[166] (1989)	≤40		68%	
		41–69		84%	
		≥70		84%	
Hancock II	David[167] (2001)	<65			76%
		≥65			89%
	Rizzoli[174] (2003)	<65			82%
		≥65			92%
	Borger[27] (2006)	<65			27% (20 y)
		≥65			59% (20 y)
Carpentier-Edwards standard	Akins[22] (1990)	≤40		71%	
		41–50		82%	
		51–60		65%	
		61–70		79%	
		≤70		98%	
	Jamieson[169] (1995)	≤35	79%	51%	
		36–40	99%	68%	48%
		51–64	98%	72%	42%
		65–69	98%	74%	64%
		≥70	100%	90%	90%
	Corbineau[88] (2001)	≤35			0% (14 y)
		36–50			22% (14 y)
		51–60			34% (14 y)
		61–65			50% (14 y)
		66–70			93% (14 y)
		≥70			96% (14 y)
Carpentier-Edwards pericardial	Aupart[111] (1997)	<60	47%		
		≥60	100%		
	Pelletier[32] (1995)	≤59	100%	64% (8 y)	
		60–69	100%	91% (8 y)	
		≥70	100%	100% (8 y)	
	Marchand[29] (1998)	≤60		78% (11 y)	
		61–70		89% (11 y)	
		>70		100% (11 y)	
	Neville[31] (1998)	<60		70%	
		≥60		100%	
	Poirer[33] (1998)	<60	100%	78%	
		60–69	100%	78%	
		≥70	100%	100%	
Biocor	Myken[172] (2000)	<50			71%
		51–60			90%
		>61			100%

Table 43–7.

Prosthetic Valve Endocarditis

Valve	Reference (year)	PVE rate (%/pt-y)	Freedom from PVE at 5 y
Starr-Edwards	Miller[145] (1983)	0.5	97%
	Akins[274] (1987)	0.4	95%
	Agathos[144] (1993)	0.6	
	Godje[239] (1997)		99% (10 y)
Omniscience/Omnicarbon	Carrier[298] (1987)	0.8	98%
	Damle[236] (1987)	0.8	98%
	Peter[246] (1993)	0.0	100%
	Otaki[257] (1993)	1.5	
	Misawa[255] (1993)	0.0	100% (3 y)
	Ohta[283] (1995)	0.5	
	Thenevet[258] (1995)	0.2	
	Torregrosa[259] (1999)	0.2	99% (10 y)
	di Summa[117] (2002)	0.0	100% (10 y)
Medtronic Hall	Keenan[300] (1990)	0.5	98%
	Akins[275] (1991)	0.1	100%
	Fiore[15] (1998)		94% (10 y)
	Masters[244] (1995)	0.1	
	Butchart[216] (2001)	0.4	94% (10 y)
	Masters[243] (2001)	0.6	
St. Jude	Antunes[276] (1988)	0.5	97%
	Kratz[240] (1993)	0.4	
	Aoyagi[215] (1994)	0.1	100%
	Fiore[15] (1998)		100% (10 y)
	Camilleri[234] (2001)	0.8	
	Masters[243] (2001)	0.4	
	Khan[281] (2001)	0.3	
	Ikonamidis[219] (2003)		98% (10 y)
	Emery[217] (2005)	0.3	
Carbomedics	De Luca[237] (1993)	0.0	100%
	Copeland[235] (1995)	0.3	96%
	Nistal[245] (1996)	0.0	100%
	Yamauchi[253] (1996)	0.0	100%
	Jamieson[280] (2000)	0.4	
	Masters[243] (2001)	0.6	
	Santini[222] (2002)		100%
	Soga[248] (2002)	0.0	100%
	Tominaga[250] (2005)	0.3	97% (10 y)
	Carrier[112] (2006)	0.3	97% (15 y)
	Wu[223] (2006)	0.4	98% (10 y)
ATS	Emery[279] (2004)	0.4	
	Stefanitis[284] (2005)	0.0	100%
ON-X	Laczkovics[160] (2001)	0.5	
	Moidl[282] (2002)	0.7	99% (2 y)
	Williams[252] (2006)		95% (4 y)
	McNicholas[162] (2006)	0.0	100%

Table 43–7.

Prosthetic Valve Endocarditis (*Continued*)

Valve	Reference (year)	PVE rate (%/pt-y)	Freedom from PVE at 5 y	
Hancock standard	Cohn[166] (1989)		93%	
	Bernal[265] (1991)	0.3		
	Sarris[175] (1993)		93%	
	Bortolotti[165] (1995)	0.3		
Hancock II	Legarra[170] (1999)		97% (15 y)	
	David[167] (2001)		91% (15 y)	
	Rizzoli[174] (2003)	0.4	96% (15 y)	
	Masters[171] (2004)		99% (8 y)	
	Borger[27] (2006)		85% (20 y)	
Carpentier-Edwards porcine	Pelletier[301] (1989)	0.4		
	Akins[22] (1990)	1.0		
	Louagie[242] (1992)	0.0	100%	
	Sarris[175] (1993)		91%	
	van Doorn[91] (1995)		97%	92% (10 y)
	Glower[266] (1998)	0.3	97%	96% (10 y)
Carpentier-Edwards pericardial	Pelletier[32] (1995)	0.3%	93% (10 y)	
	Murakami[256] (1996)	0.86	94% (10 y)	
	Aupart[111] (1997)	0.4%	97% (10 y)	
	Marchand[29] (1998)	0.1%		
	Neville[31] (1998)	0.6%	94% (12 y)	
	Poirer[33] (1998)	0.3%	95% (10 y)	
Mosaic	Jasinski[124] (2000)		100% (3 y)	
	Fradet[120] (2004)	0.8	98% (7 y)	
	Thomson[138] (2001)	0.8		
	Eichinger[168] (2002)	0.8	94%	
Biocor	Myken[172] (2000)	0.7	93% (15 y)	
	Rizzoli1[134] (2005)		94% (8 y)	

The surgical indications for mitral valve prosthetic endocarditis are persistent sepsis, congestive failure, perivalvular leak, large vegetations, or systemic infected emboli.[75,76,303] Operative technique is similar to other mitral procedures with respect to anesthesia, monitoring, cardioplegia, left atrial incision, and exposure of the valve. Usually biologic valves are used for patients older than 65 years of age or younger patients with short life expectancy.[76] Mechanical valves can be used in younger patients. Excision of the valve and débridement of the annulus and abscesses must be meticulous and extensive. All necrotic and infected tissue must be removed. After local application of an antibacterial solution such as Betadine and local antibiotic irrigation, the annulus and areas of tissue loss are reconstructed using autologous pericardium. Pericardium must be used to reconstruct the mitral valve annulus, and all sutures must be placed through the pericardial-lined annulus to obtain secure anchorage of the new prosthesis. Autologous pericardial pledgets can be made and used instead of conventional cloth pledgets to avoid synthetic material as much as possible. Examples of operative techniques for closure and repair of local abscesses and infectious destruction of the mitral valve annulus are shown in Figs. 43-12 and 43-13.[304]

Postoperative care should include at least 6 weeks of appropriate intravenous antibiotics. Hospital mortality is related primarily to ongoing sepsis, multisystem organ failure,

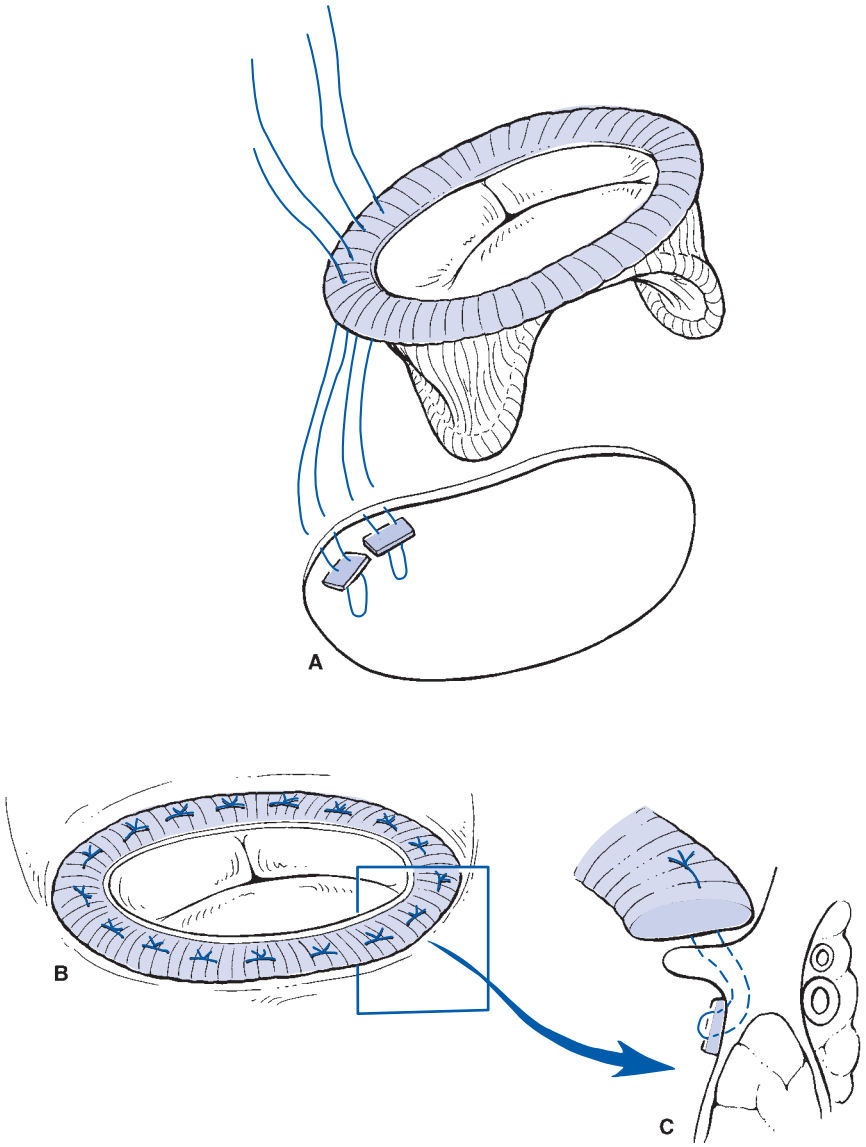

Figure 43-12. Preferred technique for inserting a mitral bioprosthesis in a patient with bacterial endocarditis. Pledgets are made from pericardium to minimize foreign material.

or failure to eradicate the local infection and subsequent recurrent perivalvular leak.[305,306] Recurrence of infection depends on the type of organism and the surgeon's ability to remove all areas of infection completely. Recurrence of infection is the single most important long-term complication.

CONCLUSION

Mitral valve replacement by mechanical or bioprosthetic valves revolutionized the care of patients with severe mitral valve disease. Reconstructive operations of the mitral valve now have assumed an equally important role for mitral regurgitation. A number of advanced lesions of the mitral valve still require mitral valve replacement with reliable devices. The bileaflet, tilting-disk, and ball-and-cage prosthetic valves are extremely reliable in terms of durability but require long-term anticoagulation and have a high risk of thromboembolism or thrombosis without anticoagulation. Bioprosthetic porcine valves, conversely, in patients in sinus rhythm do not need long-term anticoagulation and are used mainly in elderly patients who are not likely to outlive the valve and in women who plan to become pregnant and do not wish to accept the risks of warfarin or heparin. The long-term durability of these valves is limited, and the probability of valve failure at 15 years is at least 40%. Improvements in mechanical valve design and biologic valve preservation of collagen structure and resistance to calcification are ongoing and are the hopes for the future. In addition, there is renewed interest in homograft mitral valves, which may offer better long-term durability, as has been observed with cryopreserved homograft aortic valves. Improved valve

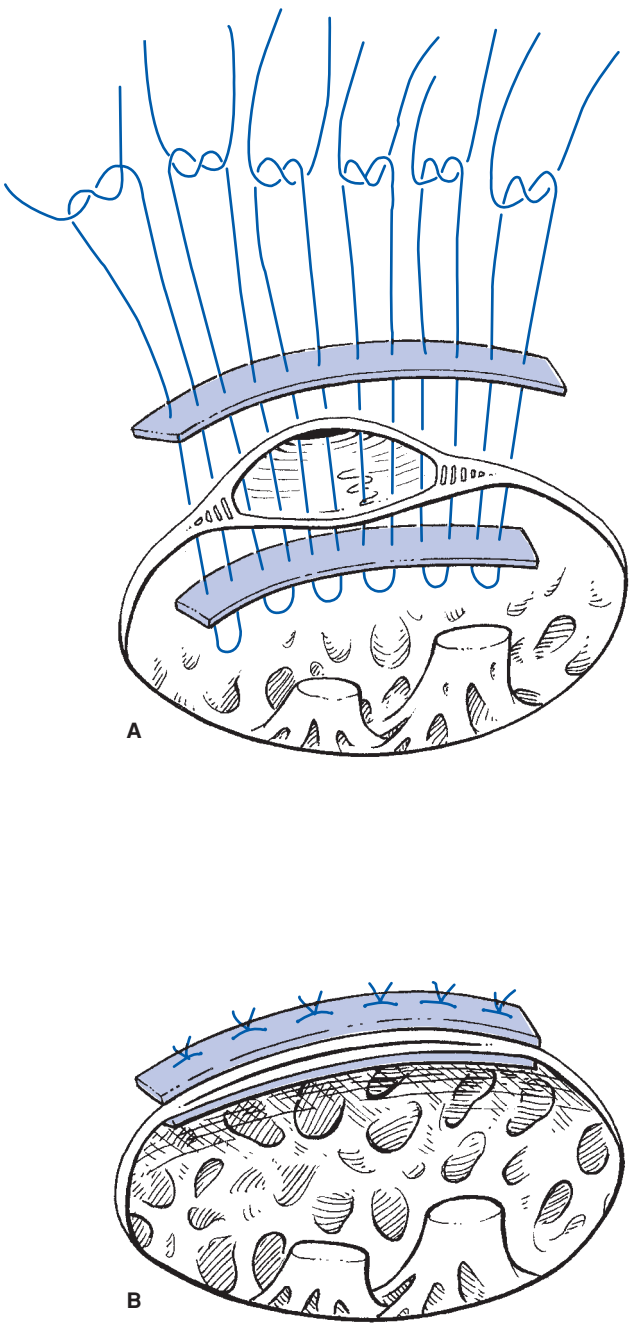

Figure 43-13. Repair of a mitral annular abscess using strips of pericardium. *A.* Reconstruction of the annulus after débridement of the annulus. *B.* The reconstructed annulus before insertion of the prosthesis.

design and development of better biomaterials eventually will improve clinical results; however, current FDA restrictions on the development and evaluation of new prosthetic valves have an important impact on this process.

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CHAPTER 44

Surgical Treatment of Mitral Valve Endocarditis

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Mitral valve infective endocarditis is one of the more devastating complications of heart valve disease. Although the distribution of causes of mitral valve dysfunction has changed in recent years, the incidence of infective endocarditis has remained constant over the past several decades.[1] Underlying rheumatic valvular disease, which was a frequent predisposing factor to infective endocarditis in the 1980s, is now rare in industrialized nations.[2] Other predisposing factors more frequently encountered today include intravenous drug abuse, immunosuppression, degenerative valvular disease, intravascular prostheses and devices, hemodialysis catheters, and nosocomial infections. Several of these predisposing factors are consequences of advances that characterize modern medicine.[3]

Today, major improvements in surgical technique, increased experience, and more effective antimicrobial agents have improved the early and long-term outcomes of patients treated for infective endocarditis. However, endocarditis is still associated with high rates of morbidity and mortality and frequently requires operation for cure.[4]

PATHOLOGY

Native Mitral Valve Endocarditis

Native valve endocarditis (NVE) refers to infectious endocarditis involving a patient's own (native) heart valve. Crude incidence of NVE is 6.2 per 100,000 people per year, and is highest in the older age groups.[5] The pathogenesis of NVE begins with endocardial trauma resulting in alteration of the valvular endocardial surface; this allows deposition of fibrin and platelets with subsequent attachment of bacteria. Endocardial injury may be secondary to rheumatic valvulitis or other leaflet disease, or valvular or annular calcification.[5] Common reasons for bacteremia or fungemia predisposing to NVE include use of long-term indwelling catheters, intravenous drug abuse, and fungemia associated with prolonged antibiotic therapy.[6,7] Although vegetations may be seen anywhere on the leaflets or the chordae, the usual site at which infective NVE of the mitral valve causes valvular destruction and invasion is at the base of the atrial aspect of the mitral valve leaflets. Annular or subannular invasion may cause separation at the atrioventricular (AV) junction (Fig. 44-1). Invasion into the AV groove fat with abscess formation may necessitate radical débridement. Destruction of the fibrous trigones and intervalvular fibrosa between the anterior mitral valve leaflet and the aorta is usually a consequence of aortic valve endocarditis with secondary mitral involvement. Occasionally, "drop lesions" from an infected aortic valve seed the anterior mitral leaflet or the tensor apparatus of the mitral valve, resulting in double-valve endocarditis; the mechanism may be a large vegetation directly infecting the mitral leaflet or a jet lesion that becomes infected.

Prosthetic Mitral Valve Endocarditis

Prosthetic valve endocarditis (PVE) or replacement device endocarditis is infectious endocarditis involving a surgically implanted heart valve. The number of cases of PVE is on the rise as the number of patients with prosthetic heart valves continues to increase. In contradistinction to NVE, wherein the mitral valve is more likely to be infected,[8] PVE is more common in the aortic than in the mitral position.[9] The risk of PVE appears to be greatest at approximately 5 weeks following valve implantation and thereafter declines.[10–13]

PVE identified within the first postoperative year is considered early endocarditis, and those cases appearing more than 1 year after operation are termed late.[13,14] The incidence of early PVE is 1%.[14] Once past the early phase, the incidence of late PVE is 0.5 to 1% per year.[15–18] The type of prosthesis (mechanical versus bioprosthetic) does not influence the risk of PVE.

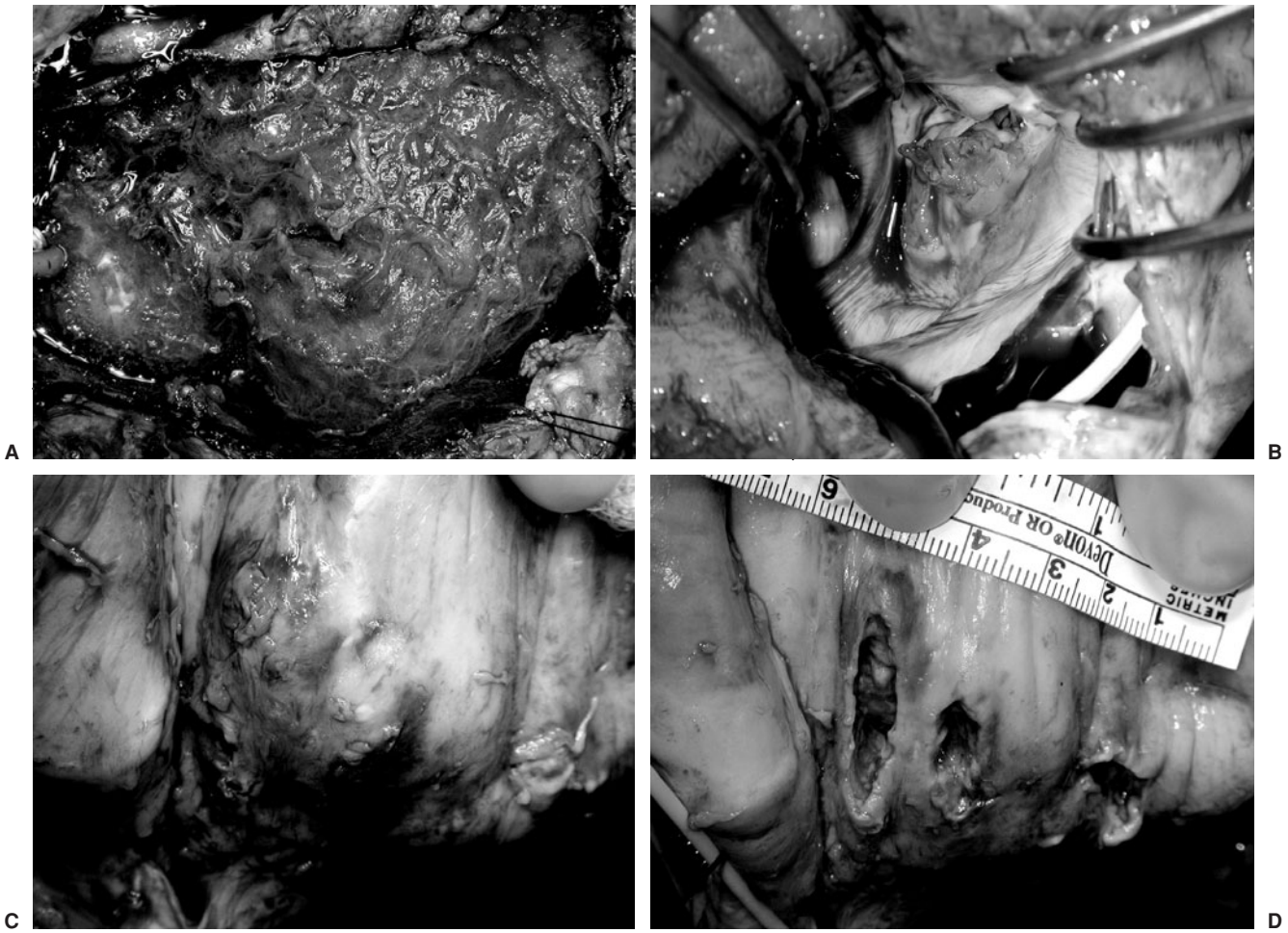

Figure 44-1. (A) Severe hemorrhagic pericarditis with a thick fibrin coat on the heart. (B) Left atrial view, showing vegetation on the posterior leaflet of the mitral valve. (C) Outside view of the inferior basal wall of the left ventricle, showing atrioventricular groove abscess. (D) Outside view of the atrioventricular groove after débridement, showing three contiguous areas of perforation related to mitral valve abscess. (*Reproduced with permission from Atik et al.*[54])

Early PVE is usually the result of intraoperative infection.[19] Common portals of entry for bacteria that cause PVE are intravascular catheters and skin infection.[20,21] Nosocomial infections contribute to late PVE, particularly in patients with medical comorbidities that require frequent hospital admission or instrumentation (e.g., hemodialysis patients) or immunosuppression (e.g., organ transplantation).[19]

Early PVE usually affects the sewing ring or the interface of the prosthetic valve and the annulus (often a site of clot formation), resulting in periprosthetic leak. Progression of the infection may lead to abscess formation. Mitral PVE may extend anteriorly to the fibrous trigone or posteriorly, causing AV separation. PVE may be classified into different subgroups based on the anatomic distribution of the infection. According to this classification, PVE cases are classified as those involving the prosthesis alone, those involving the prosthesis–native annular junction (annular infection), and those extending beyond the annulus (extensive infection).[13,19] Another useful classification that applies to both NVE and PVE involves the distinction between *active* and *healed* endocarditis. The latter includes cases in whom organisms cannot be demonstrated but remote infection is still presumed.[13,22]

MICROBIOLOGY

Endocarditis of native valves is most often caused by *Streptococcus viridans, Staphylococcus aureus* or *epidermidis,* or *Enterococci.* The distribution of microorganisms responsible for early PVE includes coagulase-negative staphylococci (52%), *S. aureus* (10%), *Enterococci* (8%), *S. viridans* (5%), and gram-negative organisms (6%).[19] Fungi account for 10% of cases of early PVE (*Candida albicans* in 8 of 10). Although gram-positive cocci are dominant in both early and late PVE,

in early PVE staphylococci predominate while in late PVE streptococci are the most common organisms isolated.[9] *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* are collectively termed the HACEK group and account for 3% of culture-negative late PVE.[23] Patients with PVE and negative cultures may be infected by fastidious organisms. In general, late PVE is more amenable to successful antibiotic therapy than is early PVE; however, PVE always warrants surgical consideration.

DIAGNOSIS

Clinical Presentation

The most common clinical finding is fever;[9] however, it is nonspecific. Other findings include a new murmur or a change in an existing murmur. Embolic phenomena may cause petechiae, Roth spots, Osler nodes, and Janeway lesions. Splenomegaly may be present in both NVE and PVE.

Laboratory findings include a white blood cell count $>12{,}000/mm^3$, anemia (hematocrit $<34\%$), and hematuria.[9] Blood cultures from separate sites are usually positive in patients with bacterial endocarditis; two of three positive cultures is considered diagnostic. However, cultures in patients with fastidious organisms or fungi may take more than 3 weeks to become positive. Blood cultures should be drawn before antibiotics are started.

Electrocardiographic Findings

Conduction abnormalities are present in up to 23% of patients with NVE and 47% of patients with PVE. This usually indicates extension of the infection and formation of a paravalvular abscess.[24]

Echocardiographic Findings

The present gold standard diagnostic modality for documenting infective endocarditis is transesophageal echocardiography. Specificity for transesophageal echocardiography is approximately 90% and sensitivity is 95%.[26,27] In contrast, transthoracic echocardiography is more operator-dependent and its images may be compromised by surrounding structures; it is only 50% sensitive and 90% specific for infective endocarditis.[25] Echocardiographic findings of endocarditis include vegetations, periprosthetic leak in patients with PVE, intracardiac fistulae, and abscesses. The echocardiographic examination is very good at evaluating the valve function but less reliable for assessing the severity and invasiveness of the infection. A negative echocardiogram does not exclude the diagnosis of endocarditis. In situations with strong suspicion of endocarditis, the diagnosis may be pursued by magnetic resonance imaging (MRI). In the majority of patients with endocarditis, MRI will demonstrate abnormal consistency of tissue in the annulus. Metastatic infection is a possibility and patients with infective endocarditis and abdominal symptoms should be investigated with computed tomography (CT) scanning to rule out splenic or hepatic abscesses. Metastatic infection of viscera is typically caused by staphylococcal organisms.[5] The brain is the most frequent site for emboli.[28,29] Any neurologic deficit or abnormality should trigger investigation with CT or MRI of the brain, funduscopic examination, and occasionally cerebrospinal fluid examination. CT or MRI of the brain is also justified in the absence of symptoms if there are stigmata of other embolic events. Preoperative coronary angiography is indicated in patients with coronary artery disease or history of previous revascularization procedures and in patients in whom coronary embolization is suspected.

Duke Criteria

The Duke University criteria were developed to improve the specificity and sensitivity of the diagnosis of infective endocarditis. These criteria include echocardiographic results along with clinical, microbiologic, and pathologic findings.[30] Most authorities accept a modification of these criteria for PVE that includes progressive heart failure in the presence of positive blood cultures and new conduction disturbances (Table 44-1). The Duke criteria are classified as "major criteria" (typical positive blood culture and positive echocardiogram) and "minor" criteria (predisposition, fever, vascular phenomena, immunologic phenomena, suggestive echocardiogram, suggestive microbiologic findings, and new-onset heart failure or conduction disturbances). There are three diagnostic categories: (1) patients with a *low clinical likelihood of infective endocarditis* are those with resolution of manifestations of endocarditis with antibiotic therapy for 4 days or less, or no pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy for 4 days or less; (2) patients with *possible endocarditis* have one or two minor clinical criteria of the Duke classification system; and (3) patients with a *definite* diagnosis of infective endocarditis are those (a) in whom pathologic specimens from surgery or autopsy reveal positive histology and/or culture, (b) who have two major criteria, (c) who have one major and three minor criteria, or (d) who have five minor criteria.[30] Understandably, the Duke criteria are not particularly relevant in patients who have had surgical treatment, those in whom the diagnosis is based on surgical findings, and those with analysis of surgical specimens by microscopy, culture, and polymerase chain reaction.

INDICATIONS FOR SURGERY

Surgery plays a pivotal role in the management of native mitral valve endocarditis. Indications for surgical intervention in patients with NVE and PVE are presented in Table 44-2. Congestive heart failure is the most common indication for surgery.

Table 44–1.

Duke Criteria for Native Valve Endocarditis and Prosthetic Valve Endocarditis

Major criteria
Positive blood cultures for infective endocarditis
Typical microorganism for infective endocarditis from two separate blood cultures: *Streptococcus viridans, S. bovis,* and HACEK group or community-acquired *Staphylococcus aureus* or enterococci in the absence of a primary focus, or
Persistently positive blood cultures, defined as recovery of a microorganism consistent with infective endocarditis from Blood cultures drawn >12 hours apart or All of three or most of four or more separate blood cultures, with the first and last drawn at least 1 hour apart
Evidence of endocardial involvement
Positive echocardiogram for infective endocarditis Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation, abscess, new partial dehiscence of prosthetic valve, or new valvular regurgitation (increase or change in preexisting murmur not sufficient)
Minor criteria
Predisposition: predisposing heart condition or intravenous drug use
Fever: temperature ≥38°C (100.4°F)
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, and Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously or serologic evidence of active infection with organisms consistent with infective endocarditis
Echocardiogram: consistent with infective endocarditis but not meeting major criterion as noted previously
New-onset heart failure
New conduction disturbances

HACEK group = Haemophilus spp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae
Source: Modified with permission from Perez-Vasquez et al.[55]

The majority of patients with PVE require surgery.[31,32] Indications for surgical intervention in patients with PVE include heart failure, new heart block (possibly secondary to a myocardial abscess), ongoing sepsis, valve dehiscence, recurrent systemic embolism, relapse of infection, and fungal infection. Operation for large mobile vegetations to prevent embolization in both NVE and PVE remains a controversial indication in the absence of hemodynamic compromise or other surgical indications. Fungal PVE is uncommon but is more difficult to cure than is PVE caused by other organisms. The operative strategy should include perioperative intravenous amphotericin B, radical débridement of infected tissue, reconstruction using biologic tissue whenever possible, and lifelong oral suppressive antifungal therapy after completion of intravenous therapy.[33]

TIMING OF SURGERY

Many patients with NVE and the majority of patients with PVE require surgical intervention, and the challenge for the surgeon is to determine the appropriate timing of surgery.[31] In most cases, the operation should not be delayed once surgical indications are present. Patients with PVE caused by *S. aureus,* even without periannular abscess formation, should have early operation to prevent an aggressive infection with rapid progression and invasion. The same principle

Table 44–2.

Surgical Indications for Native Valve Endocarditis and Prosthetic Valve Endocarditis

1. Severe mitral regurgitation, with or without symptoms of congestive heart failure
2. Uncontrolled sepsis despite proper antibiotic therapy
3. Presence of an antibiotic-resistant organism
4. Fungal endocarditis or endocarditis caused by *Staphylococcus aureus* or gram-negative bacteria
5. Presence of mitral annular abscess, extension of infection to intervalvular fibrous body, or formation of intracardiac fistulas
6. Onset of a new conduction disturbance
7. Large vegetations (>1 cm), particularly those that are mobile and located on the anterior leaflet, and thus at high risk for embolic complications
8. Multiple emboli despite appropriate antibiotic therapy

applies to fungal infective endocarditis, as a mortality rate as high as 93% has been reported.[9]

However, delaying repair is usually advised in the presence of central nervous system complications.[28] Before undergoing valve surgery, patients with endocarditis should have careful neurologic evaluation and significant findings should be evaluated by head CT or MRI. Occasionally, angiography is required to exclude a mycotic aneurysm. Patients with hemorrhagic strokes should have surgery delayed for 4 weeks to reduce the risk of further intracranial bleeding during heart surgery. Intracranial hemorrhage in the setting of PVE has been associated with mortality as high as 28 to 69%.[35] The main concern with nonhemorrhagic embolic stroke is transformation of an ischemic infarct into a hemorrhagic infarct as a complication of the anticoagulation required during cardiopulmonary bypass.[34] Patients who suffered recent ischemic stroke should have their operation delayed for 2 to 4 weeks, particularly if the stroke is large.[36,37] The risk of worsening neurologic symptoms as a consequence of operation is time-related, decreasing with increasing interval from the initial neurologic event. This risk must be weighed against the indications for surgery and the risk of additional emboli during the waiting period.

OPERATIVE TECHNIQUES

General Principles

Operations for endocarditis are guided by some basic principles: optimal timing of surgery as discussed above, good exposure of the valve, radical débridement, optimal choice for reconstruction of the heart and repair or replacement of the valve, and adequate postoperative antibiotic treatment. Radical débridement with removal of all infected and necrotic tissue and foreign material is more difficult to accomplish in mitral cases with AV groove invasion and abscess formation, particularly when compared to aortic root infections. In addition, reconstruction after invasion of the AV groove and AV separation entails closing off the infected space, leaving it without drainage.

Native Mitral Valve Endocarditis

Intraoperative transesophageal echocardiography should be performed in all cases to evaluate the valve before commencing the procedure. Surgical treatment options for NVE affecting the mitral valve include valve replacement and valve repair. Although there is some experience with the mitral valve allograft for treatment of mitral valve endocarditis, there are too few data available to support this strategy.[38]

Most operations for NVE are best conducted through a full median sternotomy. Cannulation for cardiopulmonary bypass involves arterial return via the ascending aorta and bicaval cannulation for venous return. In case of large mobile vegetations, it is advisable to arrest the heart before placing transatrial retrograde cardioplegia. Protection is achieved using antegrade and retrograde substrate-enhanced cardioplegia.[39]

The mitral valve is exposed via a left atriotomy through the interatrial groove or transseptally. If the left atrium is small, an extended transseptal approach is employed. Once exposure of the mitral valve is accomplished, the valve is evaluated to assess for presence of paravalvular abscesses, intracardiac fistulae, or intervalvular fibrous body/ventricular involvement. Radical resection of all necrotic tissue is performed with a margin of normal tissue. All grossly infected tissue is removed without concern for the possibility of repair. Specimens are sent for microbiologic analysis and culture.

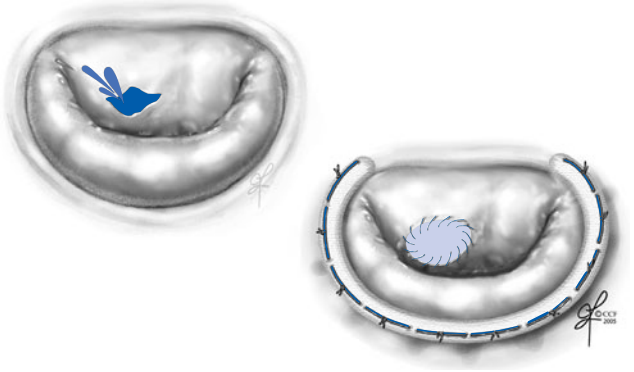

Figure 44-2. Repair of anterior leaflet perforation by patch with autologous pericardium followed by annuloplasty.

For NVE, our approach is to attempt repair if feasible. Mitral valve repair can be performed safely provided there is sufficient remaining tissue to allow valvular reconstruction without tension.[40–44] In the event of extensive destruction of the subvalvular apparatus, prosthetic valve replacement is performed. Regardless of the mitral procedure performed, all patients with active infection receive 6 weeks of postoperative antibiotic therapy.

Anterior leaflet repair

"Drop lesions" of the anterior leaflet encountered in association with aortic endocarditis can be repaired with autologous or glutaraldehyde-preserved pericardium.[38] A patch of pericardium is fixed to the remaining tissue of the anterior leaflet with running polypropylene suture (Fig. 44-2). The smooth surface of the patch should face the atrium to decrease the risk of thromboembolic complications.[37] More extensive destruction involving both the aortic valve and the anterior leaflet of the mitral valve can be repaired using a free-standing aortic root homograft with the anterior leaflet of the mitral valve still attached. The homograft's attached aortomitral curtain can be used to reconstruct the base of the native anterior mitral leaflet.[37,45]

Involvement of the free margin of the anterior leaflet can be managed with triangular resection and closure with interrupted fine sutures. Anterior leaflet chordal rupture can be repaired with chordal transposition from the posterior leaflet or with secondary chordal transfer to the free margin of the anterior leaflet. Artificial chordae may also be used to replace ruptured anterior leaflet chordae.

Posterior leaflet repair

The middle scallop (P_2 segment) of the posterior segment is frequently affected by the infectious process. Repair can be performed with quadrangular resection of the middle scallop, and a sliding repair is frequently required to close the gap between the remaining two scallops (Fig. 44-3). Extensive destruction of the posterior annulus requires removal of all devitalized tissue and annular reconstruction with autologous pericardium. Occasionally, repair of the annulus and

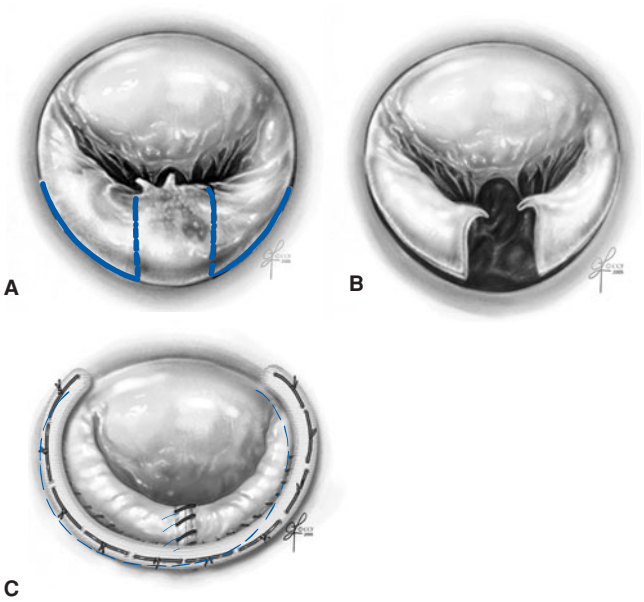

Figure 44-3. Quadrangular resection and sliding repair for posterior leaflet vegetation with ruptured chordae. (A,B) Segment of posterior leaflet is resected and a portion of leaflet detached from the annulus. (C) Leaflet remnants are sutured to the annulus, taking deep bites to reduce leaflet height. Leaflet edges are reapproximated in the center. Annuloplasty completes the repair.

the posterior leaflet can be accomplished with the same patch if chordal support to the leaflet is good. A running polypropylene suture is used on the ventricular, atrial, and valvular aspects of the patch. If replacement is required, a mechanical or bioprosthetic valve may then be inserted, affixing the prosthesis to the patch.[45] It is important that the patch is generous enough to minimize tension on the sutures in ventricular muscle.

The use of prosthetic ring annuloplasty in NVE is controversial. Favoring repair over replacement, we use a ring whenever the annulus is not infected.

Prosthetic Valve Endocarditis

Surgical approach

Operations for PVE are reoperations, usually performed via a median sternotomy. An alternative approach is right anterolateral thoracotomy in the fourth intercostal space; this is particularly useful in patients with multiple previous sternotomies, bypass grafts near the sternum, or a history of mediastinal radiation and/or mediastinitis.[46,47] However, a right thoracotomy for mitral reoperations allows limited access, sometimes denies aortic cross-clamping, and may be associated with a risk of stroke.

Myocardial protection

Cardiopulmonary bypass is instituted using the ascending aorta and bicaval cannulation. A transatrial retrograde cardioplegia cannula is used and myocardial protection is achieved using antegrade and retrograde cardioplegia.

Mitral valve exposure

The main issues in achieving mitral valve exposure are related to obtaining mobility of the right atrium and vena cavae.[19] Our usual approach to obtain mitral valve exposure is to use an extended transseptal approach. If the left atrium is large and adhesions modest, a standard left atriotomy may be employed. Exposure may be enhanced by division of the superior vena cava and extending the left atriotomy toward the aortic root. This approach provides good exposure even when the left atrium is small.

Reconstruction of the mitral annulus

Once exposure of the mitral valve is obtained, the infected prosthesis is removed. Mitral valve PVE may produce an abscess cavity separating the left atrium, left ventricle, and prosthesis. In these situations the operation includes débridement of the annulus with subsequent annulus reconstruction using autologous or glutaraldehyde-fixed bovine pericardium (David technique).[48,49] With this technique, a semicircular pericardial patch is used to reconstruct the annulus with one side of the patch sutured to the endocardium of the left ventricle and the other side to the left atrium. This patch closes off the cavity, which must be thoroughly débrided before the patch is affixed. The new valve prosthesis is affixed to this reconstructed annulus (Fig. 44-4). In most situations with annular reconstruction we employ a bioprosthesis because of the larger and softer sewing ring and to avoid anticoagulation in the postoperative period.

An alternative technique for mitral annular reconstruction is the technique described by Carpentier and colleagues.[50] This technique involves using figure-of-eight atrial and ventricular sutures to reconstruct the AV junction. Exerting traction on these sutures reduces the size of the annulus and closes the AV groove without injury to the circumflex vessels. The main potential disadvantage of this technique is that sutures may pull through stiff and noncompliant ventricular tissue.[19]

Reconstruction of the fibrous trigones

Extension of PVE into the intervalular fibrosa/fibrous trigones may necessitate replacement of both mitral and aortic valves. This usually occurs in the setting of PVE affecting both the aortic and the mitral valves and seldom with isolated mitral valve endocarditis. Reconstruction of the intervalvular fibrosa as well as replacement of both the aortic and mitral valve are required (Fig. 44-5). In such circumstances the fibrous trigones may be reconstructed with autologous or bovine pericardium that is used to secure the new prosthesis.[13,19] Perfect exposure is mandatory whether it is provided by the extended transseptal approach or by dividing the superior vena cava and extending the left atriotomy from anterior to the right superior pulmonary vein toward the dome of the

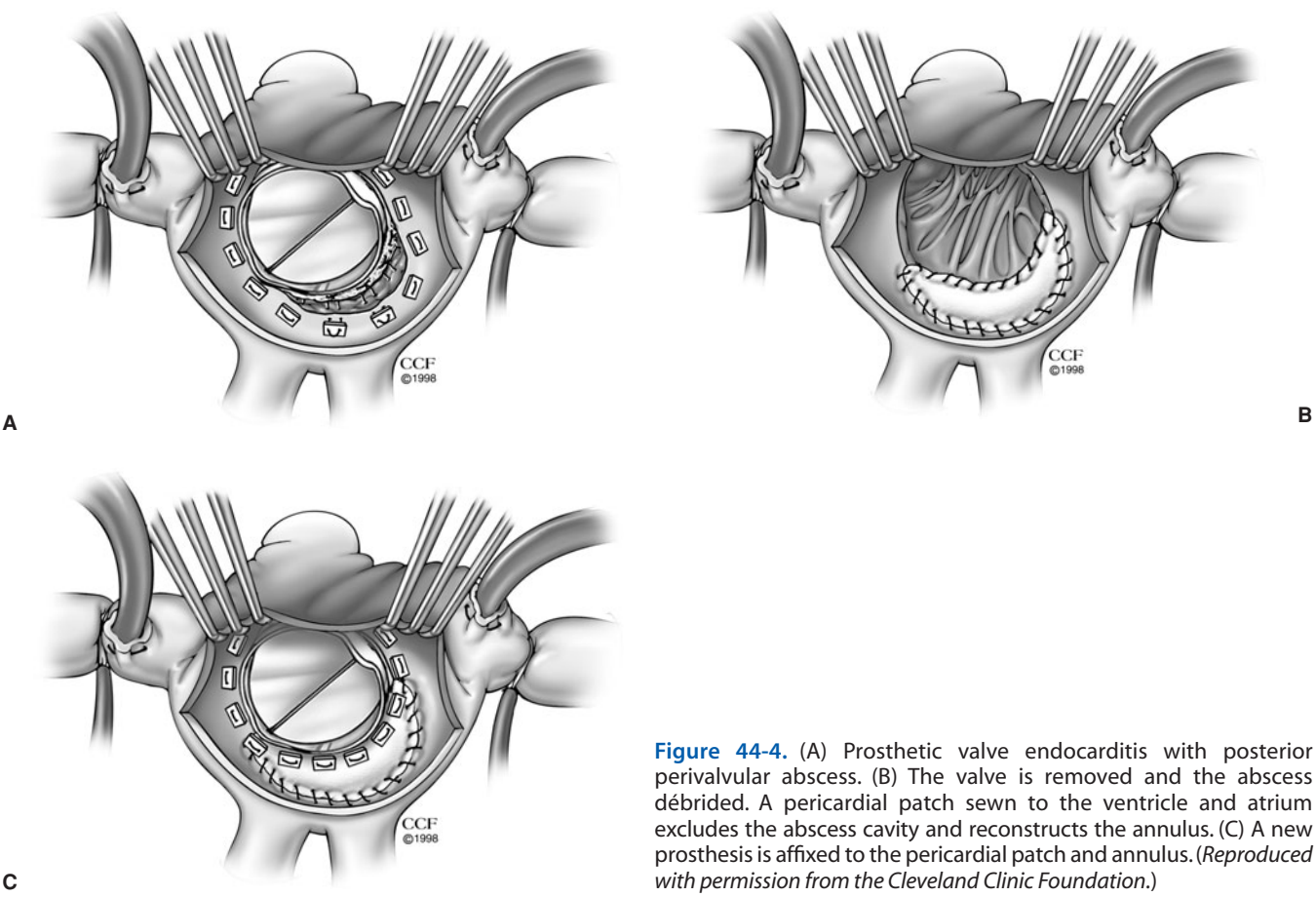

Figure 44-4. (A) Prosthetic valve endocarditis with posterior perivalvular abscess. (B) The valve is removed and the abscess débrided. A pericardial patch sewn to the ventricle and atrium excludes the abscess cavity and reconstructs the annulus. (C) A new prosthesis is affixed to the pericardial patch and annulus. (*Reproduced with permission from the Cleveland Clinic Foundation.*)

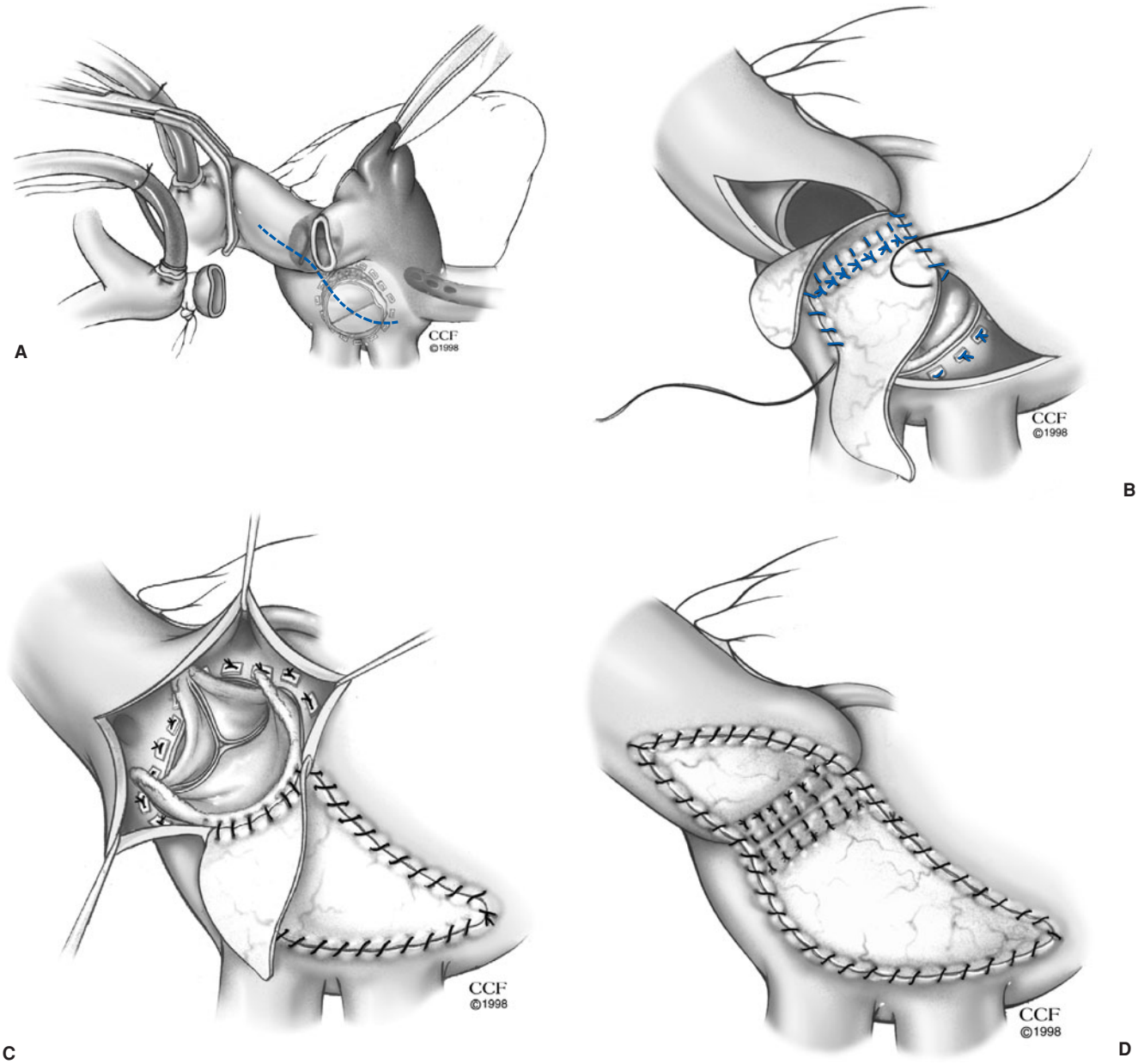

Figure 44-5. Reconstruction of the fibrous trigones. (A) Infection involves the mitral and aortic valves. Division of the superior vena cava facilitates exposure of the aortic valve, mitral valve, and fibrous trigones. (B) The new prosthetic mitral valve is sewn to the annulus posteriorly, medially, and laterally, but the superior portion of the mitral valve annulus is reconstructed by a pericardial patch that recreates the fibrous trigone. The valve is then sewn to this patch with horizontal mattress sutures. (C) Once the mitral valve prosthesis is in place, the aortic valve prosthesis is secured throughout most of the annulus. The pericardial patch reconstructs the medial part of the aortic valve annulus and the aortic valve is then sewn to the patch. (D) After the valve replacements are complete, the pericardial patch is extended to finish the closure of the aorta and the left atrium. (*Reproduced with permission from the Cleveland Clinic Foundation.*)

left atrium. This approach allows débridement of both the aortic and mitral valves, as well as the fibrous trigones. The prosthetic mitral valve is then sewn to the annulus posteriorly, medially, and laterally, and the superior portion of the mitral valve annulus is reconstructed with a pericardial patch that replaces the fibrous trigones. The valve is then sewn to the patch with horizontal mattress sutures. Once the mitral valve is secured in place, the aortic valve prosthesis is affixed to the aortic annulus. The pericardial patch is used to reconstruct the medial part of the aortic valve annulus. The aortic valve is then sewn to that patch.[13,19] An alternative option is aortic valve and root replacement in an anatomic position, suturing the intervalvular fibrosa/mitral valve of the homograft to the mitral valve prosthesis.

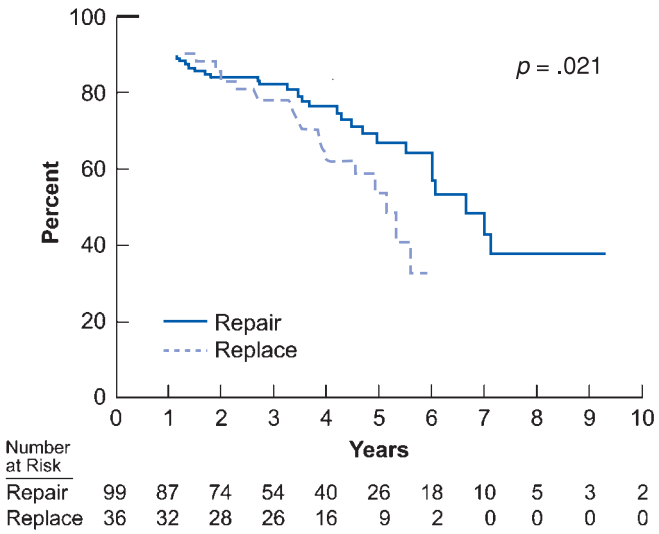

Figure 44-6. Event-free survival for all patients undergoing mitral valve repair or replacement. (*Reproduced with permission from Muehrcke et al.*[43])

RESULTS

Native Mitral Valve Endocarditis

In patients with NVE, mitral valve repair is preferable to mitral valve replacement, since repair has been associated with lower hospital mortality and improved long-term survival (Fig. 44-6).[43,51] In our series of 146 patients having surgery for NVE, patients undergoing repair had a lower hospital mortality ($p = .008$) and improved long-term survival ($p = .05$) compared to those having replacement.[43] Several recent series have reported excellent results with valve repair in the setting of mitral valve endocarditis, with mortality rates ranging between 0% and 9%.[40–43] The infection-free survival is also better for mitral valve repair compared to replacement with a less than 1% per year reinfection rate.[43] The likely explanations for these excellent outcomes are the avoidance of prosthetic material in the infected field and the preservation of left ventricular function associated with repairing mitral valves.[43] Second, the replacement group contains the sickest patients with the most advanced and destructive disease.

Prosthetic Valve Endocarditis

PVE is associated with a much higher operative mortality than is native valve endocarditis.[24,49,52,53] Despite improved antimicrobial regimens, outcomes of medical therapy only without reoperation are poor in PVE, particularly for patients with annular involvement or early endocarditis after valve surgery.[13] The success of homografts in the aortic position has led to attempts to use mitral valve homografts to treat mitral valve PVE. The outcomes of that experimental strategy are at present unknown.

For all patients with mitral valve PVE, prolonged postoperative treatment with intravenous antibiotics is required. Most patients with active endocarditis are treated for at least 6 weeks after surgery and are followed with transesophageal echo studies. In comparison to aortic valve endocarditis, radical débridement and drainage of posterior mitral annulus abscesses is far more difficult. Patients with fungal endocarditis require 2 months of intravenous antifungal therapy followed by indefinite oral antifungal therapy.[33]

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CHAPTER 45

Minimally Invasive and Robotic Mitral Valve Surgery

W. Randolph Chitwood, Jr. • Evelio Rodriguez

Surgeons and their patients are now seeing the benefits and extended possibilities of minimally invasive mitral valve surgery (MIMVS). Until 1995, cardiac surgery lagged far behind other specialties in the development of minimal access methods. Then, Cohn and Cosgrove, along with several European surgeons, first modified cardiopulmonary bypass techniques and reduced incision sizes to enable safe, effective minimally invasive aortic and mitral valve surgery.[1–3] Concurrently, Port-access methods using endoaortic balloon occluders were developed and had a period of popularity.[4,5] However, procedural complexity, cost, and complications inhibited widespread adoption of the endoballoon technique. Despite expanding enthusiasm for minimally invasive valve surgery, many surgeons remained skeptical and became critical of complex operations done through small incisions, owing to possibilities of unsafe operations, unknown operative complexities, and inferior results.[6–9]

Despite circumspect reticence, significant advances were made and impressive clinical series emerged. Most surgeons who performed MIMVS in this era selected either a variation of a sternal incision or a minithoracotomy, and used direct vision with longer instruments. Simultaneous advances in cardiopulmonary perfusion, intracardiac visualization, instrumentation, and robotic telemanipulation then hastened a technological shift with more surgeons adopting minimally invasive valve surgery in their practice. Today, both replacing and repairing cardiac valves through small incisions have become a standard practice for many surgeons as patients have become more aware of its increasing availability. Clearly, cardiologists have set a new standard for the least invasive approach to cardiac care, and its increasing use will now follow.

EVOLUTION OF MINIMALLY INVASIVE MITRAL VALVE SURGERY

To perform the ideal cardiac valve operation (Table 45-1) surgeons need to operate in restricted spaces through tiny incisions, which requires assisted vision and advanced instrumentation. Although this goal has not been achieved widely, MIMVS has continued to evolve toward video-assisted or video-directed operations. Moreover, new robotic methods offer endoscopic possibilities for mitral valve surgeons that heretofore were impossible. Via both video-assisted and direct vision, MIMVS now is within the reach of most cardiac surgeons. Yet the steep learning curve still can be an impediment to its more widespread adoption.

Minimally invasive cardiac surgery has not enjoyed a standardized nomenclature. The terms *minimally invasive*, or *limited access*, cardiac surgery have suggested reduced size of the incision, the avoidance of a sternotomy, the use of a partial sternotomy or minithoracotomy, or lack of need for cardiopulmonary bypass. The development of less invasive heart surgery may be considered analogous to a Mount Everest ascent, embarking from a conventional median sternotomy operation or "base camp" and advancing progressively toward less invasiveness through experience and methodologic acclimatization. The nomenclature that parallels this "mountaineering" analogy is shown in Table 45-2. In this schema entry levels of technical complexity are mastered before advancing past small-incision, direct-vision approaches (Level 1), toward more complex video-assisted procedures (Level 2 or 3), and finally to robotic valve operations (Level 4). With the constant evolution of new technology and surgical expertise, many established surgeons already have attained serial "comfort zones" along this trek. It is interesting that advancements in robotic surgery have allowed more and more surgeons to flatten this curve, favoring robotic mitral repairs.

Level 1: Direct Vision

The first steps were to establish safety and efficacy of less invasive cardiac operations. Early minimally invasive valve operations were based solely on modifications of previous

Table 45–1.

The Ideal Cardiac Valve Operation

Tiny incisions and endoscopic ports
Central antegrade perfusion
Tactile feedback
Clear visualization
Facile, secure valve attachment
Intracardiac access
No instrument conflicts
Minimal requirements for: Cardiopulmonary perfusion Blood product usage Ventilation and ICU care Extended hospitalization
Same or better quality as open procedures: Valve repairs in 60 to 80% Few reoperations (1 to 2%) Low mortality (1 to 2%)
Computerized surgical pathway memory
Instrument navigation systems

incisions, and nearly all operations were done under direct vision. In 1996 the first truly minimally invasive aortic valve operations were reported.[1–3,10–12] At that time surgeons found that minimal access incisions also provided adequate exposure of the mitral valve.[10,11,13,14] Using either a mini-sternal or parasternal incision, Cosgrove, Cohn, Gundry, and Arom showed encouraging results with low surgical mortality (1 to 3%) and morbidity.[1,2,11,15] In Cosgrove's first 50 minimally invasive aortic operations, perfusion and cardioplegia times approximated those of conventional operations, and his operative mortality was 2%. Over half the patients were discharged by postoperative day 5.[2] In early 1997 Cohn described 41 minimally invasive aortic operations and first defined the economic benefits of these operations.[1]

Table 45–2.

Levels of Ascent in Minimally Invasive Cardiac Surgery

Level 1 Direct vision: Mini (10- to 12-cm) incisions
Level 2 Video-assisted: Micro (4- to 6-cm) incisions
Level 3 Video-directed and robot-assisted: Micro or port incisions (1 cm)
Level 4 Robotic telemanipulation: Port incisions (1 cm)

In early 1996, the Stanford group performed the first MIMVS using intra-aortic balloon occlusion (Port-access) and cardioplegia.[13,15–17] Subsequently, surgeons at the University of Leipzig reported 24 mitral valve repairs done through a minithoracotomy using Port-access techniques.[4] This group later reported a high incidence of retrograde aortic dissections and neurologic complications, which seemed to be related to new catheter technology and limited surgeon experience.[18] By early 1997 Colvin and Galloway had performed 27 direct-vision, Port-access mitral repairs or replacements with a single death. Their patients experienced no aortic dissections, and 63% of patients had mitral valve repairs with no reoperations for leakage.[19] By December 1998, Cosgrove had done 250 minimally invasive mitral valve operations using either a ministernotomy or parasternal incision with no mortality.[3] The successes of these early MIMVS procedures became the springboard to the current direct-vision techniques described herein.

Level 2: Video-Assisted

The radical endoscopic surgical techniques of the 1980s became routine general, urologic, orthopedic, and gynecologic operations in the 1990s. This was related primarily to successes with extirpative or ablative endoscopic operations. In contrast, fine vascular anastomotic and complex reparative procedures are the centerpieces of cardiac surgery. Because of difficulty in acquiring the fine video-assisted dexterity needed for these operations, cardiac surgeons were reluctant to explore the benefits of operative video assistance.

As mentioned, most Port-access, sternal modification, and parasternal mitral valve operations have been done using direct vision. In early 1996, Carpentier performed the first video assisted mitral valve repair through a minithoracotomy using hypothermic ventricular fibrillation.[20] Shortly thereafter, we reported the first video-assisted mitral valve replacement, done through a minithoracotomy, using a percutaneous transthoracic aortic clamp and retrograde cardioplegia.[21,22] This clamping and visualization technique was simple, cost-effective, and has remained the mainstay of isolated mitral valve operations at several centers.[18,23]

In 1997 Mohr reported 51 minimally invasive mitral valve operations, done using Port-access cardioplegia techniques, a 4-cm incision, and for the first time three-dimensional (3-D) videoscopy.[24] In this series 3-D assistance aided mitral

replacement; however, these surgeons found that even simple reconstructions were significantly more difficult than those done through a sternotomy. At about the same time Loulmet and Carpentier deployed an intracardiac "mini-camera" for lighting and subvalvular visualization; however, they also concluded that two-dimensional (2-D) visualization was inadequate for detailed repairs.[25] Concurrently, our group reported 31 successful mitral valve operations done using 2-D video-assistance [26] Complex repairs were possible, and these included quadrangular resections, sliding valvuloplasties, chordal transfers, and synthetic chordal replacements. Our initial results were encouraging.

Level 3: Video-Directed

In 1997 Mohr first used the Aesop 3000 voice-activated camera robot (Intuitive Surgical, Inc., Mountainview, Calif) in minimally invasive videoscopic mitral valve surgery.[24] Six months later we began using the Aesop 3000 routinely to perform both video-assisted and video-directed minimally invasive mitral valve repairs.[27] We have continued to use this device during most isolated mitral valve operations, including reoperations. This device provides surgeon camera-site voice activation, precluding translation errors inherent with verbal transmission to an assistant. Camera motion has been shown to be much smoother, more predictable, and requires less lens cleaning than during manual direction. Currently, we are able to do over 90% of a mitral repair under video direction with the Aesop 3000. Mohr first termed this method "solo mitral surgery" and reported 8 patients undergoing successful mitral repairs using this robotic technique.[24] Vanermen has perfected a method to perform repairs completely endoscopically with excellent results. In nearly 1000 mitral valve operations, he and his colleagues have shown that after a significant learning curve totally video-directed repairs could be done with excellent results using long instruments.[28,29]

Level 4: Robotic (Computer Telemanipulation)

In June 1998 Carpentier and Mohr did the first true robotic mitral valve operations using the da Vinci surgical system.[30,31] In May 2000 the East Carolina University group performed the first da Vinci mitral valve repair in the United States.[32] This computer-driven system provides both tele- and micromanipulation of tissues in small spaces. The surgeon operates from a console through end-affecter, microwrist instruments, which are mounted on robotic arms that are inserted through the chest wall (Fig. 45-1). These devices emulate human X-Y-Z axis wrist activity throughout seven full degrees of manipulative excursion. These motions occur through two joints that each affect pitch, yaw, and rotation. Additionally, arm insertion and rotation, as well as variable grip strength, give additional freedom to the operating "wrist."[31,33] Grossi and associates performed a partial mitral valve repair but had limited ergonomic freedom using the Zeus system.[34] Lange and associates in Munich were the first to perform a totally robotic mitral valve repair using only 1-cm ports and the da Vinci device.[35] To date, Chitwood, Murphy, and Smith have the largest experiences with robotic mitral valve repairs, and independently have shown da Vinci to be very effective, even for performing complex bileaflet repairs.[33,36] Repairs are done routinely using only ports and a 3- to 4-cm mini-incision, and are performed with greater facility than endoscopic level III operations. To this end, we are on the cusp of developing a closed-chest operation that can be done by many surgeons.

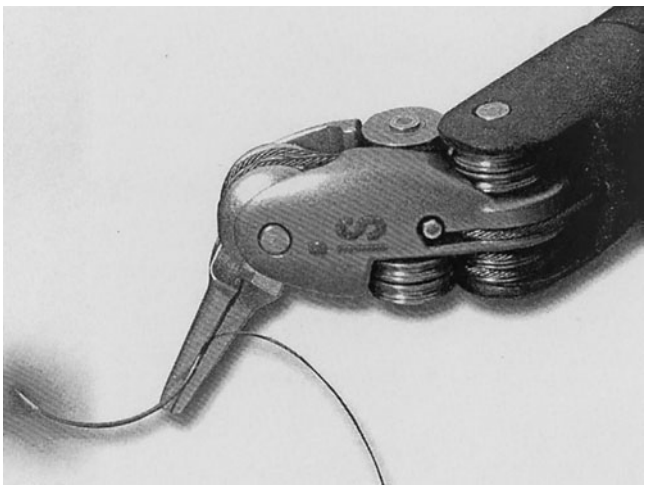


Figure 45-1. The da Vinci microwrist needle-holder instrument. This instrument is inserted into the robotic arm and controlled from the surgeon's console.

INCISIONS

The type and size of the musculoskeletal incision remains central to minimally invasive cardiac surgery discussions. A myriad of modified small sternal, parasternal, and thoracotomy incisions have been used for cardiac valve access. In the largest patient series modified sternal incisions were used.[37–39] Although many surgeons prefer the hemi-sternotomy approach, a right minithoracotomy yields excellent exposure for both direct-vision and videoscopic mitral valve access (Fig. 45-2A and B). To access the left atrium for direct vision, using a limited access minithoracotomy, a 4- to 6-cm submammary incision is placed along the anterior axillary line. The pectoralis and intercostal muscle fibers are divided, and the thorax is entered through the fourth intercostal space with minimal rib distraction and no rib cutting. The New York University group has been quite successful in combining this incision, Port-access methods, and direct vision for both mitral and tricuspid repairs/replacements.[40,41] A smaller 4- to 5-cm incision with minimal rib retraction can be used in video-assisted cases and is large enough for prosthesis passage (Fig. 45-3). Vanermen and Mohr perform video-assisted mitral operations routinely through 4-cm,

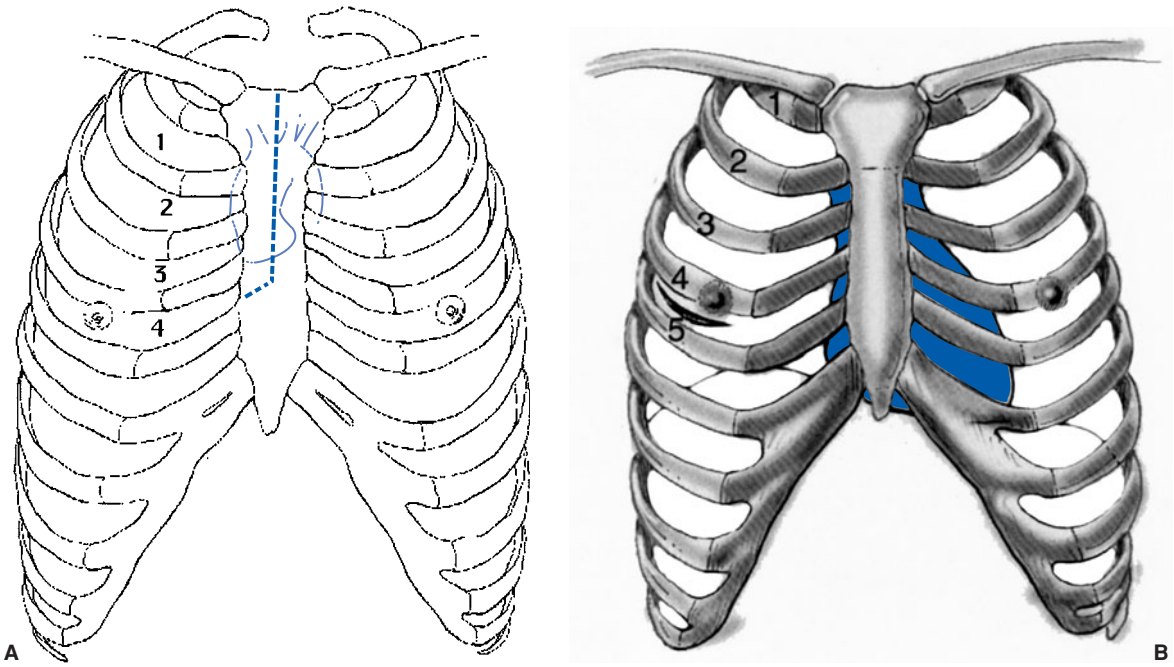


Figure 45-2. (A) The hemisternotomy, used for minimally invasive mitral and aortic valve surgery. (B) The minithoracotomy, used for minimally invasive mitral valve surgery.

nonretracted thoracic incisions with excellent results[42–44] (Fig. 45-4). Minimal rib spreading, prevention of intercostal nerve injury, and intraoperative local anesthetics are the keys to minimizing postoperative discomfort. We generally use a soft tissue retractor to obviate any rib spreading. Tricuspid operations can be performed through this incision when combined with bicaval cannulation with isolation. Murphy and colleagues in Atlanta prefer a more lateral approach for access in robotic mitral valve surgery.[45]

We consider the term "minimally invasive" to include the size of the actual cardiac incision. Most superior and transseptal mitral valve approaches, through a hemi-sternotomy, require a larger cardiac incision. For aortic, mitral, and tricuspid valve operations, surgeons at the Cleveland Clinic use a hemisternotomy, extended only to the fourth interspace, with direct aortic arch and right atrial cannulation.[3,12] To access the mitral valve, they extend the atriotomy

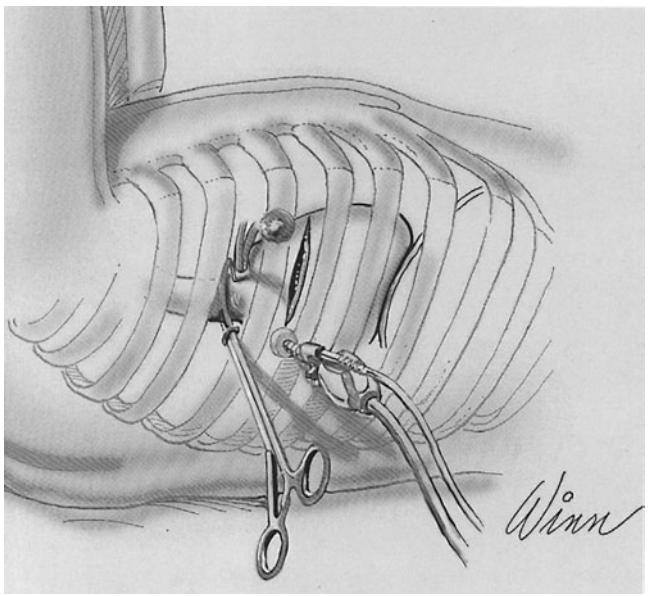


Figure 45-3. Right minithoracotomy and video access. The right minithoracotomy allows aortic access for the transthoracic clamp shown here as well as the video camera. With this arrangement minimal rib spreading is needed to perform mitral surgery.

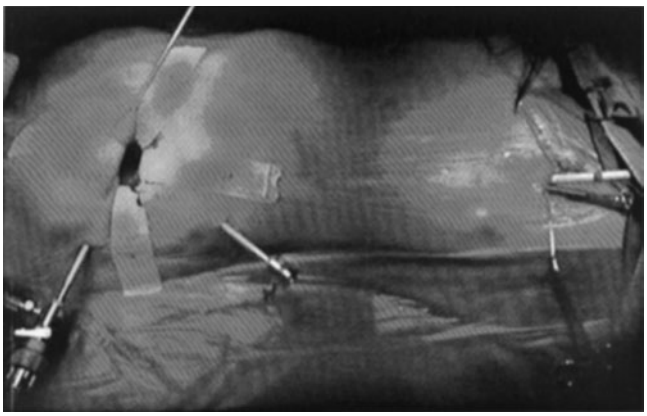


Figure 45-4. Small nonretracted minithoracotomy for video-directed mitral surgery. Using videoscopic techniques, a small nonretracted minithoracotomy provides excellent access for long instrument manipulation. Here, a soft tissue retractor mobilizes skin edges away from the incision. (*Courtesy of Dr. H. Vanermen.*)

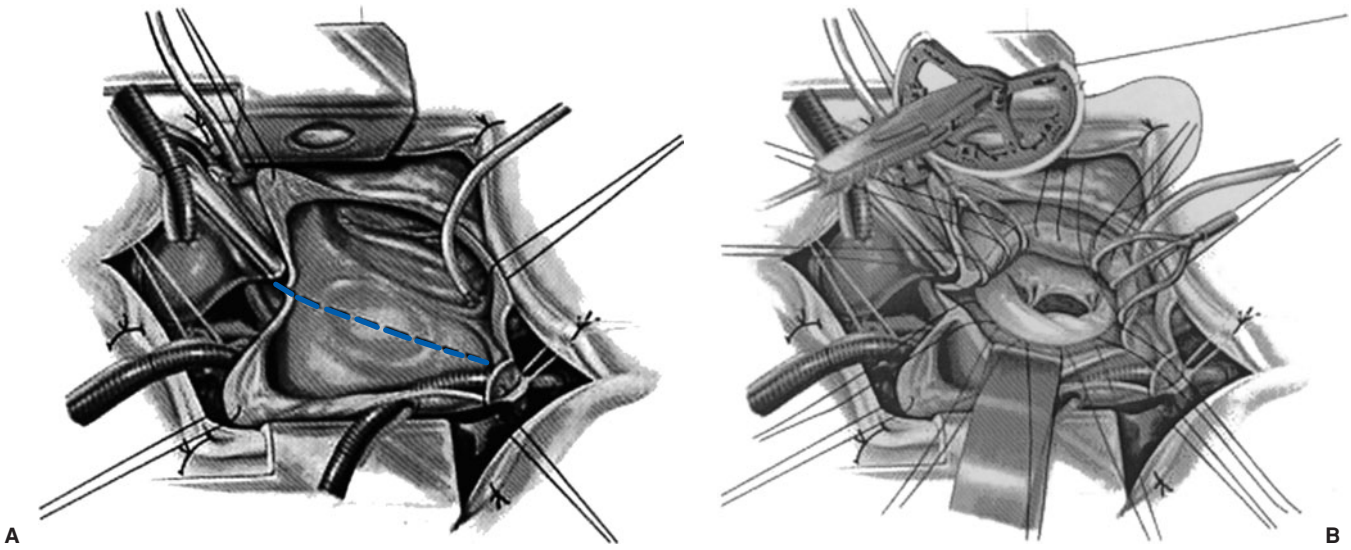


Figure 45-5. (A) Hemisternotomy with an extended atrial incision. Popularized by Dr. Cosgrove, the incision begins along the ventral right atrium and extends over the dome of the left atrium and through the left atrial wall and interatrial septum. (B) Mitral valve exposure is excellent through this hemisternotomy with an extended atrial incision, and complex repairs are similar in difficulty to full-sternotomy operations. (*Courtesy of Dr. D.M. Cosgrove.*)

from the right atrium, across the left atrial roof, and continuing caudally to divide the interatrial septum (Fig. 45-5A and B). This incision provides excellent exposure for aortic, mitral, and tricuspid valve replacements as well as repairs. Although the septal artery is divided, the incidence of atrial arrhythmias seems to parallel traditional interatrial groove atriotomies. For mitral and aortic surgery, Gundry suggested a similar hemisternotomy with single right atrial cannulation. This provides similar exposure to that described by opening the atrial roof, between the superior vena cava and aorta, without entering the right atrium.[15] Cohn now prefers a lower hemisternotomy for mitral surgery and uses a transseptal approach for valve exposure.[46] Loulmet and Carpentier reported using a midsternal, C-shaped, partial sternotomy for exposing mitral valves through the interatrial septum.[25] All of these incisions provide generous direct-vision exposure, if combined with pericardial retraction.

PERFUSION AND MYOCARDIAL PROTECTION

Cannulation for cardiopulmonary perfusion can be done in a number of ways for MIMVS. By combining modified traditional perfusion methods and new technology, surgeons have been able to speed the development of less invasive mitral operations. Thin-walled arterial and venous cannulas, transthoracic aortic cannulas, endoaortic balloon occluders, modified aortic clamping devices, percutaneous coronary sinus cardioplegia catheters, and assisted venous drainage all have aided in evolution of these operations.

We prefer to establish arterial access via femoral cannulation, employing small wire-wound Bio-Medicus (Medtronic, Inc., Minneapolis, Minn) arterial cannulas (17 to 21F) inserted over a guidewire (Fig. 45-6). Exposure of the femoral artery is gained through a 1.5-cm incision placed in the right groin crease. We ask our referring cardiologists to perform cardiac catheterizations via the left groin to avoid hematoma and scar formation. However, if the right groin vessels were used at catheterization, we still use the right femoral vessels for cannulation, as a better trajectory exists when introducing cannulas into the femoral-iliac venous system. Minimal dissection of the femoral vessels is performed without encircling the vessels. Lessened dissection has reduced seroma formation, which is now rare. For both venous and arterial cannulations, we believe that transesophageal echocardiographic guidance is mandatory to ensure proper guidewire insertion, prior to dilator and cannula passage. In our patients excellent flow rates have been attained with acceptable perfusion pressures in over 800 cases. Using this method, we have had only one retrograde aortic dissection and it was in a reoperative case. Mitral valve patients having either peripheral atherosclerosis or small iliac vessels may require direct aortic cannulation either through the incision or via a transthoracic Seldinger approach. Alternatively, cannulation of the right axillary artery has proven very successful for ascending aortic dissection surgery and could be used here as well.

Venous cannulation and drainage can be established in a variety of ways. At the Brigham and Women's Hospital, the right atrium is cannulated directly either through the incision or via a separate skin incision. Cosgrove introduces a small (23F) cannula directly into the right atrium through

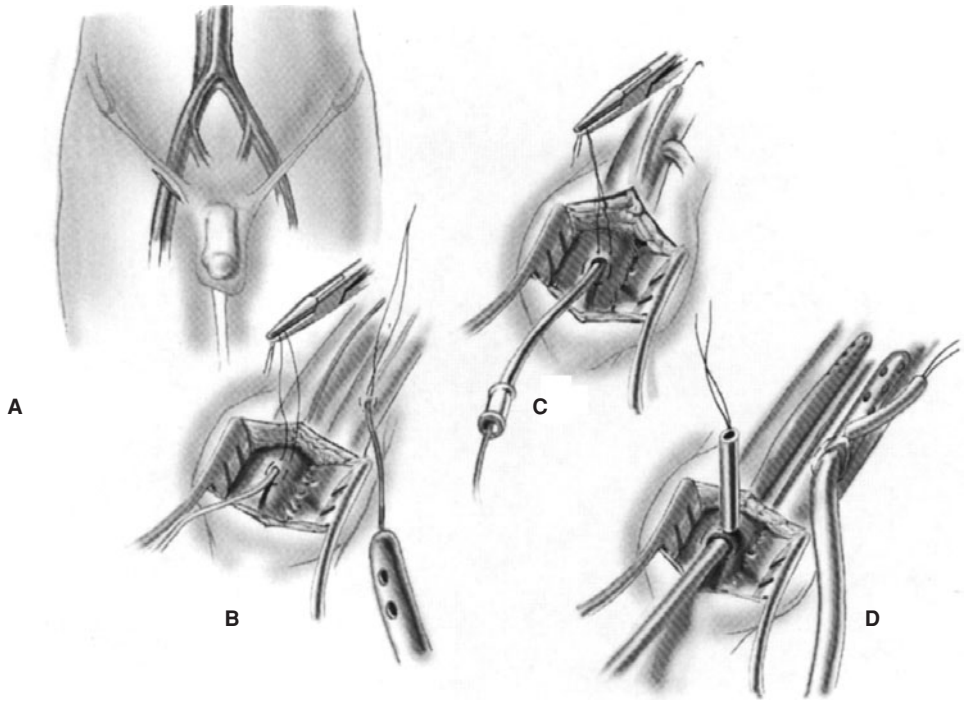


Figure 45-6. Thin-walled arterial perfusion cannula from Bio-Medicus (Medtronic Inc., Minneapolis, Minn) and percutaneous Carpentier dual-stage venous drainage cannula. (Medtronic Inc., Minneapolis, Minn). These cannulas are inserted from the femoral approach using the Seldinger guidewire method.

the ministernotomy.[47] Konertz and Gundry insert an oval-flat or "pancake" cannula into the right atrium to maximize hemisternotomy exposure.[12,15] Assisted venous drainage has been a major advance, as this technique enhances the efficiency of smaller cannulas. At our institution we use the Bio-Medicus centrifugal vortex pump to create variable negative pressures for venous drainage. Similarly, by combining wall suction (<40-cm H_2O pressure) and a closed-bag or hard-shell cardiotomy reservoir, a safe, simple, and economical assisted venous drainage system can be developed.[47] For superior caval drainage a 15 to 17F Biomedicus cannula is placed by the anesthesia team via the right internal jugular vein using the Seldinger technique with the tip positioned at the pericardial-caval junction (Fig. 45-7). In addition, a 22 or 25F Cardiovations (Johnson & Johnson, Inc., Sommerville, NJ) or a 21 or 23F Biomedicus cannula is inserted via the right femoral vein and advanced over a guidewire into the right atrium. Again, it is important to use transesophageal echocardiographic guidance for proper cannula placement and safety.

Myocardial preservation techniques used with MIMVS are similar to those used in sternotomy-based operations. We cool systemically to 28°C, as the ambient cardiac temperature generally is warmer than during conventional valve operations. With either a ministernotomy or mini-thoracotomy, a retrograde coronary sinus cardioplegia catheter can be inserted directly into the right atrium and position confirmed echocardiographically. Also, Port-Access technology provides a percutaneous retrograde cardioplegia

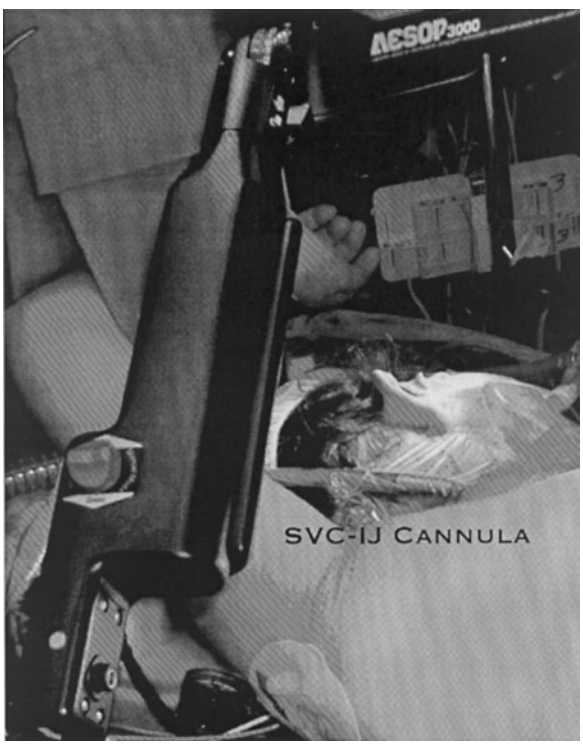


Figure 45-7. A right internal jugular venous catheter (15 or 17F) is combined with femoro-atrial active venous drainage for full bicaval access. This is important during atrial retraction in a near closed chest where the cavae can be kinked with distraction. The Aesop 3000 robotic camera arm is seen in the foreground.

catheter, which is introduced using echo via the internal jugular vein preoperatively. Although retrograde cardioplegia seems preferable, to ensure uniform cardiac cooling and even distribution of cardioplegia solutions, we have found antegrade cardioplegia efficient and preferable. In the presence of significant aortic insufficiency, a retrograde cardioplegia catheter is inserted before bypass is established. After aortic clamping, cold antegrade blood cardioplegia is infused every 15 minutes into the aortic root via a vent/cardioplegia cannula passed through the incision. An extra long Medtronic cardioplegia catheter facilitates aortic root positioning. During both videoscopic and robotic mitral surgery, we place a flexible sucker via the left atriotomy directly into the left superior pulmonary vein to clear residual blood from the surgical field.

For most minimally invasive mitral valve surgery, aortic occlusion is done using a standard cross-clamp placed through the incision. Cosgrove developed a flexible-handle aortic clamp to increase exposure through the hemi-sternotomy while minimizing inadvertent dislodgment (Fig. 45-8). For minithoracotomy mitral operations, we use a percutaneous transthoracic aortic cross-clamp. The clamp is inserted through a 4-mm incision placed in the right lateral third intercostal space. The posterior immobile "tine" of the clamp is positioned through the transverse sinus dorsal to the aorta (see Fig. 45-3; Fig 45-9A and B).[48] During placement, attention is necessary to prevent injury to the left atrial appendage and right pulmonary artery behind the aorta. This clamp has provided very secure occlusion without any aortic injuries. Occasionally we will apply this clamp in the "verso" direction with the mobile tine posterior to the aorta in the transverse sinus. In a short aorta this approach provides more length for cardioplegia needle insertion, and also arches the clamp away from the atriocaval junction, enabling atrial septal ventral retraction. The "verso" approach introduces a somewhat greater risk of pulmonary artery injury, and thus excellent visualization during deployment is essential.

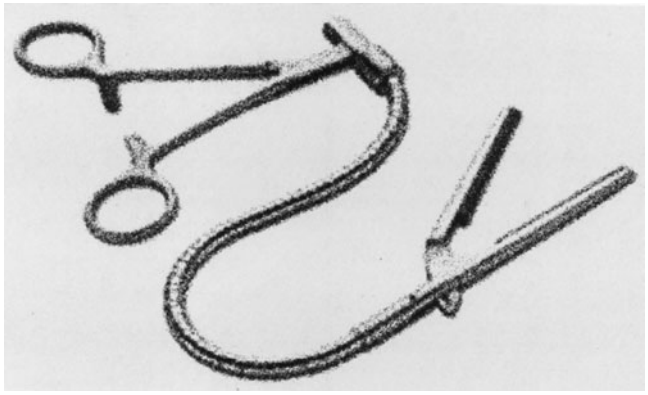


Figure 45-8. Flexible arm Cosgrove Aortic Clamp (V Muller Inc.). This mobile arm clamp allows complete aortic occlusion through limited access incisions, such as the ministernotomy. We have also used it for transthoracic aortic occlusion in mitral valve surgery.

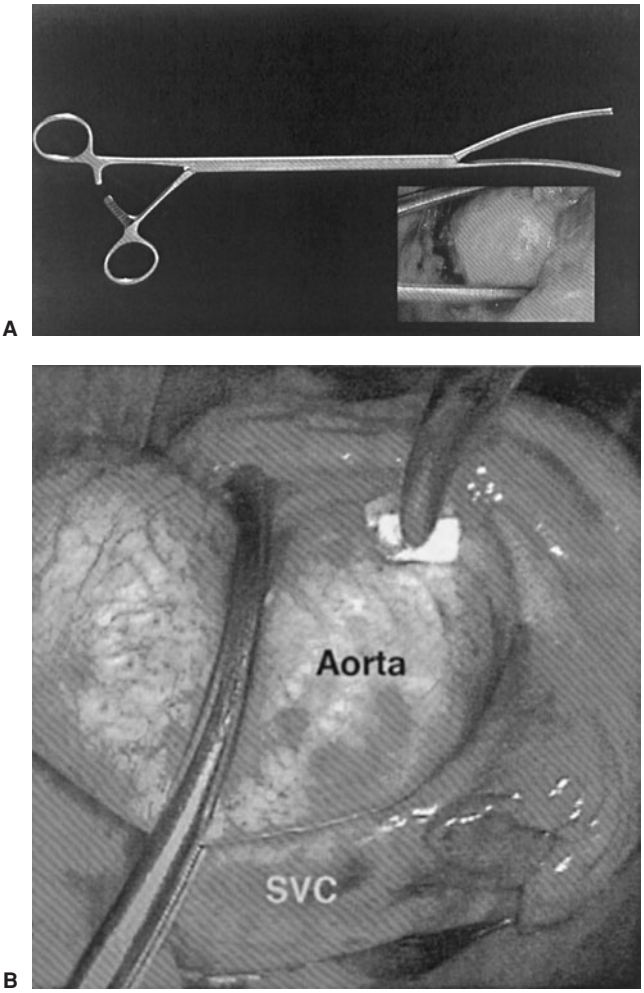


Figure 45-9. (A) The Chitwood transthoracic aortic cross-clamp (Scanlan International Inc., Minneapolis, Minn). The shaft is 4 mm in diameter and is passed through the third intercostal space (inset). The posterior or fixed prong of the clamp is passed through the transverse sinus under direct or video visualization to avoid injury to the right pulmonary artery, left atrial appendage, or left main coronary artery. The mobile prong is passed ventral to the aorta as far as the main pulmonary artery. (B) A videoscopic view of the deployed transthoracic aortic clamp. The aorta is fully compressed and an antegrade cardioplegia needle is shown in position just distal to the right coronary artery origin.

Vanermen, Murphy, Colvin, and Hargrove continue to be strong advocates for intra-aortic balloon occlusion for minimally invasive and robotic mitral surgery.[28,29,45,49] Most commonly these devices are introduced retrograde through the femoral artery. The occlusive balloon should be positioned, under echocardiographic control, just above the tubulosinus ridge in the ascending aorta[4,50] (Fig. 45-10). Balloon pressures often approximate 300 torr during complete occlusion, and the catheter tip position must be monitored continuously. Antegrade cardioplegia is given via the catheter central lumen. Balloon dislodgment can cause innominate artery occlusion, potentially causing neurologic injury, or prolapse into the left ventricle with inferior

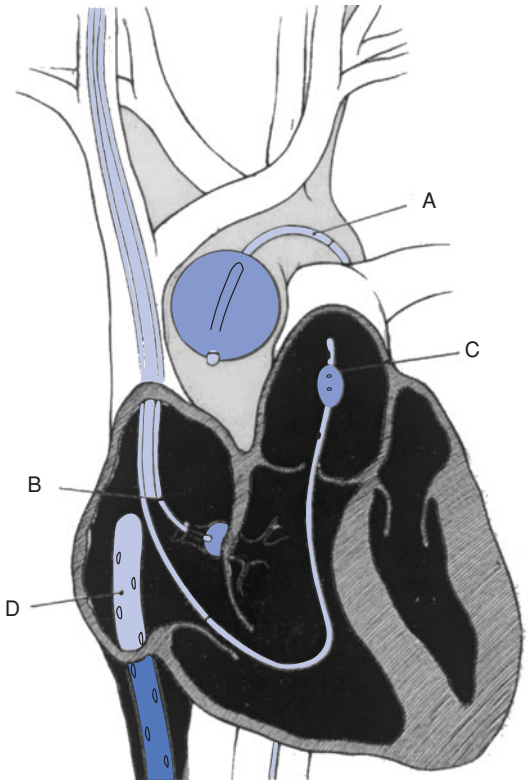


Figure 45-10. Port-Access system with transfemoral artery endoaortic balloon occluder (A), percutaneous internal jugular retrograde coronary sinus cardioplegia catheter (B), pulmonary artery vent (C), and femoral venous drainage catheter (D). (*Courtesy Cardiovations, Ethicon, Inc., Norwalk, Conn.*)

myocardial preservation. Thus, continuous echocardiographic monitoring is essential to detect any balloon migration. However, balloon occlusion has some advantages when there is limited access to the aorta compared to the transthoracic clamp method. Reichenspurner and colleagues demonstrated increased morbidity, cost, and operative/cross-clamp times when the endoballoon technique was used for mitral valve surgery.[23]

Meticulous cardiac air removal is most important in these operations, as difficulty exists in manipulating and deairing the cardiac apex. Also, in the right anterolateral minithoracotomy, air tends to be retained along the more dorsal ventricular septum and in the right pulmonary veins. Continuous carbon dioxide (CO_2) insufflation has been helpful in minimizing cardiac air and should be begun before cardiac chambers are opened. CO_2 is much more soluble in blood than air and displaces it very efficiently. We infuse CO_2 continuously (4 to 5 L/min) into the thorax via a 14-gauge angiocath, and prior to cross-clamp release, ventilate both lungs vigorously to draw the gas deep into all pulmonary veins. After atriotomy closure and following cross-clamp release, suction is applied to the aortic root vent, and the right coronary artery origin is compressed during early ejection. As the heart beats, nonatherosclerotic aortas can be partially reclamped to expel residual air into the vent suction. Constant transesophageal echocardiographic monitoring is essential to ensure adequate air removal before weaning from cardiopulmonary bypass. We have found that during ventral retraction fixed transthoracic atrial retractors distort the aortic root sinuses, causing air introduction. The robotic retractor can be positioned to minimize this problem.

Mitral Valve Exposure

Using a hemisternotomy, exposure of the mitral valve is best established using either extended right to left atrial incision or the transseptal approach championed by Cosgrove and Cohn, respectively (see Figs. 45-2A and 45-5A and B). A hand-held retractor placed through the incision facilitates valvular exposure using these incisions. For endoscopic and robotic mitral repairs most of us have used a fixed-blade transthoracic retractor immobilized by a table-mounted clamp. Blades of various sizes are available; however, after fixed-retractor deployment, movement to provide additional exposure is limited. For reoperative mitral surgery through a minithoracotomy, we prefer to use the hand-held retractor shown in Fig. 45-11. It allows variable access to all parts of the left atrium and subvalvular structures; moreover, it can provide access in very deep chests. Recently, a fourth arm robotic retractor for the da Vinci system was developed (Fig. 45-12). Using a separate robotic arm retractor, activated alternately through the left instrument arm control, blade positions

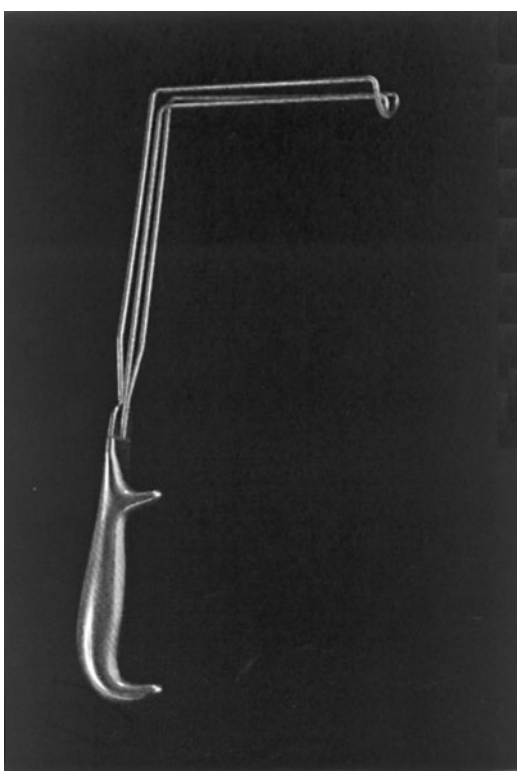


Figure 45-11. Chitwood hand-held left atrial retractor.

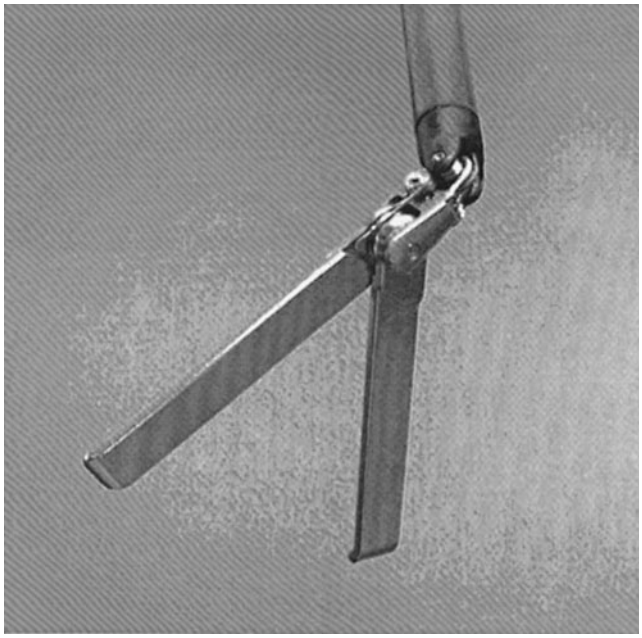


Figure 45-12. Left atrial endowrist retractor for the da Vinci system.

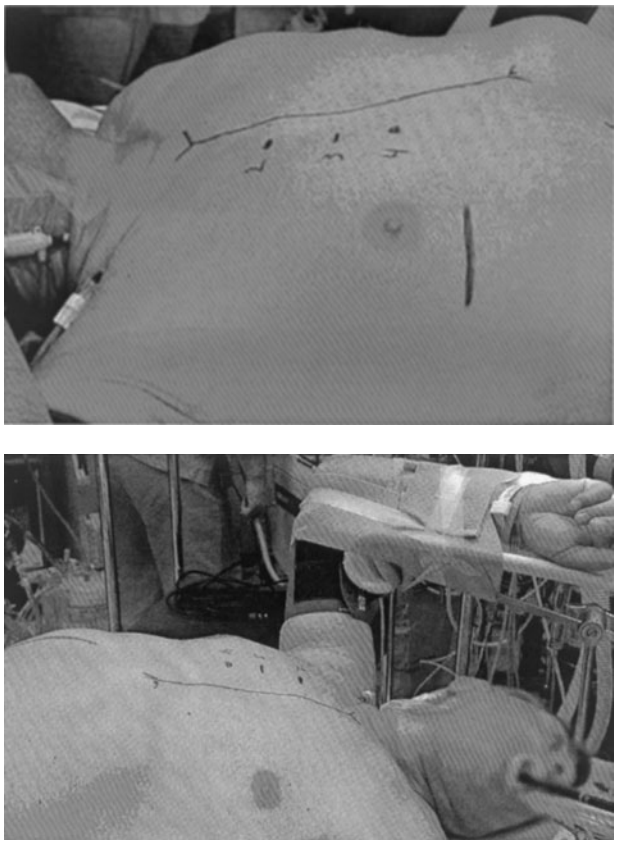


Figure 45-13. (A) The sternum and intercostal spaces are marked. A 3- to 4-cm incision is made in the inframammary fold. The chest is entered via the fourth intercostal space. (B) The patient is positioned in the semi–left lateral decubitus position. In most patients the arm is best left on the side, obviating the need for an arm rest, which allows more room for positioning the da Vinci robotic arms.

and length can be altered dynamically. The retractor arm is inserted via a third interspace port, medial to the anterior axillary line. We have used it in over 50 mitral repairs and have found that this device enables these operations greatly.

Robotic Mitral Valve Surgery

For both video-assisted and robotic mitral surgery we position the patient as shown in Fig. 45-13A and B. However, in larger patients the right arm is best left by the side, requiring the cross-clamp to be placed through the mid-axilla. The Aesop 3000 computed-activated camera manipulator has remained a pillar of control for our minimally invasive video-assisted approach. Figure 45-14A and B shows how this device is positioned during these operations. Even though automatic vision control has proved valuable, using this video-assistance method, surgeons still must operate with long instruments in a 2-D operative field (Fig. 45-15). Knots are tied and sutures cut using specialized hand-held shafted instruments (Figs. 45-16A and B and 45-17) The da Vinci surgical system is comprised of three components: a surgeon console, an instrument cart, and a visioning platform (Fig. 45-18A and B).[51] This device provides intracardiac telepresence and tissue micromanipulation. The operative console is removed physically from the patient and allows the surgeon to sit comfortably, resting the arms ergonomically with his or her head positioned in a 3-D vision array. The surgeon's finger and wrist movements are registered, through sensors, in computer memory banks, and then these actions are transferred efficiently to an instrument cart, which operates the synchronous end-effecter instruments (Fig. 45-19). Through 1-cm ports, instruments are positioned near cardiac operative sites in the thorax, and the camera is passed via a 4-cm working port used for suture and prosthesis passage (Fig. 45-20A). Every analog finger movement, along with inherent human tremor at 8 to 10 Hz/s, is converted into binary digital data, which are smoothed and filtered to increase micro-instrument precision. Wrist-like instrument articulation emulates precisely the surgeon's actions at the tissue level, and dexterity becomes enhanced through combined tremor suppression and motion scaling. This allows both increased precision and dexterity with the surgeon becoming truly ambidextrous. A clutching mechanism enables re-adjustment of hand positions to maintain an optimal ergonomic attitude with respect to the visual field. This clutch acts very much like a computer mouse, which can be reoriented by lifting and repositioning it to reestablish unrestrained freedom of computer activation. The 3-D digital visioning system enables natural depth perception with high-power magnification (10×). Both 0° and 30° endoscopes can be manipulated electronically to

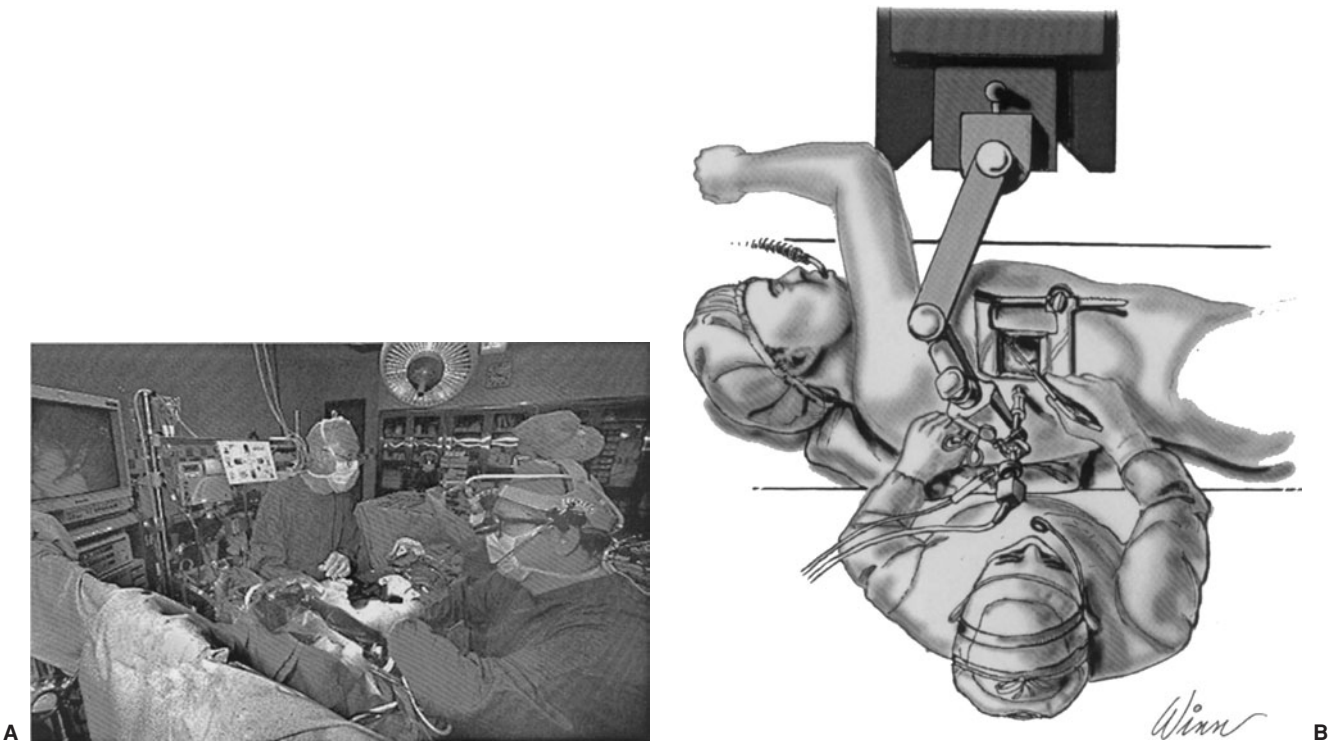


Figure 45-14. (A, B) During minimally invasive video-assisted mitral surgery, the camera is voice activated and positioned by the surgeon using the Aesop 3000 robot. Operative maneuvers are made through the 5-cm incision using long instruments and secondary vision.

look either "up" or "down" within the heart. Access to and visualization of the internal thoracic artery, coronary arteries, and mitral apparatus have been shown to be excellent. The operator becomes ensconced in the 3-D operative topography and can perform extremely precise surgical manipulations, devoid of traditional distractions. Figure 45-20B shows the surgeon's operative field during a da Vinci mitral repair. Perfusion technology is the same as described above for video-assisted operations and a larger mini-thoracotomy.

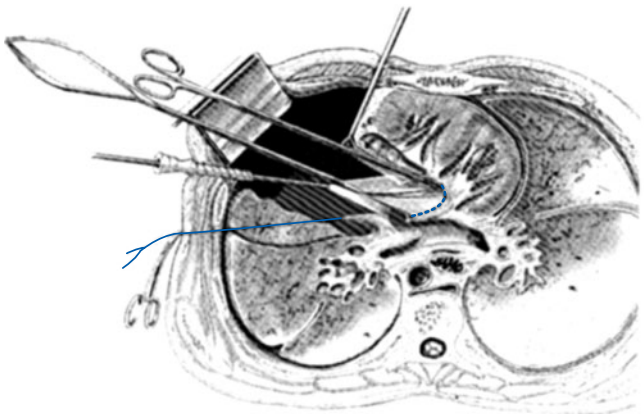


Figure 45-15. Mini right thoracotomy approach for mitral surgery. Long instruments are required to operate in a two-dimensional operative field.

Complex Mitral Valve Repairs with the da Vinci System

Heretofore, many surgeons avoided repairing valves with large bileaflet defects. However, we have found that repairs of these maladies are particularly amenable to robotic telemanipulation because of high-definition 3-D magnified vision and the ability to translocate multiple individual chordae tendineae to new leaflet sites. After the first 50 mitral repairs our group began to repair more complex valves as well as develop and use new adjunctive technology during robotic surgery. Figures 45-21 through 45-27 illustrate the variety of methods we use routinely for both simple and complex repairs. The mainstay of our repairs for posterior leaflet prolapses, secondary to ruptured or redundant chordae, has been a modification of the classic quadrangular resection. As seen in Fig. 45-21, a trapezoidal or triangular resection is made of the central portion of redundant posterior leaflet segment. This conserves annular distance that must be closed and limits tension along the posterior annulus, especially when one of the scallops is much larger than the others. This is often the case in P_2 prolapse, where P_1 and P_3 may be diminutive. The minor base of the trapezoid is closed with a figure-of-eight braided suture (2-0 Cardioflon [Peters, Inc., Paris, France]). Often we conserve leaflet tissue by decreasing the size of P_2, and when the leading edges are approximated, chordae are shortened effectively as they assume a new angle with the leaflet insertions, thus reducing the prolapse to below the annular plane. When there is an

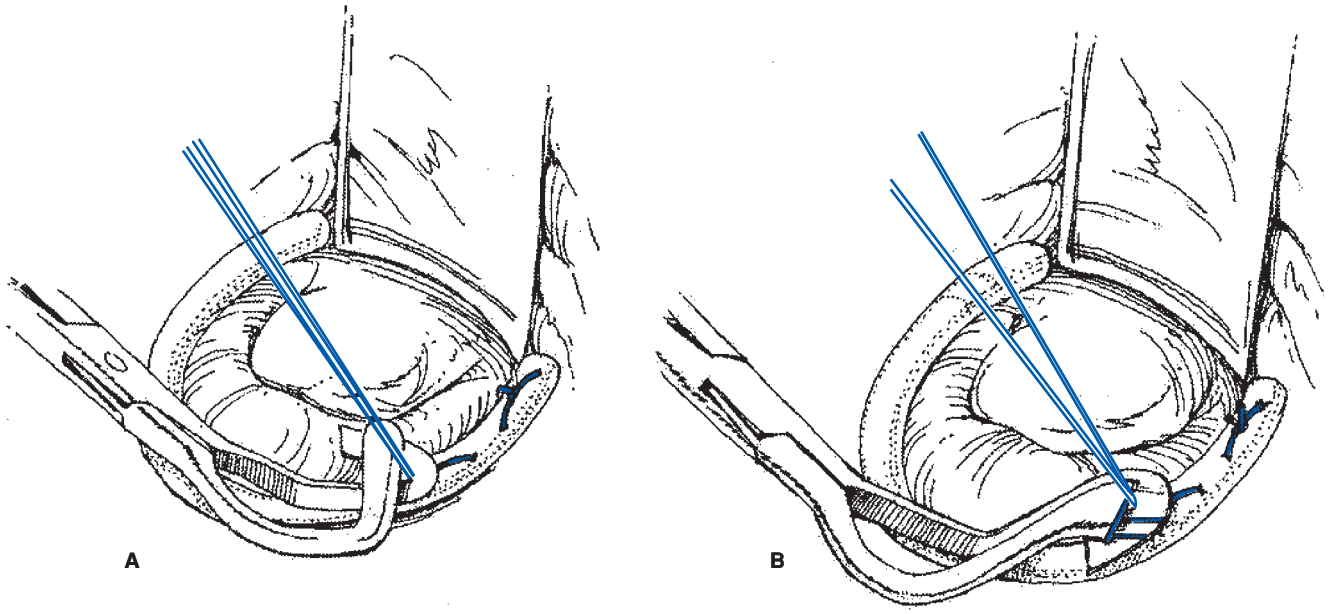


Figure 45-16. Knot pusher (A) and cutter (B).

isolated anterior leaflet prolapse, chordae can either be transferred from the posterior leaflet (Fig. 45-22A and B) or the redundancy reduced using PTFE neochords (Fig. 45-23A and B). When any posterior leaflet scallop is radially higher than 2 cm or the anterior leaflet is longer than 3 cm, there is a greater chance of systolic anterior motion of the anterior leaflet occurring. This is especially true when the aortic outflow is narrowed by a thickened interventricular septum or a relatively acute angle between the aortic and mitral valve planes. Generally, systolic anterior motion can be avoided by reducing the posterior leaflet height with a sliding-plasty

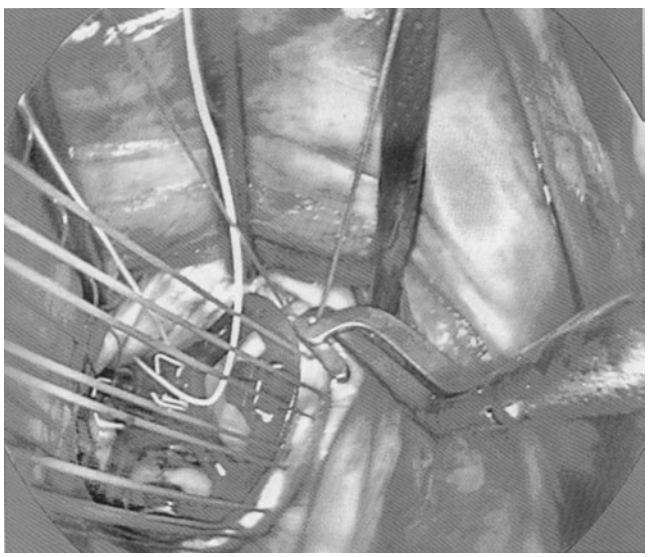


Figure 45-17. Knot pusher used to secure knots during annuloplasty band placement.

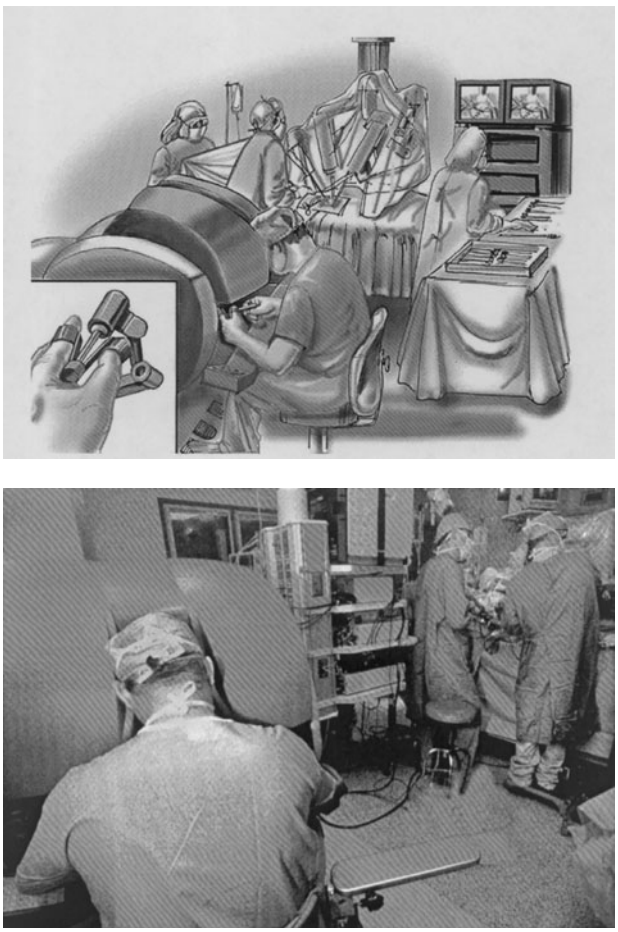


Figure 45-18. (A) The da Vinci Robotic Telemanipulation System. The operative console is in the foreground while the instrument cart is at the table. Both the operating surgeon and patient-side assistant are shown. (B) da Vinci robotic mitral valve repair. The surgeon is positioned approximately 10 feet from the patient. The instrument cart is placed on the left side of the tilted patient with arms entering the right thorax.

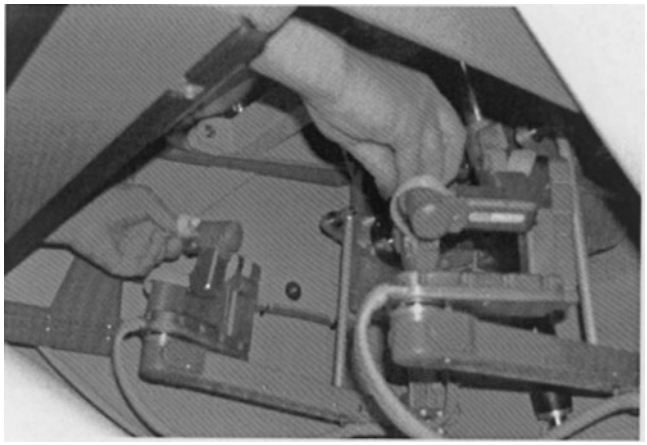
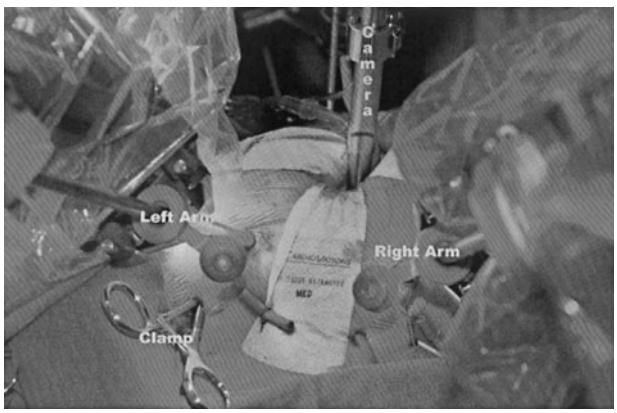
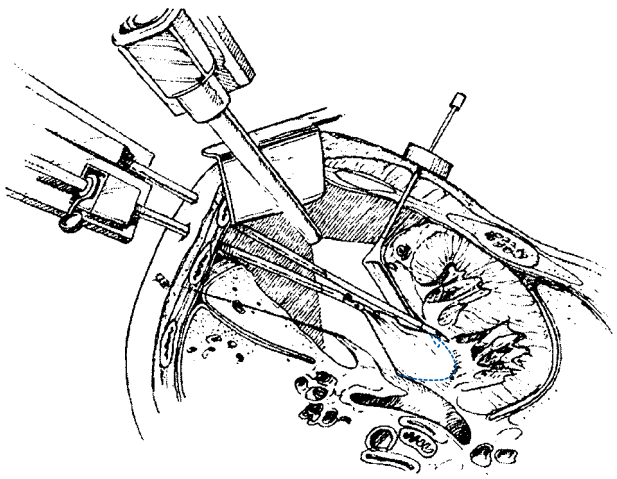


Figure 45-19. The operating surgeon manipulates affecter instrument tips in the patient's thorax via ergonomic handpieces that transfer filtered digitized data into smoothed movements.



A



B

Figure 45-20. (A) da Vinci bedside setup for mitral valve surgery. (B) This thoracic cross-section during a da Vinci mitral operation shows how both instrument arms and the visual field converge at the operative plane to allow an unobstructed topographic view with full access to valvular and subvalvular structures.

after prolapsing segments are resected (Fig. 45-24A through E). In patients with bileaflet prolapse or Barlow's disease, part of resected segments from the posterior leaflet is transposed to the redundant anterior leaflet segments and attached with monofilament 4-0 sutures. Again, "swinging" a chord-bearing piece of posterior leaflet to the undersurface of the anterior leaflet generally reduces the prolapse of the latter (Fig. 45-25A through E). To date, all of our robotic repairs have been supported by an annuloplasty using a Cosgrove-Edwards band (Edwards Lifesciences, Inc., Irvine, Calif). We have used two suturing methods to attach the band. We either use single-arm 2-0 braided sutures as shown in Fig. 45-26 A or nitinol U-clips (Medtronic, Inc., Minneapolis, Minn) as shown in Figs. 45-26B and C and 45-27. For insertion of a band alone or when a limited resection is done, we prefer to use the U-clips, which enable faster deployment. However, when tension is applied, as in larger resections and sliding-plasties, the compressive force of sutures provides seemingly better reinforcement of the repair.

CURRENT STATUS OF MINIMALLY INVASIVE MITRAL VALVE SURGERY

Cosgrove and Gundry have been consistent proponents of using the hemisternotomy for mitral valve surgery. They have considered the ministernotomy technique to be more reproducible for surgeons with variable experiences and abilities. Both complex replacements and repairs have been done through this incision and to date few repair failures have resulted from this exposure method. Between 1996 and early 2002, Cosgrove and his Cleveland Clinic group performed 1427 minimally invasive mitral operations, using direct vision, the upper hemi-sternotomy, and modified perfusion methods. As noted earlier, the extended atriotomy, first proposed by Guiardon and used continually by the Cleveland Clinic group, apparently has caused excessive atrial arrhythmias. Of these patients, 82% had degenerative and 9% had rheumatic disease. Of all mitral valves 90% were insufficient and nearly all were repaired, with 98% having a band annuloplasty and 85% undergoing leaflet resections. Perfusion and aortic occlusion times averaged 80 and 60 minutes, respectively, and were shorter than those of many experienced surgeons using a full sternotomy. Moreover, since 1996 perfusion times have decreased more significantly than arrest times. Their series presents impressive mortality (0.3%) and complication rates (bleeding [3.1%], strokes [1.8%], and respiratory insufficiency [0.8%]). Conversions to a full sternotomy have fallen at the Cleveland Clinic from 5% in 1997 to 0.5% in 2002 (1.5% mean), and most of these were related to poor exposure and not bleeding. Only 7% of patients were transfused, and the mean hospitalization was 6.5 days with 20% being discharged in less than 4 days.

After initially using a right parasternal incision with bicaval cannulation and left atrial entry via the interatrial septum, Cohn and associates now prefer a lower hemi-

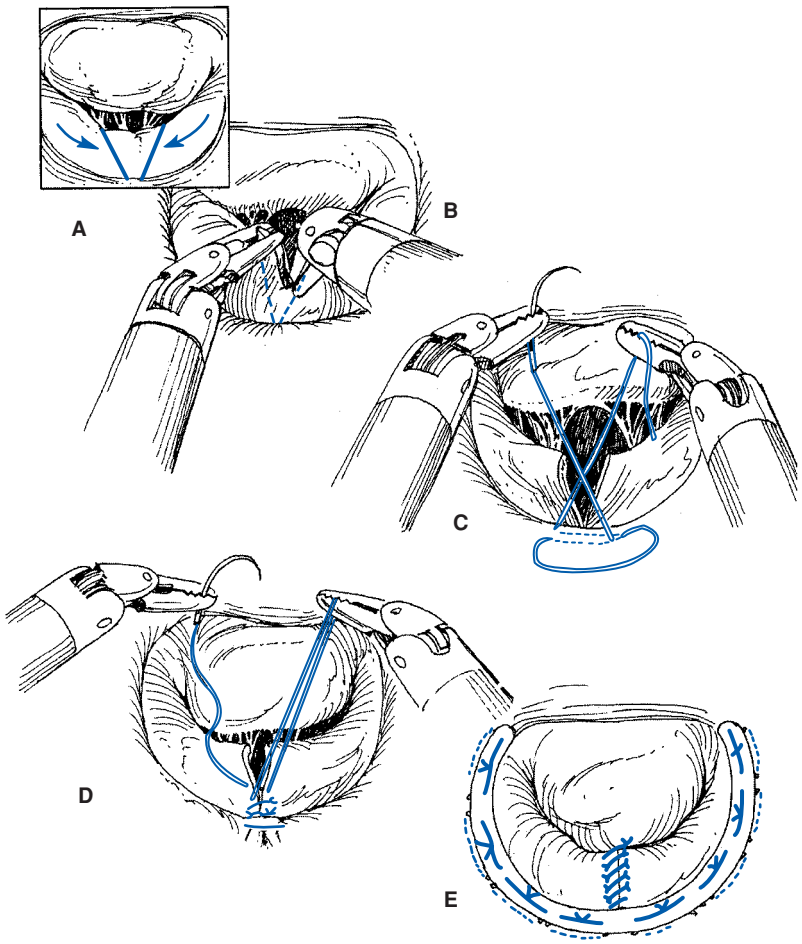


Figure 45-21. Triangular or trapezoidal resection of the central portion of a redundant P_2 segment.

sternotomy for mitral valve surgery. Of the 411 mitral patients operated between 1996 and early 2002, 201 had hemisternotomies and 201 had parasternal incisions, with 8 having a minithoracotomy. Myxomatous (81%), rheumatic (10%), and endocarditis (4%) were the most common etiologies. In 88% repairs were done, and in the remaining 12% replacements were done using mechanical valves (84%). Their operative mortality was 0.2% with no deaths in the repair group. Bleeding occurred in 2% and 38% were transfused with an average of one unit of packed cells per patient. Strokes occurred in 2.2% of patients and myocardial infarctions in 1.0%. Patients were hospitalized for a mean of 6 days and 8.3% required additional rehabilitation prior to discharge. Recently, this series was updated to a total of 1000 minimally invasive valve operations (526 aortic and 474 mitral procedures). In the mitral group 416 had repairs while 58 patients had replacements. They compared this group to a cohort of 337 patients undergoing mitral valve surgery via a sternotomy. The median perfusion and cross-clamp times were 121 minutes and 82 minutes for the minimally invasive group versus 125 minutes and 87 minutes ($p < .01$) for the sternotomy cohort, respectively. In the sternotomy group 18 patients (5%) had perioperative myocardial infarction compared with 2 patients (0.4%) in the minimally invasive group. Also, the minimally invasive group had a shorter length of stay (5 versus 7 days) and was discharged home more frequently.[52] Both of these large series demonstrate benefits using a less invasive approach and that repair results are comparable to operations done through a full sternotomy. Wound healing has not presented a problem using a modified sternotomy.

Grossi and associates at New York University compared 100 minimally invasive mitral operations, done through a 6- to 8-cm mini-thoracotomy, using direct vision and Port-access methods, to a cohort of 100 conventional mitral operations.[40] They reported a perioperative mortality of 1.0%. In these patients 80% had a posterior leaflet repair and 30% had an anterior leaflet reconstruction. Their results suggested that minimally invasive mitral operations can be done safely using Port-access methods with similar results as conventional operations and with no added mortality or morbidity. At the same time they had fewer transfusions, shorter lengths of hospital stay, and fewer septic complications, despite longer cardiopulmonary bypass times. In a multi-institutional analysis of 491 Port-access mitral repairs from 104 centers, Glower reported that 86% of all valves were repaired with aortic cross-clamp times of 90 minutes and perfusion times of 137 minutes.[53,54] The overall

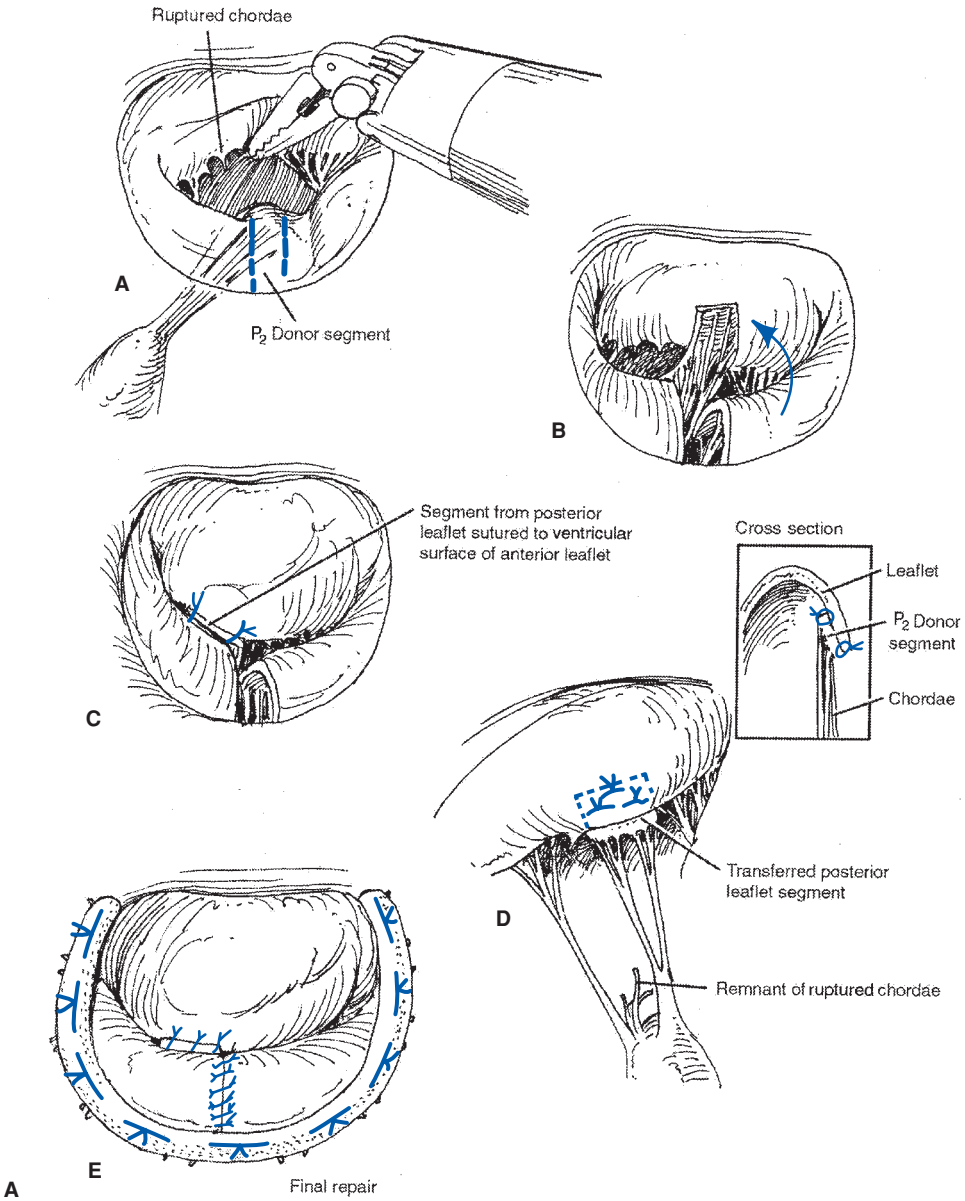
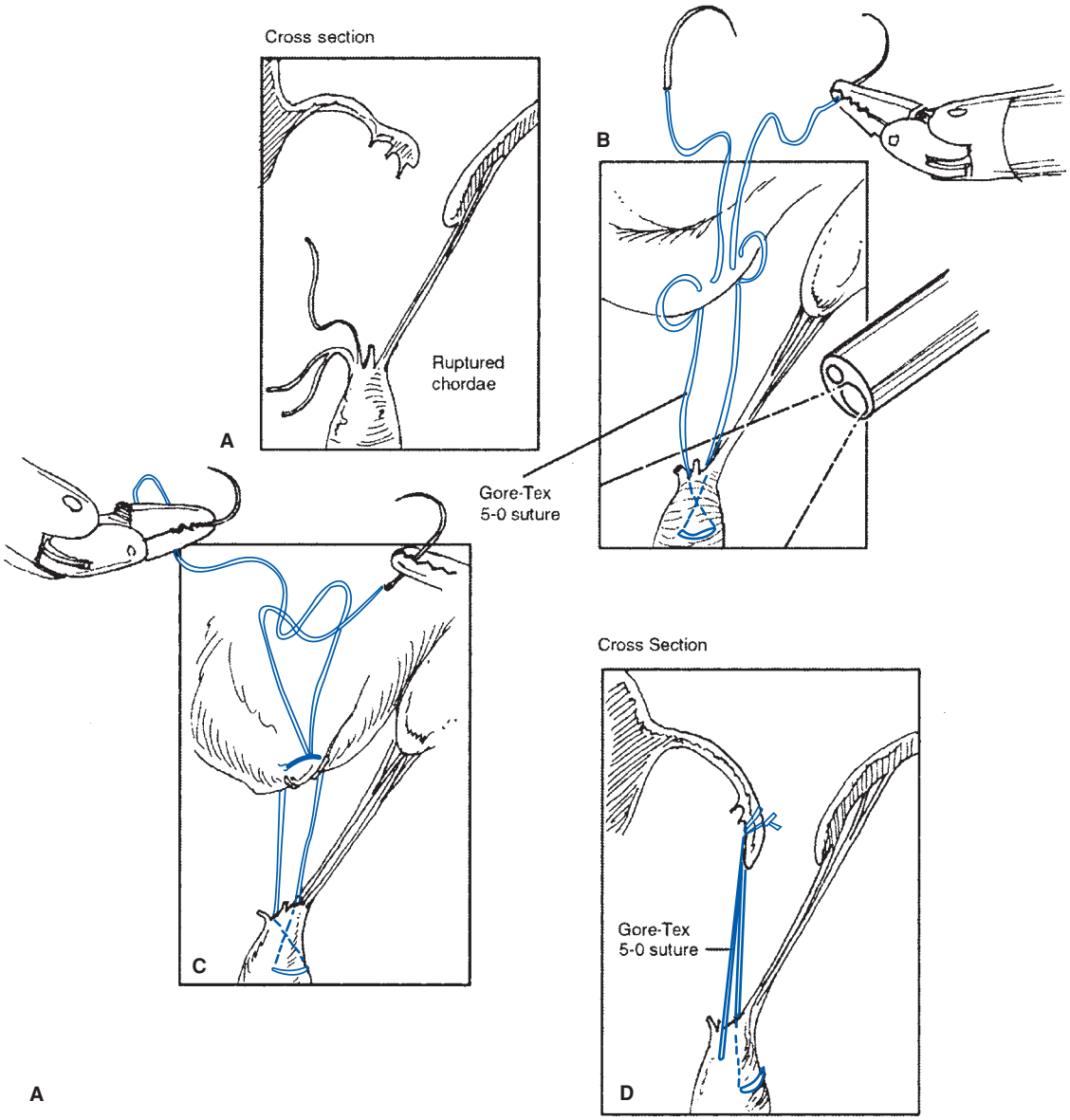


Figure 45-22. (A, B) Chordal transfer from posterior leaflet for the treatment of isolated anterior leaflet prolapse.



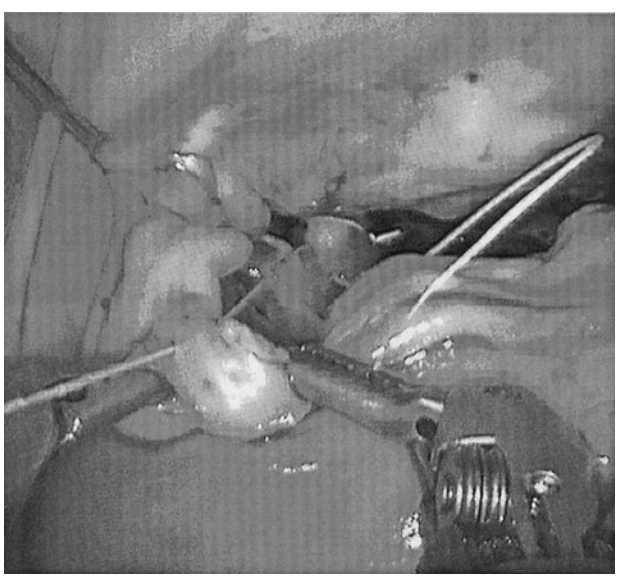
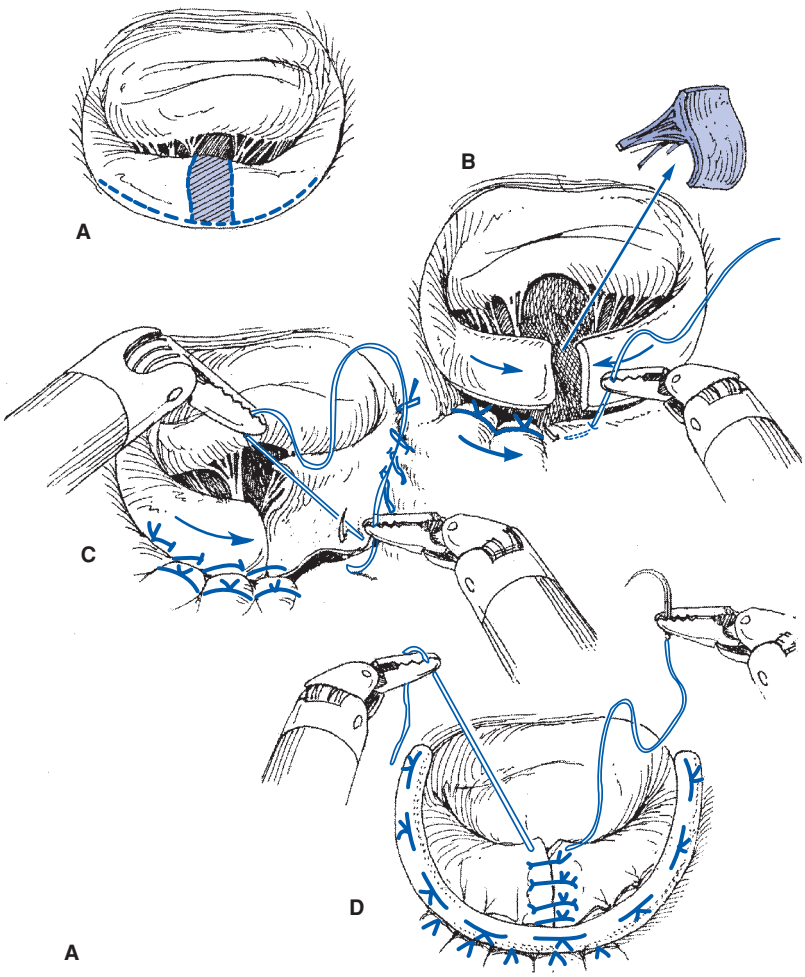


Figure 45-23. (A, B) Gore-Tex neochords are used for treating leaflet prolapse and/or for the replacement of ruptured chords.



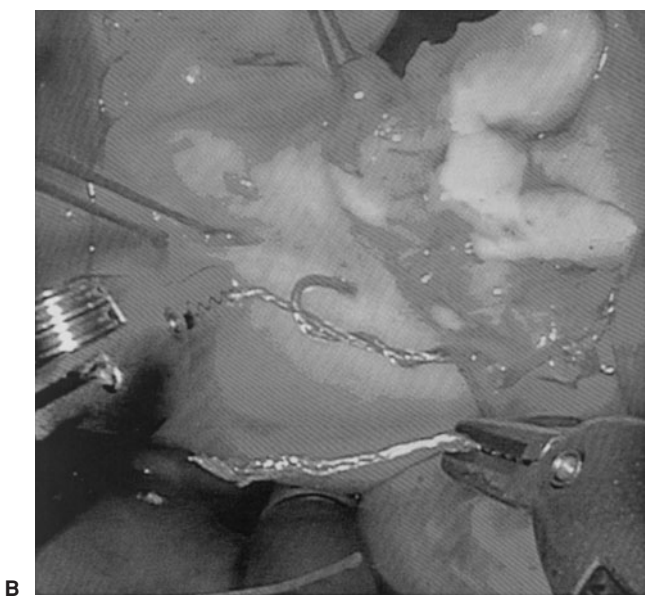


Figure 45-24. A da Vinci mitral valve repair. (A) The P_2 segment of the posterior leaflet is being resected by robotic microscissors. (B) The annulus is reduced, the sliding-plasty is completed (C), and both P_1 and P_3 are approximated (D). (E) Instrument arms of the da Vinci device are used for tying sutures intracorporally.

mortality for repairs was 1.6% and was 5.5% for replacements. Age was the only independent predictor of strokes (2.7%) in these patients. Neurologic complications associated with early use of this technique have diminished with the advent of better devices and more experience. The overall length of stay for this large group of mitral patients was 7 days.

In early 2001 the East Carolina University group reported 128 successful video-assisted mitral valve operations.[27] At first, patients with anterior leaflet pathology and

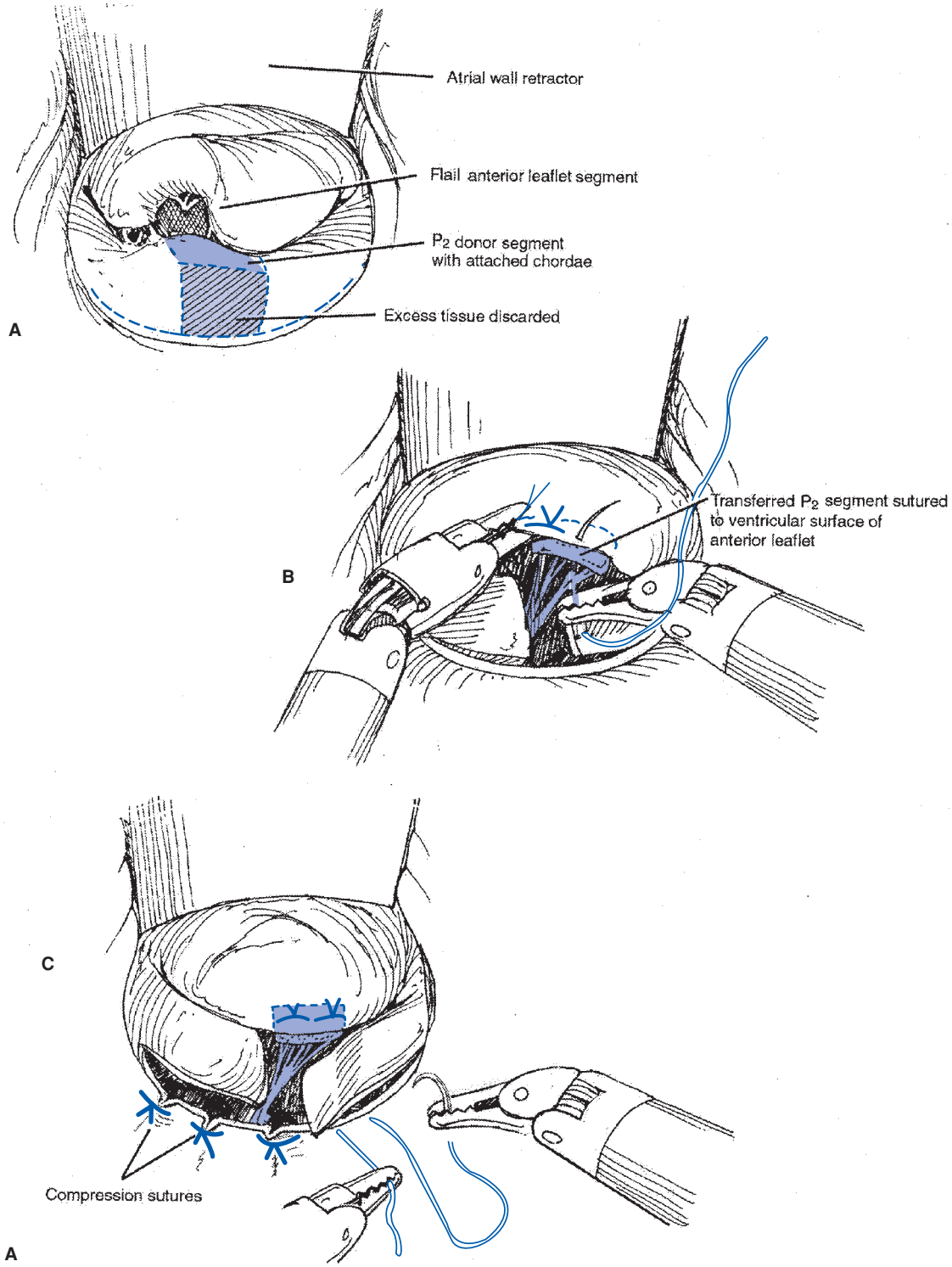


Figure 45-25. Repair of Barlow's or bileaflet disease. Resection of P_2 maintaining the chordal apparatus intact is performed (A) followed by transfer of this segment to the anterior leaflet (continued)

annular calcification were avoided. However, these patients are now operated on using video-assisted technique. Table 45-3 details our current criteria for patient selection. In this series repairs included quadrangular resections, annuloplasties, and complex chordal procedures. The majority of patients had degenerative disease and 61% of the total group underwent a repair. When the early series was combined with the next 100 video-assisted mitral operations, repairs increased to 81% of all mitral patients. The operative and 30-day mortalities for our entire series have been 0.4% and 1.7%,

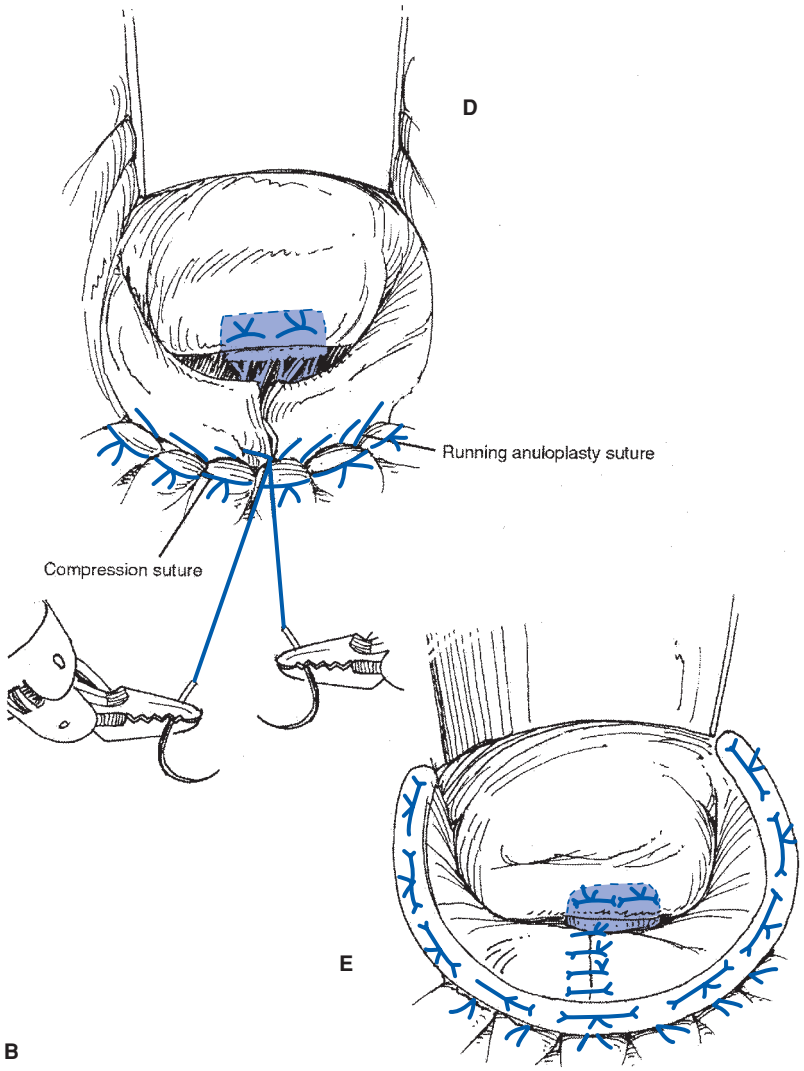


Figure 45-25. *(continued)* (B). The posterior annulus is then reduced (C). The sliding-plasty is then completed (D) followed by approximation of P_1 and P_3 (E).

respectively. After we adopted the Aesop 3000 robot for voice-activated endoscopic camera control, cross-clamp and perfusion times fell secondary to improved visualization and reduced lens cleaning. However, in the latter half of the early series cross-clamp (90 minutes) and perfusion times (143 minutes) still remained longer than those of conventional operations. Currently at our institution cardiac arrest and perfusion times have fallen to 70 and 100 minutes, respectively, for video-assisted mitral operations. Interestingly, we have seen no difference in bleeding and transfusion requirements between our conventional and minimally invasive cases. However, the hospital lengths of stay have averaged 4.9 days compared to 8 days for conventional operations. Of these 324 patients there were 2 (0.6%) operative deaths, 9 (2.8%) in-hospital deaths, 2 (0.6%) conversions to a sternotomy, 3 (0.9%) strokes, 14 (4.3%) re-explorations for bleeding, 3 (0.9%) perioperative myocardial infarctions, and 1 (0.3%) aortic dissection. A total of 31.8% of the patients received a blood product transfusion. In this series, 14 patients (4.3%) have required a mitral valve reoperation. We have operated on 71 patients (31 mitral valve repairs and 40 mitral valve replacements) having had prior coronary or mitral surgery. These patients underwent video-assisted reoperations with a 9.8% mortality as well as four re-explorations for bleeding and one stroke (1.4%).[55]

Mohr and associates reported 154 video-assisted mitral valve operations using Aesop 3000 robotic camera control.[24,31,56] In these patients the aortic cross-clamp and perfusion times were similar to those of their conventional operations, and the operative mortality was 1.2%. They considered 3-D visualization to be the key to excellent results during videoscopic valve reconstructions. In a study comparing the Port-access technique to transthoracic clamping, Wimmer-Greinecker obtained similar repair results but with faster operations, fewer technical difficulties, and lower cost using the latter method.[57] In early 2002, Vanermen described 187 patients undergoing totally video-directed repairs using the Port-access method and no rib spreading. He used a 2-D endoscopic camera to perform complex repairs with excellent results at follow-up 19 months later.[43] The hospital mortality was 0.5%, and there were two conversions to a sternotomy for bleeding. Freedom from reoperation was 95% at 4 years. Over 90% of patients had minimal postoperative pain. Although this and other series have not been randomized,

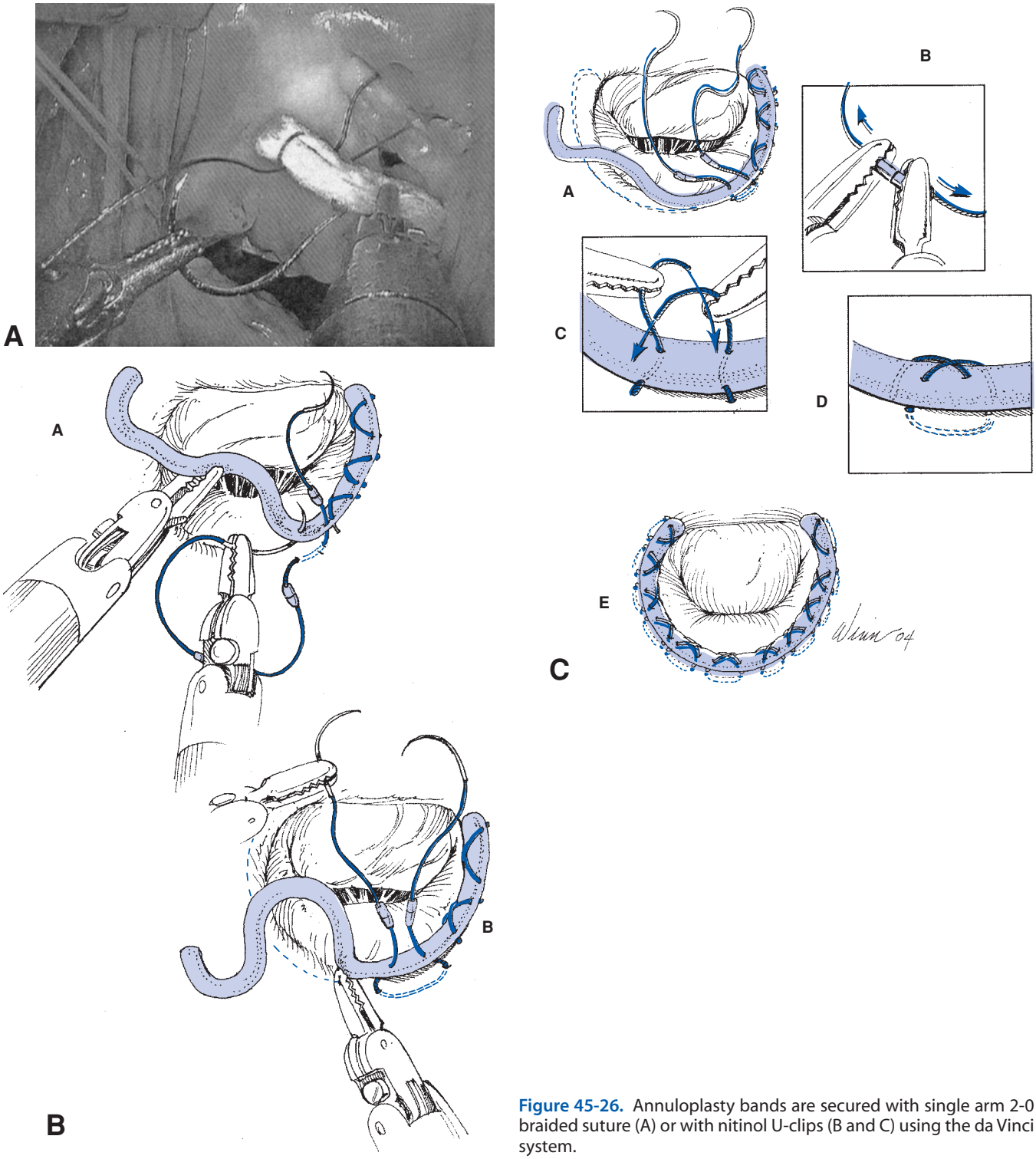


Figure 45-26. Annuloplasty bands are secured with single arm 2-0 braided suture (A) or with nitinol U-clips (B and C) using the da Vinci system.

there are strong suggestions that mitral valve surgery has entered a new era and that video techniques can facilitate these operations.

In 2003 Vanermen and associates updated their results in 306 mitral patients (226 repairs and 80 replacements). Six patients were converted to median sternotomy because of peripheral cannulation complications, and there was a 1% (n = 3) 30-day mortality. In this series 46% of patients were back to work within 4 weeks, and the overall freedom from reoperation was 91% at 4 years. Their results continued to suggest that endoscopic mitral valve surgery is safe with excellent results.[58]

Hargrove at the University of Pennsylvania–Presbyterian Hospital has performed over 530 video-assisted minimally invasive mitral valve operations since 1998. The mean age for his first 520 patients (437 repairs and 83 replacements) was 60 years in 271 male and 249 female patients. Mean perfusion and cross-clamp times were 142 and 102

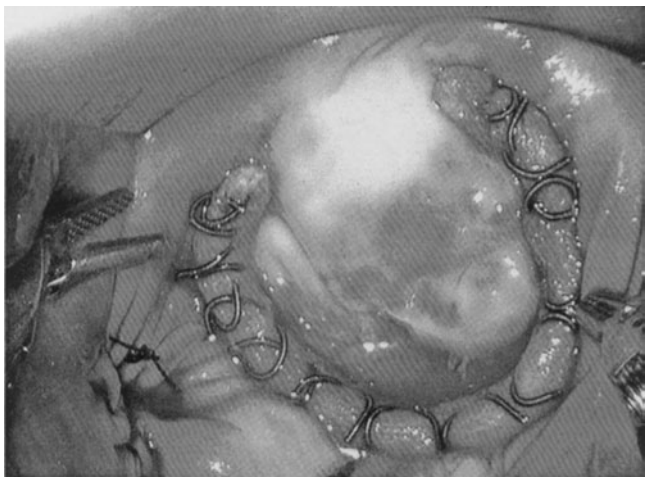


Figure 45-27. Completed repair using nitinol U-clips to secure the annuloplasty band.

minutes, respectively. Of his patients 19 were operated on using hypothermic fibrillatory arrest at a mean perfusion time of 122 minutes. Postoperative repair transesophageal echocardiograms showed no leak in 305 patients, 1+ regurgitation in 129 patients, and 2+ insufficiency in 3 patients. There were 11 (2%) deaths, 14 (2.6%) strokes, and 32 (6.1%) re-explorations for bleeding. The average length of stay was 8 days and freedom from reoperation 97%. Hargrove has become convinced that small-incision and videoscopic mitral surgery is safe, effective, economical, and better accepted by patients than conventional sternotomy operations. The long-term results of all of the above series continue to confirm that minimally invasive mitral operations already have taken a prominent place in the evolution of cardiac surgery.

Table 45–3.

Current Patient Selection: Videoscopic or Video-Assisted Mitral Valve Surgery

Unsuitable candidates
Highly calcified mitral annulus
Severe pulmonary hypertension, especially with a small right coronary artery
Significant untreated coronary disease
Severe peripheral atherosclerosis
Prior right chest surgery
Suitable candidates
Patients with primary mitral valve disease
Reoperative mitral valve patients
Bileaflet and/or anterior leaflet disease
Combined tricuspid and mitral operations
Mild annular calcification
Obese or large patients
Elderly patients

Robotic Mitral Valve Surgery

The East Carolina University group performed the first da Vinci system robotic mitral valve repair in North America in May 2000. Since then, we have performed over 270 robotic mitral valve repairs. The first Food and Drug Administration (FDA) safety and efficacy trial was conducted at our institution in 2000 and included 20 patients.[33,59] Leaflet resections, sliding-plasties, chordal transfers, neochord insertions, and annuloplasties all were performed successfully. This initial study demonstrated that although operative times were longer, when compared with conventional mitral valve surgery, the results were comparable. There were no device-related complications. Postoperative hospital stays averaged 4 days, and all patients returned to normal activity by 1 month following surgery. Early postoperative echocardiograms at 3 months demonstrated that none of the patients had more than trace mitral regurgitation.

These initial results were encouraging and prompted a phase II multicenter FDA trial, which was completed in 2002.[60] A total of 112 patients were enrolled at 10 different institutions and all types of repairs were performed. Following surgery nine patients (8%) had grade 2 or higher mitral regurgitation, and six patients (5%) required a reoperation. Although the reoperative number was high for the number of patients, failures were distributed evenly among centers, with some centers having performed fewer than 10 procedures. There were no deaths, strokes, or device-related complications. These results prompted FDA approval (2002) of the da Vinci system for mitral valve surgery. Subsequently, at the 2005 American Heart Association meeting, we reported results in our first 200 robotic mitral repair patients.[61] The average patient age was 57 years with total operative time of 285 minutes, cardiopulmonary bypass time of 156 minutes, and cross-clamp time of 119 minutes. Repairs included quadrangular resections, sliding-plasties, chordal transfers, chordal shortening, neochord insertion, and annuloplasties. There was only one (0.5%) operative death secondary to a protamine reaction and no device- or perfusion-related complications. In addition, there were 3 (1.5%) in-hospital deaths. The hospital length of stay was 4.8 ± 0.2 days. Postoperative echocardiograms showed that 187 patients (93.5%) had no mitral regurgitation, 6 patients (3%) demonstrated trace mitral regurgitation, 5 patients (2.5%) had moderate mitral regurgitation, and 2 patients (1%) had systolic anterior motion of the anterior leaflet. A total of 5 patients (2.5%) required a reoperation for failed repairs.

We have also used the da Vinci system to perform mitral valve replacements as well as combined mitral valve repairs with atrial fibrillation ablation.[62] As we continue to perform further robotic mitral operations, the operative times have continued to decrease. In addition, we are able to repair more complex valves due to the enhanced visualization and fine dexterity offered by the da Vinci system.

MINIMALLY INVASIVE HEART VALVE SURGERY: CONCLUSIONS

The above information suggests that minimally invasive valve surgery is well on the way to becoming reality. Although operative philosophies, patient populations, and surgeon abilities differ among centers, the compendium of recent results remains very encouraging. The advent of true 3-D vision with tactile instrument feedback will be the major bridge to truly tele-micro-access operations. Also, to perform these operations optimally, extracorporeal surgeons and engineers will need to continue to improve methods by which instruments are directed by computers. Recent successes with direct-vision, videoscopic, and robotic minimally invasive surgery all have reaffirmed that this evolution can be extremely fast, albeit through various pathways. In fact, catheter-based technology is even moving toward treating aortic valve disease, and mitral annuloplasties have been done experimentally through the coronary sinus.[63]

Patient requirements, technology developments, and surgeon capabilities all must become aligned to drive these needed changes. In addition, we must work closer with our cardiology colleagues in these developments. This is an evolutionary process, and even the greatest skeptics must concede that progress has been made. However, curmudgeons and surgical scientists alike must continue to interject their concerns. Caution cannot be overemphasized. Traditional valve operations enjoy long-term success with ever-decreasing morbidity and mortality, and remain our measure for comparison. Surgeons and cardiologists must remember that less invasive approaches to treating valve disease cannot capitulate to poorer operative quality or unsatisfactory valve and/or patient longevity.

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CHAPTER 46

Percutaneous Catheter-Based Mitral Valve Repair

Michael J. Davidson • Donald S. Baim

While mitral stenosis and regurgitation traditionally have been addressed by surgical means, both now have emerging percutaneous treatment options. Mitral stenosis, although now relatively uncommon in developed countries, represents the first heart valve pathology to be treated by surgical techniques (in 1923[1]) and by percutaneous techniques (in 1982[2]). While percutaneous balloon mitral valvuloplasty for rheumatic mitral stenosis now has a 20-year track record with excellent success in patients with suitable valvular and subvalvular morphology,[3,4] heretofore there have been no clinically viable percutaneous treatment options for patients with mitral regurgitation.

One subset that might benefit from percutaneous mitral valve repair consists of patients with ischemic or functional mitral regurgitation. Moderate to severe mitral regurgitation is present in up to half of patients with significant congestive heart failure largely as the result of leaflet malapposition owing to annular dilatation combined (in some patients) with downward traction on the posterior leaflet by outward displacement of the lateral papillary muscle by lateral wall infarction.[5] The resulting chronic volume overload of mitral regurgitation begets further left ventricular dilatation, thus worsening mitral regurgitation, in a classic vicious cycle.[6] Several studies have shown that the presence of significant mitral regurgitation is an independent predictor of mortality in congestive heart failure and that surgical correction with an undersized mitral annuloplasty ring may improve both left ventricular enlargement and survival.[7–9] On the other hand, surgical mitral valve repair in this population carries a nontrivial procedural risk,[9,10] and significant mitral regurgitation may recur over 1 to 5 years despite an initially successful surgical repair.[11] There thus has been a growing interest in percutaneous techniques for the reduction of ischemic mitral regurgitation to see if such procedures could be performed with less associated morbidity.[3,12]

A second subset that potentially might benefit from percutaneous mitral valve repair consists of patients with degenerative or structural mitral regurgitation. Traditionally, these patients have been referred for surgery when they become symptomatic. Since most are free of coronary artery disease or other cardiac lesions, they usually can be approached through minimally invasive surgical valve repair techniques (i.e., limited partial sternotomy and valve repair rather than replacement). Insofar as a percutaneous catheter-based approach avoids the use of cardiopulmonary bypass and the morbidity of an open-heart procedure, it can be seen as a further extension of this trend toward minimally invasive mitral repair. Given the excellent surgical results for open repair of degenerative valve disease, however, it is unlikely that percutaneous techniques will replace surgery for operable symptomatic patients with degenerative mitral valve disease. However, the development of a less morbid technique may enable intervention at an earlier stage in the disease process, particularly if it leaves the options for later surgical repair intact, if needed.

BALLOON MITRAL VALVULOPLASTY

The first catheter-based technique for the treatment of mitral stenosis was performed by Inoue in 1982[2] and almost concurrently by Lock and colleagues.[13] This technique now has been applied to thousands of patients, and its success has caused it to supplant surgical open commissurotomy or valve replacement in patients with isolated mitral stenosis and suitable anatomy. Patients are evaluated by echocardiography to ensure the absence of left atrial thrombus and the presence of appropriate valve anatomy.[3] The technique has changed little since its inception; a venous approach with transseptal puncture is used, and a guidewire is advanced through the valve into the left ventricle. The valve then can be dilated using one of several devices. The most popular

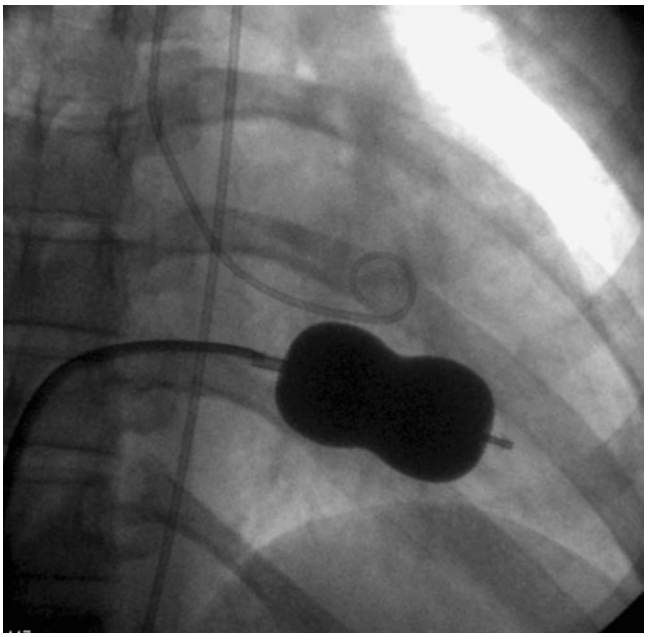

Figure 46-1. Transcatheter mitral commissurotomy. Inoue single-balloon mitral commissurotomy via a transseptal approach. Note the balloon "waist" as the valve is dilated.

and technically simple approach uses the Inoue single balloon, which allows progressive dilation to diameters of 23 to 28 mm at various inflation volumes (Fig. 46-1).

A second alternative is the double-balloon technique using side-by-side 18- to 20-mm-diameter balloons, which has the same efficacy as the Inoue technique but a tendency for higher complication rates (especially ventricular perforation). Lastly, Cribier has used a metal commissurotomy device modeled on the Tubbs dilator. The primary advantage is that the device is reusable, allowing broader application in developing countries, although it is technically more difficult than balloon techniques and carries a higher risk of cardiac perforation.

Complications of all these techniques include failure to relieve stenosis, creation of mitral regurgitation, perforation with hemopericardium, and systemic embolization.[3,4] Immediate surgery may be required in approximately 1% of procedures for resolution of technical complications such as hemopericardium or creation of severe mitral regurgitation. When there is insufficient resolution or recurrence of stenosis, repeat balloon valvuloplasty or elective mitral valve replacement can be performed. Most patients with immediate procedural success (approximately 90% of patients) have continued good functional results at 10 years after treatment.[4]

PERCUTANEOUS TREATMENT OF MITRAL REGURGITATION

The percutaneous approaches currently being evaluated attempt to emulate one or more of the components of surgical mitral valve repair,[14] e.g., annular reduction and edge-to-edge repair (Alfieri stitch).[15] On the other hand, these catheter techniques currently cannot duplicate some of the other aspects of surgical repair (including quadrangular or sliding leaflet resection and chordal modification).[14] Moreover, the catheter-based therapies for mitral repair are currently in their very earliest stages (animal testing or in some cases early human pilot trials). Thus it is not clear whether they can offer the *same level of improvement and durability* as the current open surgical approaches, nor how large a subset of patients with mitral regurgitation each catheter therapy will be able to address. It seems likely that each of the catheter approaches may be suitable for only a particular anatomic subset (e.g., prolapse with a normal annulus size or a dilated annulus without prolapse) and (as with the surgical techniques) that some patients will require more than one catheter approach used in concert to achieve an adequate repair. Finally, it is not clear whether the regulatory pathway will require the randomized demonstration of noninferiority to surgical repair (more likely with devices that may make subsequent surgical repair more complex)[16] or simply demonstration of improved indices of cardiac function (e.g., ventricular diameters, mitral regurgitation grade, and peak oxygen consumption during exercise—as used in heart failure trials). It is clear, however, that a large patient population (>1 million/year) would stand to benefit from a safe and effective percutaneous means of reducing or eliminating mitral regurgitation in the setting of congestive heart failure, with more than a dozen approaches being developed to achieve that goal.

ANNULOPLASTY APPROACHES (USING THE CORONARY SINUS)

The predominant surgical approach is implantation of an *annuloplasty ring,* which reshapes the circumference of the annulus and reduces the septolateral annular dimension.[17] This moves the posterior annulus and posterior valve leaflet closer to the anterior leaflet, allowing better systolic leaflet coaptation in patients with annular dilatation. Several companies currently are exploring percutaneous approaches that emulate surgical annuloplasty. Several are doing so by implanting a device in the coronary sinus—the main venous drainage of the myocardium—which fortuitously runs just outside and roughly in the same plane as the posterior mitral annulus (Fig. 46-2). A device that is placed in the coronary sinus thus may be able to plicate or straighten the coronary sinus and thereby therapeutically deform the posterior mitral annulus.

Most coronary sinus devices (e.g., MitraLife-Edwards, Edwards Monarc, and Cardiac Dimensions) use anchors that are placed in the anterior (i.e., the great cardiac vein, near the entry of the anterior interventricular vein) and posterior (near the ostium) portions of the coronary sinus. These two points typically lie adjacent to the mitral commissures and even may approach the fibrous trigones of the cardiac skeleton.

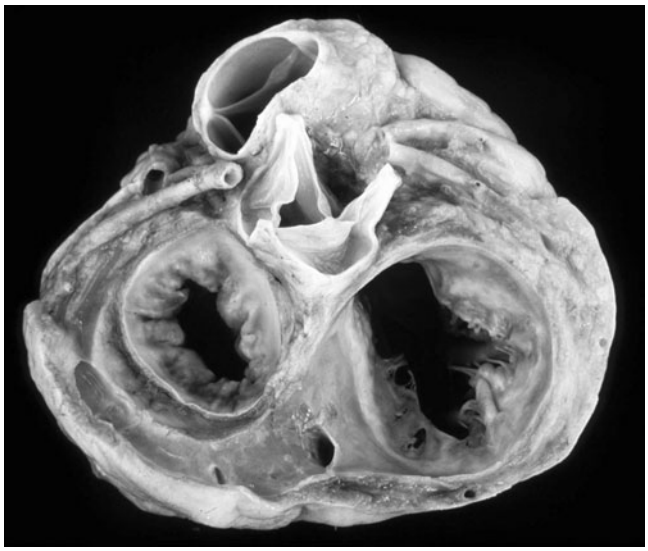

Figure 46-2. Relationship of the coronary sinus to the posterior mitral annulus and circumflex artery. The coronary sinus wraps around the atrioventricular groove behind the posterior mitral leaflet, extending nearly from its medial to lateral commissure. In this image, the circumflex coronary artery lies *outside/on top of* the coronary sinus, but it often courses *under* the coronary sinus and might be susceptible to compression during placement of a coronary sinus annuloplasty device.

The MitraLife device undergoes a shape change that reduces the commisure-to-commissure dimension (Fig. 46-3). In 2002, this device was placed on a temporary basis (i.e., the device then was restraightened and withdrawn following measurements) in Caracas. Modifications have been made to the shape of the device to also push the midportion of the posterior annulus forward, and the base intellectual property now has been acquired by Edwards. Clinical testing, however, has not yet resumed.

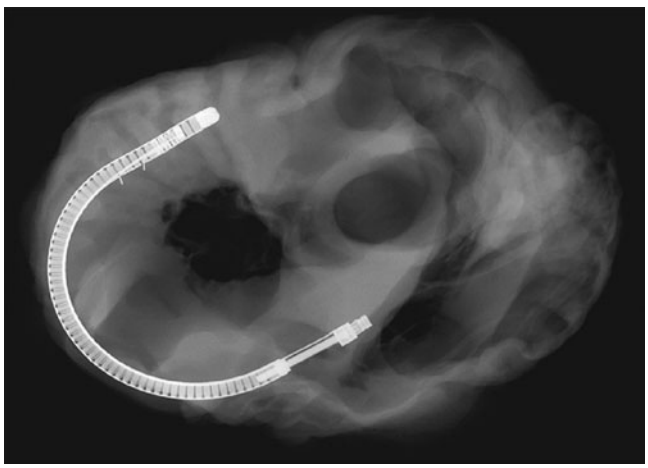

Figure 46-3. The MitraLife-Edwards device is a rod-like catheter that can change from straight to curved configuration once placed in the coronary sinus. This radiograph shows the device placed and curved within an explanted heart specimen. The commissure-to-commissure compression may not improve leaflet coaptation, and a new device shape is being considered to move the posterior leaflet forward.

The Edwards MONARC device (previously the JoMed-Edwards Viking device) is based on a patent by Jan Solem and consists of a pair of self-expanding nitinol anchoring stents located at the ends of the device and joined to each other by a connecting element that undergoes delayed shortening over 3 to 4 weeks after placement. It can be placed via a 12F jugular venous access and has shown significant reduction in animal models of mitral regurgitation induced by pacing tachycardia or left coronary artery microsphere embolization. The potential advantage of this device is that it allows stabilization of the anchors by tissue ingrowth prior to tensioning. A disadvantage is that the amount of annular reduction is uncontrolled, and the device cannot be adjusted or retrieved once deployed. Clinical trials were begun in Sweden and Canada in 2005 but were suspended after the first patient experienced device separation and return of 3+ mitral regurgitation at 3 months after an initially favorable reduction.[18] A modified device now has reentered clinical trials.

The Cardiac Dimensions Carillon device[19,20] consists of two different-sized self-expanding figure-of-eight nitinol loops located at either end of a fixed-length (6-cm) stainless-steel connector. The smaller distal loop is deployed in the anterior coronary sinus, and the device and delivery system are withdrawn to test the stability of that anchor and its ability to support plication of the coronary sinus. After demonstrating plication, reduction in mitral regurgitation, and a lack of circumflex coronary arterial compression, the proximal anchor then can be deployed to maintain this degree of plication (Fig. 46-4). At any point up to final release of the device, both anchors can be recaptured by the delivery system and the device withdrawn. Thus, unlike the Edwards MONARC, the device may be removed if it does not correct mitral regurgitation adequately. The early tensioning, however, may predispose to slipping of the anchors.

Animal testing in an ovine tachycardia model showed significant reductions in mitral annular diameter (4.2 to 3.2 cm) and echocardiographic mitral regurgitation, and acute human placements were performed in several patients in Australia during early 2005, showing safe deployment, anchoring, tensioning, and recapture. The COMPETENT single-arm safety and efficacy pilot trial began in mid-2005 at seven sites in the United States, enrolling patients with 3 to 4+ functional mitral regurgitation, class II to IV stable heart failure, and an enlarged diastolic left ventricular diameter with a left ventricular ejection fraction below 40%. Early difficulties with stability of the distal anchor during plication may require device enhancements or selection of patients with smaller coronary venous diameters before the pilot study can be concluded and a pivotal trial can be conducted to secure Food and Drug Administration approval.

Another coronary sinus approach, the Viacor device,[21,22] is used to place one or more straightening rods within a catheter that is positioned in the coronary sinus via the right subclavian or internal jugular vein. Although these rods do not plicate the coronary sinus per se, they do "bend" the sinus in a

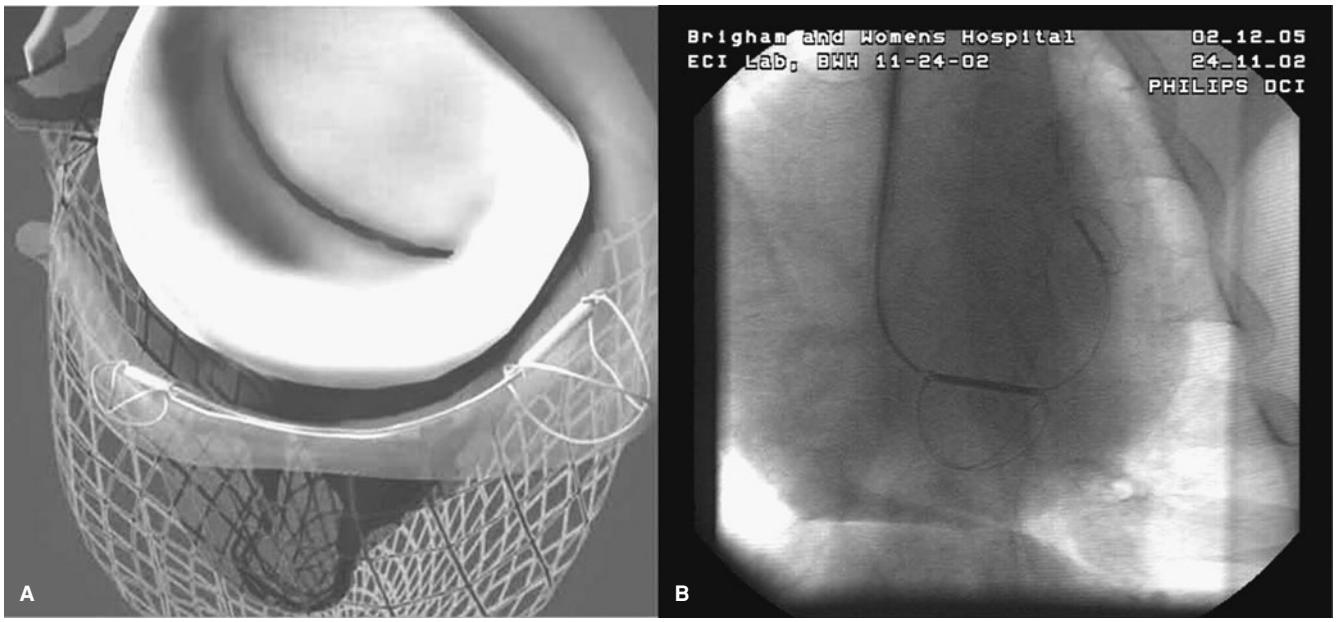

Figure 46-4. The Cardiac Dimensions device consists of a smaller distal and a larger proximal anchor joined by a 6-cm fixed-length metallic member. The device is tensioned after the distal anchor is "set," following which the proximal anchor can be set to maintain tension, and the device can be released if the effect is adequate and there is no circumflex compression (otherwise, it can be recaptured and removed). *A.* Schematic representation of the device in the coronary sinus. *B.* Fluoroscopic image of the device deployed in an in vivo animal model.

manner that pushes the posterior leaflet forward relative to the location of the commissures. In animal studies performed in an ovine multiple circumflex ligation model, this device produced a 5- to 7-mm decrease in anteroposterior mitral annular diameter with a significant reduction in echocardiographic mitral regurgitation. Several temporary placements have been performed at the Cleveland Clinic during planned surgical mitral valve repair surgery, showing the feasibility of implantation and the expected reduction in mitral regurgitation. In a permanent implant, the amount of stiffness in the device could be adjusted at the time of implantation (or readjusted chronically) to maximize benefit.

The coronary sinus devices are appealing in that catheter access is relatively straightforward from the internal jugular or subclavian vein (i.e., not requiring either transseptal puncture or extensive catheter manipulation) and conceivably could be done by most interventional cardiologists as an outpatient procedure. The challenges, however, include the fact that the coronary sinus does not have a fixed relationship with the mitral annulus—it is a mobile structure that is situated at various distances above the plane of the mitral annulus, overlying the posterior left atrial surface in many cases (see Fig. 46-2). When deformed or tensioned, this mobility actually could allow the coronary sinus to move further up onto the atrial wall, significantly limiting the efficacy of annular modification. Moreover, the walls of the coronary sinus are very thin, raising concerns that long-term placement of aggressive anchoring devices might lead to erosion, perforation, thrombosis, or denial of access for other interventions (such as the placement of biventricular cardiac resynchronization devices). Finally, computed tomographic (CT) angiograms suggest that up to half of patients may have a major circumflex coronary arterial branch that runs *under* (rather than on top of) the coronary sinus, making it vulnerable to compression during a coronary sinus plication procedure.

ANNULOPLASTY APPROACHES (I.E., TRANSVENTRICULAR, TRANSATRIAL, AND EPICARDIAL)

One other investigational approach is retrograde (i.e., transventricular suture plication of the posterior mitral annulus). In the approach developed by Guided Delivery Systems, a flexible partial annuloplasty ring is placed on the left ventricular side of the mitral annulus and secured to the annulus by a series of anchors. No further public disclosure regarding this device or animal testing has been made.

The Mitralign device represents another transventricular approach based on the earlier surgical Paneth-Burr suture annuloplasty technique.[23–26] A magnetic catheter is first placed in the midcoronary sinus; an opposing-pole magnet–tipped catheter then is placed retrograde into the left ventricle and slid up the posterior left ventricular wall behind the posterior mitral leaflet until it lies under the mitral annulus and is "locked" magnetically against the coronary sinus magnet. This left ventricular catheter then is used to place a series of anchors along the posterior annulus, which are plicated and locked together to affect

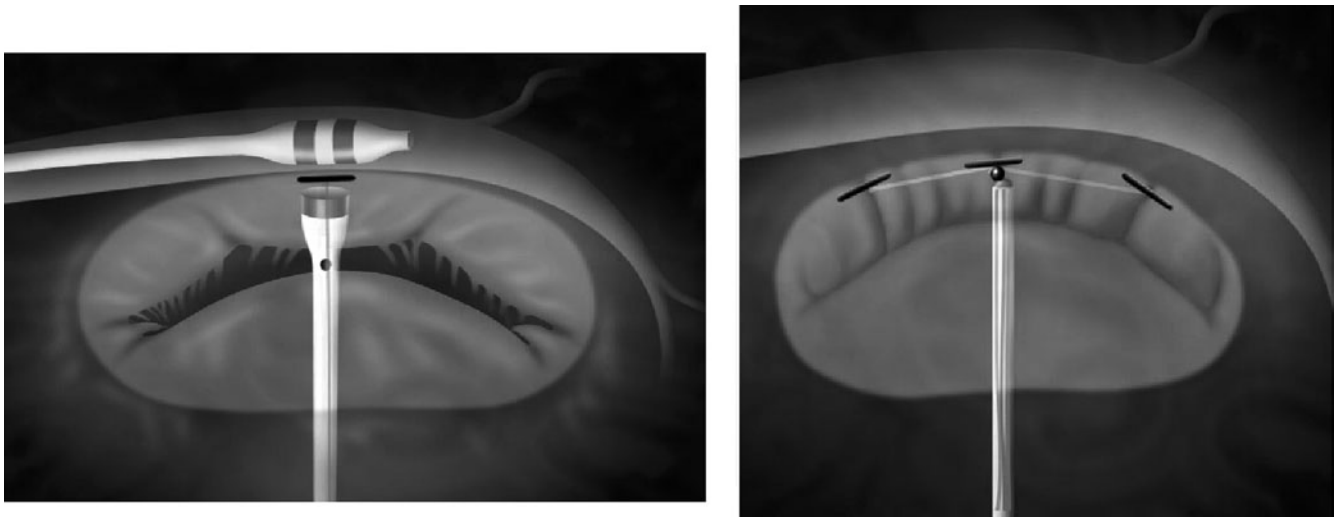

Figure 46-5. The Mitralign approach uses magnetic attraction between a retrograde left ventricular catheter (positioned between the posterior mitral leaflet and the posterior left ventricular wall) and a reference catheter positioned in the coronary sinus to securely locate the ventricular aspect of the annulus. The left ventricular catheter is then used to place a series of anchors into the posterior annulus that are drawn together to plicate the annulus, akin to the Paneth-Burr suture annuloplasty.

reduction in annular circumference (Fig. 46-5). These locked anchors remain in place as the left ventricular and coronary sinus catheters are removed. This device is still in early animal testing.

The Myocor Surgical Coapsys system uses a pair of epicardial pads connected by a rod to reduce the septolateral dimension of the subannular ventricle and mitral annulus[27] (Fig. 46-6). Clinical evaluation of 32 patients in the TRACE (Treatment of Functional Mitral Regurgitation without Atriotomy or CPB Clinical Evaluation) study has shown reduction of mitral regurgitation grade from 2.65 to 0.85 following implantation, with preserved benefit through 3-month follow-up. A nonsurgical version of this device (iCoapsys interventional mitral valve repair) has been developed in which the epicardial pads are applied lateral to the left anterior and posterior descending coronary arteries via a pericardial approach and connected to an adjustable external "deflector" that overlies the lateral wall. Shortening of the connections to the deflector thus reduces septolateral dimension, as has been demonstrated in animal implants.

The percutaneous septal sinus shortening approach (Ample Medical) uses magnetic coupling of a transseptal catheter to a coronary sinus catheter to place a suture through the interatrial septum that is coupled to an anchor positioned in the posterior coronary sinus. The suture is tensioned and secured by an atrial septal closure device to provide a reduction in the septolateral mitral annular dimension. Animal studies have suggested good maintenance of septolateral dimension, as well as of induced mitral regurgitation, with this device.[28]

Quantun Cor has performed animal testing with a multielectrode coronary sinus catheter that, although not an implant, can deliver radiofrequency energy to the mitral annulus. Heating the tissue to 65°C can cause collagen contraction of the posterior annulus. No further data on this approach are available.

There are some animal data suggesting that severing basal chordae can reduce the tethering of the valve leaflets caused by posterior wall infarction,[29,30] and potential percutaneous devices for cutting these cords have been envisioned. The benefit of chordal cutting, however, at best has not been validated in experimental models[31] and at worst may be detrimental to cardiac function. Development of a percutaneous approach thus may be premature.

EDGE-TO-EDGE REPAIR

Although it is usually done in conjunction with placement of an annuloplasty ring, the edge-to-edge (or Alfieri stitch) repair, in which the midportions of the anterior and posterior mitral leaflets are connected, sometimes is used as an adjunctive or even primary repair modality in patients with predominant leaflet prolapse.[15,32] The bulk of the percutaneous experience mimicking this surgical procedure has been obtained using the Evalve edge-to-edge clip prosthesis[33,34] (Fig. 46-7). More than 130 implants have been performed since mid-2003, mostly in the six-site phase I U.S. registry known as EVEREST (Endovascular Valve Edge-to-edge Repair Study) 1.[35] The majority had degenerative structural (i.e., leaflet prolapse) rather than functional (i.e., dilated annulus) regurgitation. The special grasping clip is manipulated with a transseptal delivery catheter using fluoroscopic and transesophageal echocardiographic guidance to confirm that the midportions of the anterior and posterior leaflets had been grasped and that the amount of mitral regurgitation had

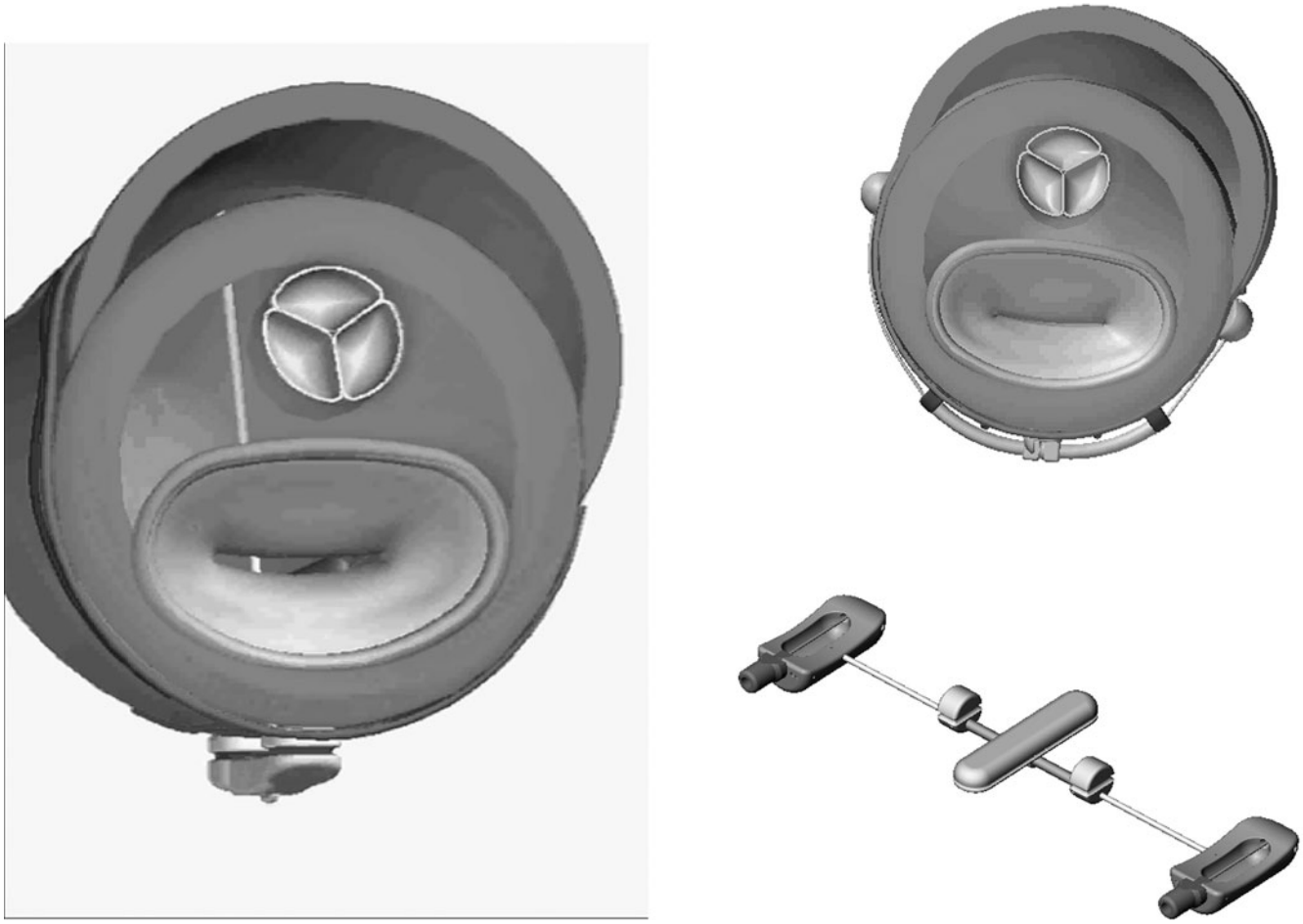

Figure 46-6. The surgical Coapsys device (*left*) uses an intracavitary shortening rod connecting two external pads (placed over the lateral and septal walls of the left ventricle) to decrease the septolateral dimension of the left ventricle and mitral annulus. The minimally invasive iCoapsys device (*right*) is designed for transpericardial insertion, fixing anterior and posterior pads on the epicardium adjacent to the left anterior descending and posterior descending coronary arteries connected to an anteroposterior deflector element positioned on the lateral wall. Tightening the connecting chords pulls the lateral wall inward, also decreasing septolateral dimension.

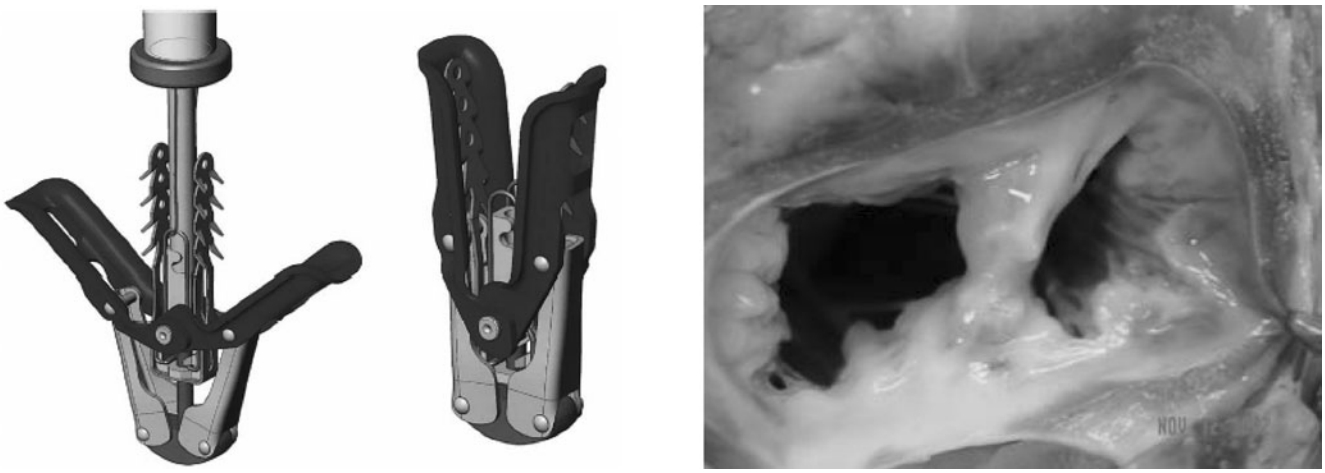

Figure 46-7. The s/b Evalve device consists of a clip that can be positioned via a transseptal puncture and oriented so that it can be pulled back to catch the tips of anterior and posterior leaflets simultaneously. The clip can be closed to evaluate the effect on mitral regurgitation and then either reopened to be repositioned more effectively or released as a permanent implant. The left panel depicts the clip mechanics, and the right panel shows it after long-term animal implantation with the classic double-orifice valve.

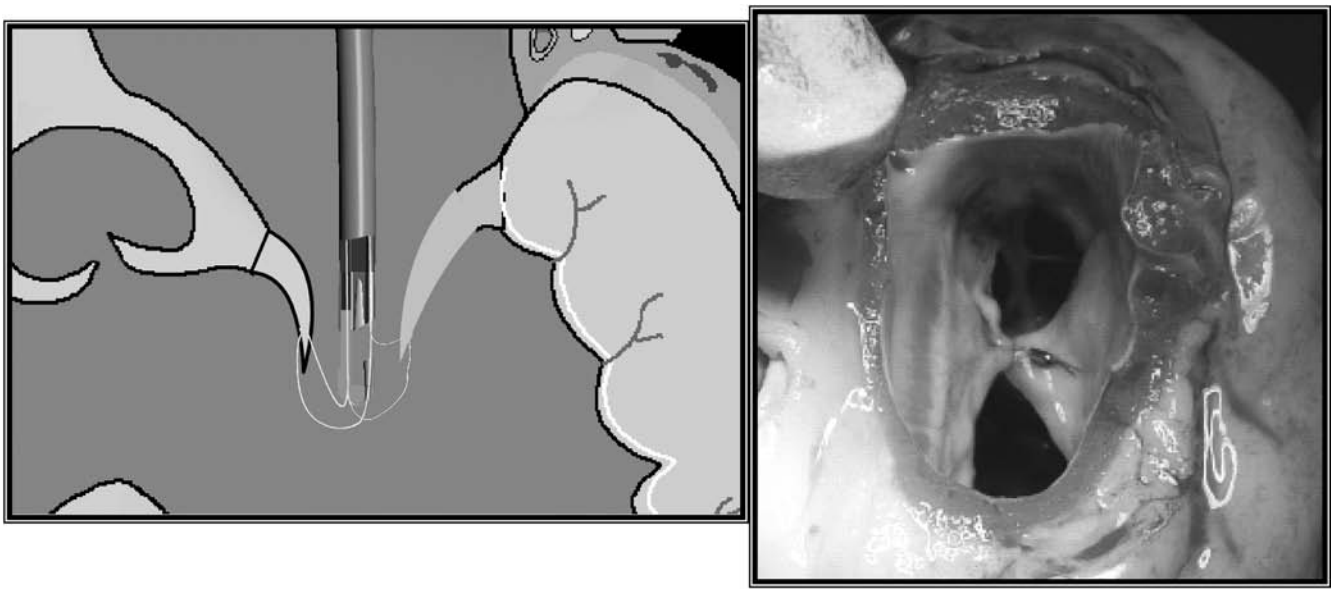

Figure 46-8. The Edwards MOBIUS device is also placed within the mitral orifice by transseptal puncture and uses suction to capture and pass a suture through first one and then the other mitral leaflet. The sutures are drawn together, locked in place, and cut to effect edge-edge mitral repair.

been reduced. In later patients, implantation of a second clip was permitted if satisfactory reduction in regurgitation could not be achieved through optimal positioning of the first clip. Of 92 patients for whom registry data are available, 82 were able to have one or more clips implanted.[35] A favorable result with 2+ mitral regurgitation or less was achieved at discharge in 68 of 82 patients (83%), with a mean core laboratory echocardiographic mitral regurgitation grade reduced from 3.7 at baseline to 1.6 at discharge and 2.1 at 30-day follow-up. The 30-day major adverse event rate was 5%. In follow-up, 17 patients have undergone elective surgery (12 via valve repair rather than replacement) owing to clip detachment from one leaflet, ongoing mitral regurgitation, or in conjunction with other cardiac surgery. There was clinical improvement (class I or II) in 72% of the nonoperated patients compared with baseline. A pivotal noninferiority trial randomizing patients with similar entry criteria to either the Evalve clip or surgical mitral valve repair has begun recently.

The Edwards MOBIUS device also emulates the surgical Alfieri stitch. A deflectable 16F device is delivered across the mitral orifice via a transseptal approach under transesophageal echocardiographic guidance. Suction through a catheter lumen is used to pull the edge of the anterior or posterior mitral leaflet against the catheter, and a needle and suture are passed through the leaflet (Fig. 46-8). The device then is rotated, and the procedure is repeated against the other mitral leaflet, with tensioning and cutting of the suture to maintain the edge-to-edge approximation. A potential advantage of this approach versus Evalve is that use of a suture rather than a clip device leaves less hardware on the mitral leaflet and theoretically may be less likely to inhibit future repair. The first clinical case was completed in mid-2005 with reduction in mitral regurgitation from 4+ to 2+ prior to scheduled surgical repair. Further device development and pilot experience are anticipated.

The main challenge to edge-to-edge repair is the fact that the surgical precedent is seldom used in a stand-alone setting (i.e., without concomitant annuloplasty). The percutaneous procedure thus would be limited clinically to patients with poor leaflet coaptation in the absence of left ventricular or annular dilatation or as a secondary procedure for residual mitral regurgitation following percutaneous annuloplasty (as is done surgically). Lastly, an edge-to-edge device may have a role as an adjunct to surgical valve repair. In particular, the Alfieri suture has been shown to be useful in treating systolic anterior motion (SAM) of the mitral valve following mitral valve repair.[36] The ability to place a device via catheter may obviate the morbidity associated with reoperation for unremitting SAM.

CONCLUSION

While the percutaneous treatment of mitral stenosis has an established record, definitive catheter-based therapies for mitral regurgitation are largely in preclinical development. It is clear, however, that a number of percutaneous approaches to mitral annuloplasty and edge-to-edge repair have been developed. Interventional cardiologists, and in particular a subset devoted to structural heart disease, have carried out the majority of clinical work in this field. However, close collaboration between cardiologists and surgeons has been integral to the development of transcatheter mitral valve interventions,[16] with one or more cardiac surgeons having been involved in virtually every one of

the projects described herein and in the clinical evaluation of this promising set of devices. The success of percutaneous treatments for mitral regurgitation will depend on close collaboration among cardiologists, cardiac surgeons, and engineers.

The clinical trial landscape is also still under active discussion. If these percutaneous techniques are to be seen as an alternative to traditional surgical methodologies in low- to medium-risk patients, the new techniques will need to demonstrate similar hemodynamic effect, safety, and durability to the current highly refined surgical techniques.[14] On the other hand, it may be that the first and best applications of these percutaneous techniques are in patients at the margins of current surgical indications—patients with mild to moderate mitral regurgitation in the setting of advanced heart failure (who may not meet current surgical indications and are at higher risk for surgical mitral valve repair). In such patients, the appropriate comparison may be exercise capacity with the device with maximal medical therapy versus maximal medical therapy alone.

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PART

IVc

Valvular Heart Disease (Other)

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CHAPTER 47

Tricuspid Valve Disease

Richard J. Shemin

The tricuspid valve is composed of three leaflets (i.e., anterior, posterior, and septal) attached to a fibrous annulus. The leaflets usually attach via chordae tendineae to three papillary muscles that are an integral part of the right ventricular wall. Surrounding structures of surgical importance are the coronary sinus, the atrioventricular node, and the right coronary artery (RCA) (Fig. 47-1A).

The tricuspid valve may malfunction due to structural malformation secondary to other cardiac pathology or due to hardware through the valve [e.g., pacemaker or automatic internal cardiac defibrillation (AICD) wires]. Congenital abnormalities such as atrial septal defect (ASD), ventricular septal defect (VSD), and Ebstein disease lead to malfunction and tricuspid regurgitation (TR). Cases of isolated tricuspid disease associated with systemic lupus erythematosus, cor pulmonale, inferior myocardial infarction, scleroderma, or methysergide intake are noteworthy but rarely encountered in surgical practice.[1–12]

ETIOLOGY

The most common presentation of TR is secondary to cardiac valvular pathology (mostly mitral valve disease) on the left side of the heart. As pulmonary hypertension develops, leading to right ventricular dilatation, the tricuspid valve annulus will dilate. The circumference of the annulus lengthens primarily along the attachments of the anterior and posterior leaflets. The septal leaflet is fixed between the fibrous trigones, preventing lengthening (Fig. 47-1B). As the annular and ventricular dilatation progresses, the chordal papillary muscle complex becomes functionally shortened. This combination prevents leaflet apposition, resulting in valvular incompetence.[13–18]

Eisenmenger syndrome and primary pulmonary hypertension lead to the same pathophysiology of progressive right ventricular dilatation, tricuspid annular enlargement, and valvular incompetence. A right ventricular infarction produces either disruption of the papillary muscle or a severe regional wall motion abnormality that prevents normal leaflet apposition by a tethering effect on the leaflets, leading to regurgitation. Marfan syndrome and other variations of myxomatous disease affecting the mitral and tricuspid valves can lead to prolapsing leaflets, elongation of chordae, or chordal rupture, producing valvular incompetence. Blunt or penetrating chest trauma may disrupt the structural components of the tricuspid valve. Dilated cardiomyopathy in the late stages of biventricular failure and pulmonary hypertension produces TR.[19–22] Infectious endocarditis can destroy leaflet tissue, mostly in drug addicts with staphylococcal infection.[23–26]

The carcinoid syndrome leads to either focal or diffuse deposits of fibrous tissue on the endocardium of valve cusps, cardiac chambers, intima of the great vessels, and coronary sinus. The white fibrous carcinoid plaques, if present on the ventricular side of the tricuspid valve cusps, adhere the leaflet tissue to the right ventricular wall, preventing leaflet coaptation.[27–29] Rheumatic disease of the tricuspid valve is always associated with mitral valve involvement, and the deformity of the tricuspid tissue results in a tricuspid valve stenosis as well as regurgitation.[30]

CLINICAL PRESENTATION AND PATHOPHYSIOLOGY

Tricuspid Regurgitation

Patients with TR have the presenting symptoms of fatigue and weakness related to a reduction in cardiac output. Right-sided heart failure leads to ascites, congestive hepatosplenomegaly, pulsatile liver, pleural effusions, and peripheral edema. In the late stages, these patients are wasted with cachexia, cyanosis, and jaundice. Atrial fibrillation is common. Impressive jugular venous distention with an *s* wave or fused *c* and *v* waves,

Figure 47-1. (A) View of the tricuspid valve and labeled structures of surgical importance. (B) Direction of progressive tricuspid valve annular dilatation.

followed by a prominent *y* descent, is present. During inspiration, this finding is accentuated because of the physiologic increase in venous return. The cardiac oscillatory examination is notable for an S_3 that increases with inspiration and decreases with a Valsalva maneuver, increased P_2 if pulmonary hypertension has developed, and a parasternal pansystolic murmur increasing with inspiration.

The chest x-ray demonstrates cardiomegaly, increased right atrial and ventricular size, a prominent azygous vein, possible pleural effusion, and upward diaphragmatic displacement owing to ascites. Echocardiography best assesses the degree of regurgitation, structural abnormalities of the valve, pulmonary artery pressures (PAPs), and right ventricular function both preoperatively and intraoperatively. A shift in the atrial septum to the left and paradoxical septal motion are consistent with right ventricular diastolic overload. Pulsed Doppler and color-flow studies help to identify systolic right ventricular to right atrial flow with inferior vena cava and hepatic vein flow reversal. Contrast-enhanced echocardiography can be useful, with a rapid saline bolus injection producing microcavities that are visible on echo, demonstrating to-and-fro motion across the valve orifice and reversal into the inferior vena cava and hepatic veins. Possible ASD or patent foramen ovale should be sought. Endocarditic lesions and vegetations are clearly visible on echo; the valve may be destroyed, and septic pulmonary emboli are a common feature. The tricuspid valve in carcinoid syndrome is thickened with retracted leaflets fixed in a semiopen position throughout the cardiac cycle.[31–42]

Cardiac catheterization will document increased right atrial and right ventricular end-diastolic pressure.[43] The right atrial pressure tracing has an absent *x* descent, prominent *v* wave, and "ventricularization" of the right atrial tracing, and the degree of pulmonary artery hypertension is documented. Pulmonary artery pressures of over 60 mm Hg usually are due to left-sided lesions leading to secondary TR. A right ventriculogram has been used but is unnecessary with current echocardiographic evaluation.

Tricuspid Stenosis

Tricuspid stenosis (TS) is most commonly rheumatic. It is extremely rare to have isolated tricuspid stenosis because some degree of TR will be present.[44–47] Mitral valve disease coexists with occasional involvement of the aortic valve. The third world and especially the Indian subcontinent still have a significant prevalence of rheumatic tricuspid valvular disease. The anatomic features are similar to those of mitral stenosis, with fusion and shortening of the chordae and leaflet thickening. Fusion along the free edges and calcific deposits on the valve are found late in the disease. The preponderance of cases are in young women.

The diastolic gradient between the right atrium and right ventricle is significantly elevated even at 2 to 5 mm Hg mean pressure. As the right atrial pressure increases, venous congestion leads to distention of the jugular veins, ascites, pleural effusion, and peripheral edema. The right atrial wall thickens, and the atrial chamber dilates.

If the patient remains in normal sinus rhythm, the right atrial tracing and jugular venous pulse have prominent *a* waves that accentuate with inspiration. The cardiac murmur

is mid-diastolic, increases with inspiration, is heard maximally along the left sternoid border, and may have an opening snap.

Clinical features are consistent with reduced cardiac output producing the symptoms of fatigue and malaise. Significant liver engorgement produces right upper quadrant tenderness with a palpable liver with a presystolic pulse. Ascites produces increased abdominal girth. Significant peripheral edema or anasarca can develop. Severe TS may mask or reduce the pulmonary congestion of mitral stenosis owing to reduced blood flow to the left side of the heart. The low output state of the patient is prominent.

The chest x-ray demonstrates cardiomegaly with an increase in the right atria and pulmonary artery size. The electrocardiogram (ECG) will demonstrate increased P-wave amplitude if the patient is in normal sinus rhythm. Echocardiography reveals the diagnostic features of diastolic doming of the thickened tricuspid valve leaflets, reduced leaflet mobility, and a reduced orifice of flow. The Doppler flow pattern across the tricuspid valve has a prolonged slope of antegrade flow.

The patient's ability to tolerate stenotic lesions of the tricuspid valve is dictated to a large degree by the natural history of the mitral or aortic valve disease. In patients with predominant TR, the negative consequences of right ventricular volume overload develop slowly. Acute TR due to traumatic rupture or complete excision of the tricuspid valve as the treatment for infective endocarditis can be well tolerated for years if the PAP is not elevated. Functional tricuspid incompetence is progressive. Surgical treatment of left-sided valvular lesions is not always adequate to resolve or prevent progressive TR. This is particularly true when pulmonary hypertension persists.

SURGICAL DECISIONS

The cardiologist and the cardiac surgeon face the decision as to when to intervene and when to surgically repair or replace the tricuspid valve. The choice of reparative technique to use for a durable result must be evaluated, as well as which type of valve, mechanical or bioprosthesis, to employ to maximize durability and minimize complications (i.e., thrombosis and thromboembolism). The surgical literature can be misleading due to case-selection bias and the various time frames of retrospective reviews. This is particularly true during the era that cage-ball and single-disk mechanical valves were in use.

SURGICAL EXPOSURE

Tricuspid valve annuloplasty performed with either mitral and/or aortic valve operations is accomplished either through a full or partial lower sternotomy approach or less invasive right mini thoracotomy exposure. Bicaval venous cannulation with caval snares is essential to isolate the right atrium. The cannula can be placed conventionally via the right atrium or less invasively via the femoral vein, and a superior vena cava cannula can be inserted via the internal jugular vein.

Left-sided valve repair or replacement (mitral and/or aortic) is performed under blood cardioplegic arrest with antegrade and/or retrograde administration, moderate systemic hypothermia, and topical cold saline surface cooling. The mitral valve can be exposed through a left atrial incision posterior to the intra-atrial septum or through a transseptal incision (Fig. 47-2).The transseptal incision is particularly useful when a prior aortic valve prosthesis is in place or in reoperations. After unclamping the aorta and completing de-airing maneuvers, attention can be turned to the tricuspid valve during rewarming and return of a cardiac rhythm. During tricuspid valve suturing, misplacement of a suture adversely affecting the cardiac conduction system can be assessed immediately and corrected. In a reoperative setting, approaching the tricuspid valve through a right mini thoracotomy has the advantage of avoiding adhesions and possible injury to the right ventricle during repeat sternotomy. If the operation will include the mitral valve, exposure can be simplified by using a right atrial incision and transseptal approach. If atrial fibrillation is present, a Maze procedure using the Cox-Maze III technique or ablation of atrial tissue using an energy source can be added to the technical maneuvers.

ANNULOPLASTY TECHNIQUES

Techniques to deal with a dilated tricuspid valve annulus with normal leaflets and chordal structures include plication of the posterior leaflet's annulus (bicuspidization), partial purse-string reduction of the anterior and posterior leaflet annulus (DeVega-style techniques), and rigid or flexible rings or bands placed to reduce the annular size and achieve leaflet coaptation. Preoperative and intraoperative echocardiograms are valuable assessment tools to help the surgeon understand the structure and function of the valve.[34–42]

The degree of pulmonary hypertension, right ventricular dilatation, and systolic function, coupled with the size of the right atrium, must be factored into the surgical decision making. The classical technique of inserting a finger via a purse-string suture into the right atrium to palpate the tricuspid valve and withdrawing the fingertip 2 to 3 cm from the valve orifice trying to access the force of the regurgitant jet is of less importance in the current era of cardiac surgery than previously. The intraoperative transesophageal echocardiogram (TEE) allows the surgeon to access the tricuspid regurgitation and look for reversal of flow in the inferior cava. The TEE assessment after the repair ensures leaving the operating room with confidence that the repair is functioning satisfactorily.[48–63]

Minimal right atrial enlargement and + 1 to + 2 regurgitation usually will resolve after surgery on left-sided

Figure 47-2. (A) The superior and inferior venae cavae are cannulated, an oblique atriotomy incision is made, and stay sutures are placed on the right atrial wall to aid exposure. For transatrial exposure of the mitral valve, an incision is placed in the fossa ovale and extended superiorly through the interatrial septum. The superior aspect of the septal incision is extended if necessary into the dome of the left atrium behind the aorta. (B) Stay sutures in the interatrial septum are used for retraction. Use of retractors is avoided to prevent injury to the AV node. The mitral prosthesis is implanted in an antianatomic orientation. (C) The interatrial septum is closed primarily or by using a pericardial patch with a continuous 4-0 Prolene suture.

valve lesions, especially if the pulmonary hypertension resolves. Recent literature has documented the variability in the resolution of TR after dealing effectively with the left-sided valvular lesions.

The pathologic process of functional TR requires an understanding that the tricuspid annulus is a component of both the tricuspid valve and the right ventricle. For the tricuspid valve to leak, the tricuspid annulus and hence, the right ventricle have to be dilated. If the tricuspid annulus and the right ventricle are not dilated, there is a very low probability that TR can occur. Dilation of the tricuspid annulus occurs in the anterior and posterior directions (Fig. 47-1B) corresponding to the free wall of the right ventricle. In addition to tricuspid dilatation, the degree of TR is also directly related to three important factors: the preload, the afterload, and right ventricular function. Thus, TR is difficult to assess accurately because these factors can interfere with the severity of TR under different conditions. Significant TR may not be detected echocardiographically despite considerable annular dilatation in the tricuspid valve. An understanding of these important fundamental concepts would seem to contradict current

practice regarding the management of secondary TR, which focuses on assessment of the severity of TR and advocates treatment of the primary lesion alone (i.e., mitral valve disease). Treatment of the mitral valve lesion alone only decreases the afterload. It does not correct tricuspid dilatation, nor does it affect preload or right ventricular function. Once the tricuspid annulus is dilated, its size cannot return to normal spontaneously, and it may, in fact, continue to dilate further. This may explain why some patients require a second operation for TR years after the initial mitral valve surgery.

Since tricuspid annular dilatation seems to be the underlying mechanism regarding nonorganic TR, Dreyfus and colleagues postulated that it may be a more reliable indicator of tricuspid valve pathology than the degree of TR. Moreover, successful treatment of secondary tricuspid valve pathology may necessitate the correction of tricuspid annular dilatation in addition to mitral valve surgery. Over a 12-year period, these authors performed tricuspid valve repair (TVR) for secondary tricuspid valve dilatation irrespective of the severity of TR because secondary tricuspid dilatation may or not be accompanied by TR. Tricuspid dilatation can be measured objectively, whereas TR can vary according to the preload, afterload, and right ventricular function.

Dreyfus and colleagues performed a prospective study of over 300 patients designed to determine whether surgical repair of the tricuspid valve based on tricuspid dilatation alone rather than TR could lead to potential benefits. Tricuspid annuloplasty was performed only if the tricuspid annular diameter was greater than twice the normal size ($\geqslant$70 mm) regardless of the grade of regurgitation. Patients in group 1 (163 patients, 52.4%) received mitral valve repair (MVR) alone. Patients in group 2 (148 patients, 47.6%) received MVR plus tricuspid annuloplasty. Tricuspid regurgitation increased by more than two grades in 48% of the patients in group 1 and in only 2% of the patients in group 2 ($p < .001$).

The authors concluded that modeling annuloplasty of the tricuspid valve based on tricuspid dilatation improved functional status irrespective of the grade of regurgitation. Considerable tricuspid dilatation can be present even in the absence of substantial TR. Tricuspid dilatation is an ongoing disease process that will, with time, lead to severe TR.[109]

More aggressive use of tricuspid annuloplasty appears to help improve the early postoperative course and prevent residual or progressive TR. Increasingly functional mitral regurgitation (MR) and TR coexist. Matsunaga and Duran analyzed TR in a group of patients who underwent successful revascularization and MVR for functional ischemic mitral regurgitation. They concluded that functional TR is frequently associated with functional ischemic MR. After MVR, close to 50% of patients have TR. The incidence of postoperative TR increases with time. Preoperative tricuspid annulus dilatation might be a predictor of late TR.[110]

Special note should be taken in assessing the foramen ovale for patency. These lesions always should be sutured closed, reducing the possibility of arterial desaturation from right-to-left shunting or paradoxical embolization.

Bicuspidization

After the caval snares are tightened, the right atrium is opened via an oblique incision. Exposure and assessment of all aspects of the tricuspid valve structure should be performed prior to choosing the technique of annuloplasty. Suture plication to deal with mild dilatation of the annulus is accomplished by placing pledgeted mattress sutures from the center of the posterior leaflet to the commissure between the septal and posterior leaflets. A second suture often is necessary to further reduce the annulus, ensuring proper leaflet coaptation while providing an adequate orifice for flow. An annuloplasty ring can be inserted to further support the annular reduction (Fig. 47-3).

DeVega Technique

The DeVega technique also can be employed for mild to moderate annular dilatation.[52] The technique employs a 2-0 Prolene or Dacron polyester suture placed at the junction of the annulus and right ventricular free wall, running from the anteroseptal commissure to the posteroseptal commissure. The second limb of the suture is placed through a pledget and run parallel and close to the first suture line in the same clockwise direction, placing it through a second pledget at the posteroseptal commissure. The suture is tightened, producing a purse-string effect and reducing the length of the anterior and posterior annulus to provide adequate leaflet coaptation and orifice of flow (Fig. 47-4).

The judgment regarding the degree of annular reduction has varied from the guideline of being able to insert two and one-half to three fingerbreadths snugly through the valve orifice to using the ring annuloplasty sizers designed for the tricuspid valve. An annuloplasty sizer, chosen by measuring the intertrigonal distance, can be used as a template while tying the purse-string suture to achieve the proper degree of reduction. The DeVega and suture plication techniques should be reserved for mild annular reductions and situations in which the structural integrity of the annulus is not absolutely necessary for long-term success (i.e., functional TR expected to resolve over time). In these situations, the annuloplasty provides a competent tricuspid valve during the early postoperative course while the heart remodels after surgical treatment of the left-sided valvular lesions.[63–65]

Rings and Bands

Significant degrees of annular reduction requiring durability are best accomplished with rigid rings (e.g., Carpentier-Edwards and MC3), flexible rings (e.g., Duran), or flexible

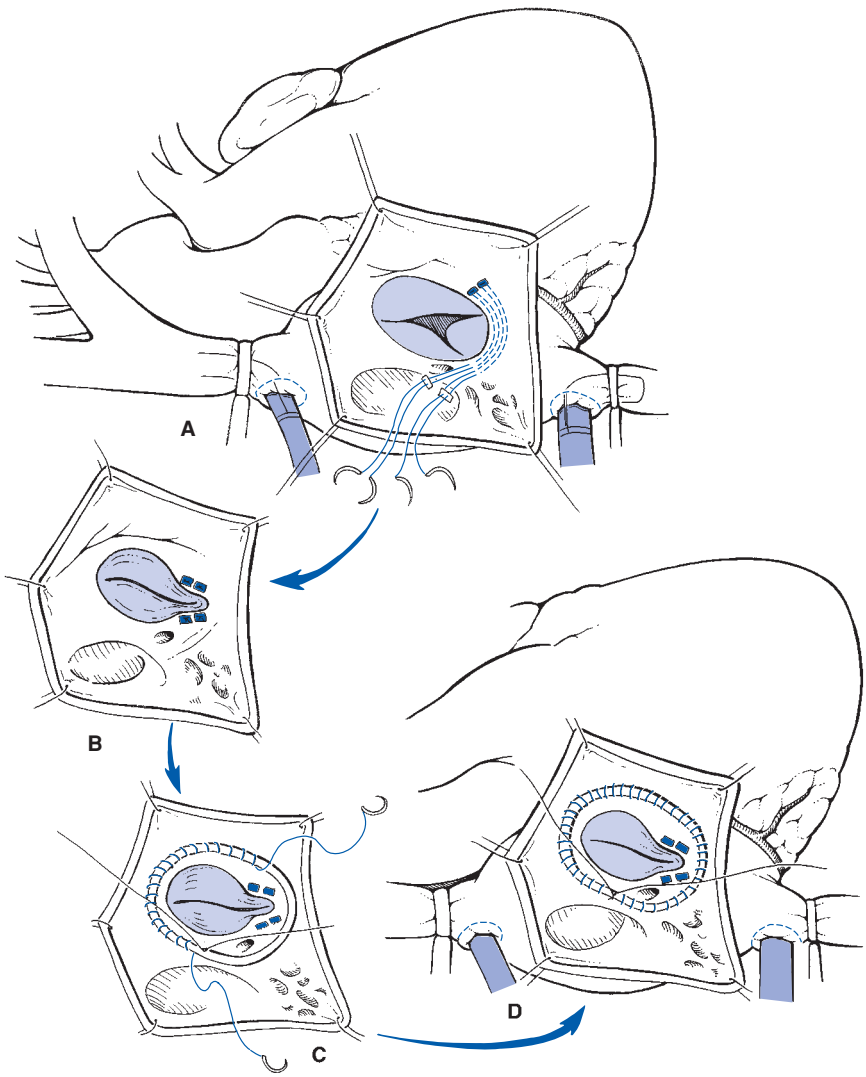


Figure 47-3. (A) Tricuspid valve bicuspidization is accomplished by plicating the annulus along the posterior leaflet. Two concentric, pledgeted 2-0 Ethibond sutures are used. (B) The sutures are tied, obliterating the posterior leaflet, effectively creating a bicuspid AV valve. Saline is injected into the right ventricle to test the competency of the repair. (C) As an option to support the bicuspidization repair, a flexible ring may be placed. Prior to ring implantation, measuring the intertrigonal distance determines the annular size. As an option, the ring can be inserted using a continuous 4-0 Prolene suture. Care is taken to avoid the AV node. As another option, the ring can be implanted above the coronary sinus.

bands (e.g., Cosgrove annuloplasty system). The length of the base of the septal leaflet (i.e., the intertrigonal distance) determines the size of the ring or band. These devices avoid suture placement in the region of the atrioventricular (AV) node (apex of the triangle of Koch) to avoid postoperative conduction problems. The mattress sutures are placed circumferentially, with wider bites on the annulus and smaller corresponding bites through the fabric of the ring or band, producing the annular plication mostly along the length of the posterior leaflet. The result allows the tricuspid valve orifice to be occluded primarily by the leaflet tissue of the anterior and septal leaflets. Overly aggressive annular reduction can lead to ring dehiscence owing to excessive tension on the tenuous tricuspid valve tissue[66–75] (Fig. 47-5).

A recent review of a 790-patient series for the durability and risk factors for failure of a repair was reported by McCarthy and colleagues. The authors reported that TR 1 week after annuloplasty was 3+ or 4+ in 14% of patients. Regurgitation severity remained stable over time with the Carpentier-Edwards ring ($P = .7$), increased slowly with the Cosgrove-Edwards band ($P = .05$), and rose more rapidly with the DeVega ($P = .002$) and Peri-Guard ($P = .0009$) procedures. Risk factors for worsening regurgitation included higher preoperative regurgitation grade, poor left ventricular function, permanent pacemaker, and repair type other than ring annuloplasty. Right ventricular systolic pressure, ring size, preoperative New York Heart Association (NYHA) functional class, and concomitant surgery were not risk factors. Tricuspid reoperation was rare (3% at 8 years), and hospital mortality after reoperation was 37%. The authors concluded that tricuspid valve annuloplasty did not consistently eliminate functional regurgitation, and over time, regurgitation increased importantly after Peri-Guard and DeVega annuloplasties. Therefore, these repair techniques should be abandoned, and transtricuspid pacing leads should be replaced with epicardial leads.[111]

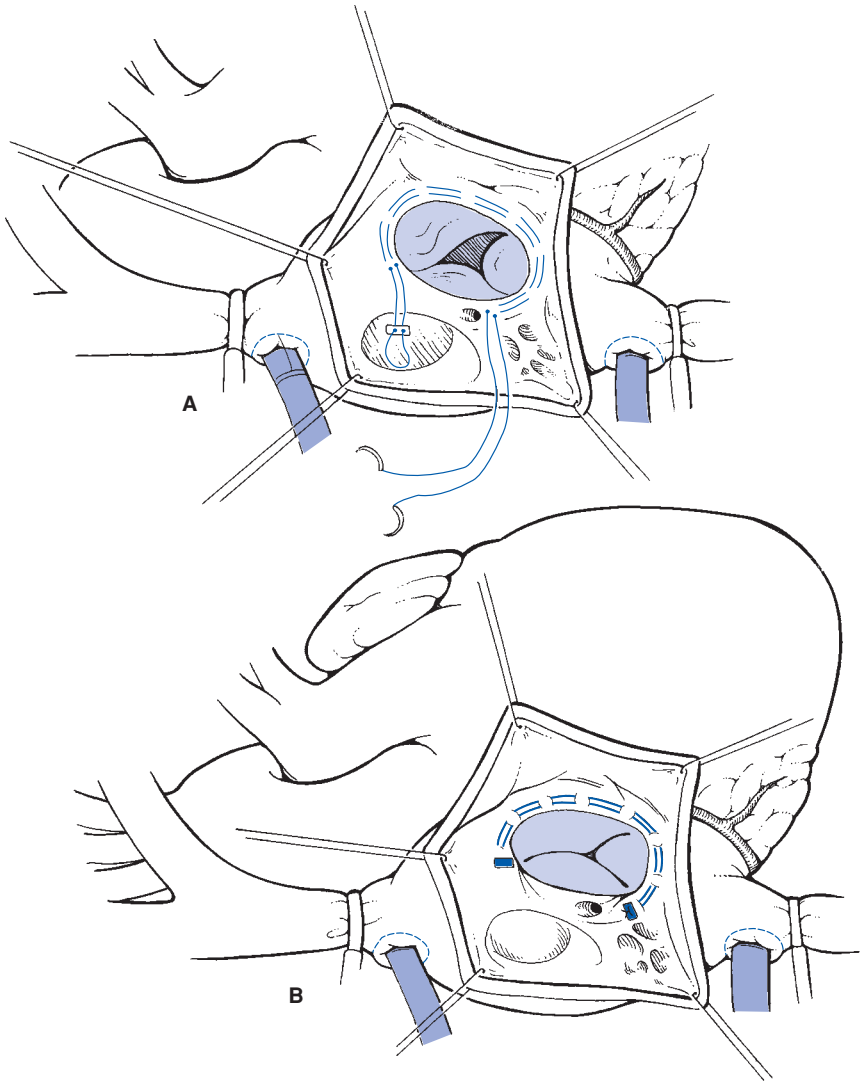


Figure 47-4. (A) A modified DeVega annuloplasty technique is shown. A single pledgeted 2-0 Prolene suture is placed. Care is taken to avoid the area of the AV node. (B) The suture is tied, completing the annuloplasty. Injecting saline into the right ventricle using a bulb syringe tests valve competency.

INTRAOPERATIVE ASSESSMENT OF THE REPAIR

Assessment of tricuspid valve competence after the annuloplasty requires filling the right ventricle with saline and observing leaflet coaptation. This assessment is best performed with the heart beating and the pulmonary artery clamped to allow right ventricular volume to generate enough intracavitary pressure to close the tricuspid valve tightly. If the result appears inadequate, downsizing the ring or ring replacement should be performed. Final assessment is by TEE examination after completely weaning from cardiopulmonary bypass with appropriate volume and afterload adjustment.

TRICUSPID VALVE REPLACEMENT

The technique for secure fixation of a tricuspid valve is with pledgeted mattress sutures using an everting suture technique for mechanical valves and either a supra-annular or an intra-annular technique for bioprostheses. The tricuspid valve leaflets are left in place, preserving the subvalvular structures and helping to avoid injury to the conduction system (Fig. 47-6). If there is concern that the anterior leaflet could billow and obstruct the right ventricular outflow tract, the central portion of the leaflet can be excised and still preserve the chordal attachments.

Tricuspid valve replacement with a homograft is more complicated. The homograft tissue is a mitral valve.[76–79] Sizing is performed by measuring the intratrigonal distances. Fixation of the papillary muscles is either intracavity (right ventricle) or through the wall of the right ventricle. This requires judgment and experience to gauge proper chordal length. The annulus is run with a monofilament suture line. An annuloplasty ring is inserted to prevent dilatation and to ensure adequate leaflet coaptation. Special care is necessary in suture placement to avoid conduction disturbances. Suture placement and tying with the heart beating provide

Figure 47-5. (A) The Carpentier-Edwards ring annuloplasty is shown. A sizer measuring the intertrigonal distance was used to determine the ring size. Multiple interrupted, pledgeted 2-0 Ethibond sutures are placed at the atrioannular junction. All sutures are inserted prior to seating the ring. (B) The valve is seated, and the sutures are tied.

immediate detection of rhythm disturbances. Similar to mitral valve replacement, leaflet and chordal preservation should be performed, or Gore-Tex suture should used as artificial chordae to maintain annular papillary muscle continuity.

A recent report documented the use of a stentless porcine valve in endocarditis in which the commissural posts were anchored to the right ventricular septal, anterior, and posterior walls. Orientation is critical to be sure that the right ventricular outflow tract is straddled by two of the commisural posts.[112]

Carpentier techniques for MVR can be applied to the tricuspid valve. Traumatic disruptions, occasionally endocarditis with healed lesions and perforations, or the rare myxomatous valve can be repaired. Pericardial patching of perforations, partial leaflet resections of the anterior (limited) or posterior (extensive) leaflets, and ring annuloplasty are standard techniques to produce competent valves and avoid replacement.[80–82]

ENDOCARDITIS

Tricuspid valve excision is possible if pulmonary pressures are not elevated and the degree of infection is extensive.[83–91] Blood flows passively through the right side of the heart to the lungs. After eradication of the infection, a second-stage procedure with valve replacement can be performed months to years later. In patients with tricuspid valve endocarditis due to drug addiction, the second-stage valve insertion should be performed preferably after controlling the drug dependence or hopefully curing the accompanying addiction. Late survival and reinfection are correlated directly with continued drug use. Patients with less severe endocarditis can have one-stage procedures with prosthetic replacement or localized leaflet excision and repair.[92,93] Homograft tissue often is versatile for partial or total tricuspid valve repair or replacement but has the limitations of availability, technical difficulty, and limited follow-up. The stentless aortic porcine valve is a novel option.[112]

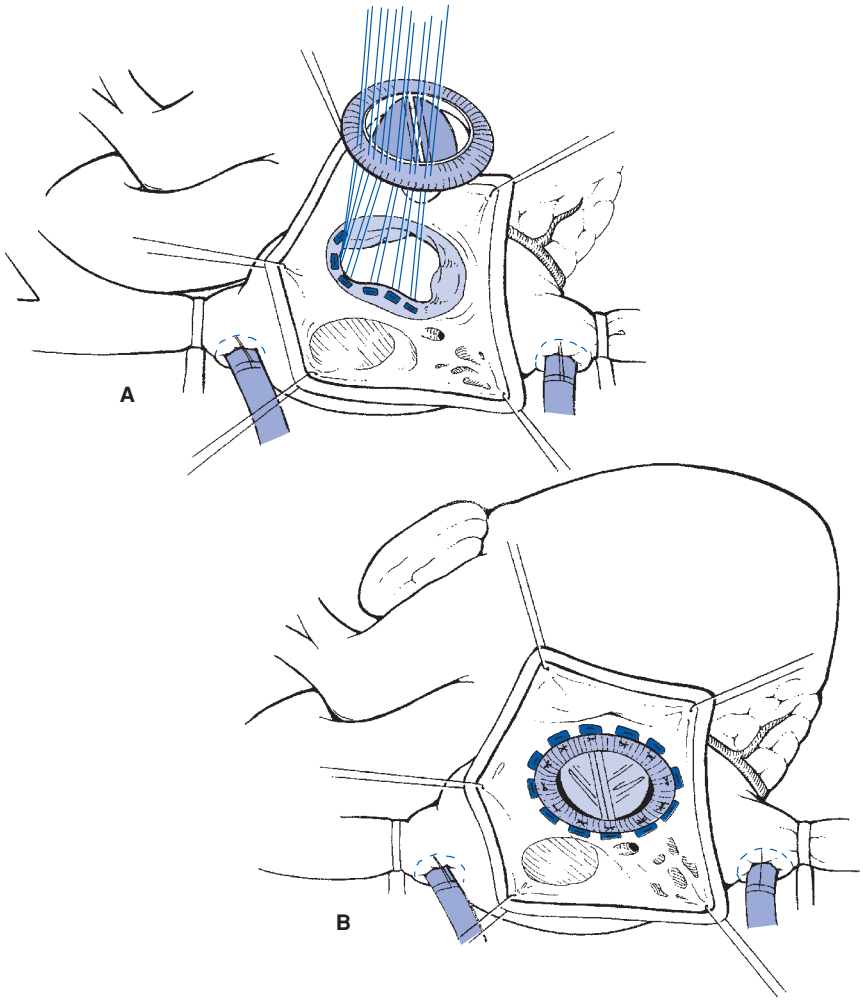


Figure 47-6. (A) Tricuspid valve replacement is performed with a St. Jude Medical valve. The native leaflets are left in situ, and the pledgeted 2-0 Ethibond sutures are passed through the annulus and the edges of the leaflets. (B) The valve is seated, and the sutures are tied. The subvalvular apparatus is visualized to ensure that there is no impingement of the prosthetic valve leaflets. The valve can be rotated if necessary to prevent leaflet contact with tissue.

PROSTHETIC VALVE CHOICE

The choice of prosthesis follows an algorithm similar to that used for valve replacement in other cardiac valve positions. The patient's age, anticoagulation considerations, whether the patient is a young woman during her childbearing years, and social issues must be considered. The previously reported poor results with mechanical valves in the tricuspid position were due to valve thrombosis. Most of these reports were during the era of cage-ball and tilting-disk prostheses.[94] More recent reports with the St. Jude bileaflet valve have provided encouraging data, allowing the surgeon to recommend a mechanical valve with confidence to younger patients who do not have a contraindication to anticoagulation.[95–101] This strategy will avoid the not uncommon situation in the past in which patients received a bioprothesis on the right side and a mechanical prosthesis on the left. Bioprostheses, both porcine and of pericardial tissue, have functioned well in the tricuspid position.[102–105] The data demonstrate a longer duration of freedom from structural valve dysfunction or re-replacement for a bioprosthetic valve in the tricuspid compared with the mitral valve position.[106]

Table 47-1 summarizes multiple reports from the literature. The reports either compare bioprosthetic and mechanical valves in the tricuspid position or present follow-up of bioprosthetic valves alone. The bioprostheses, either porcine or pericardial valves, have excellent freedom from degeneration and re-replacement for structural valve degeneration. In 1984, Cohen and colleagues reported on six simultaneously implanted and then explanted valves from the mitral and tricuspid positions. Degenerative changes were less extensive for the bioprosthetic valves in the tricuspid position than in the mitral position. However, thrombus formation and pannus formation (interpreted as organized thrombotic material) were observed more frequently in the tricuspid position.[106]

Nakano's review of the Carpentier-Edwards pericardial xenograft reported a freedom from structural degeneration of 100% at 9 years, but nonstructural dysfunction was 72.8%. The cause of nonstructural dysfunction was pannus formation on the ventricular side of the cusps. This finding is often subclinical. Echocardiographic follow-up revealed a 35% incidence of this anatomic finding in patients with at least 5 years of follow-up.[104] Guerra reported similar changes

Table 47–1.

Reports of Bioprosthetic and Mechanical Valves in the Tricuspid Position

Reference	Series dates	Patients (no.)	Operative mortality			Death			Actuarial freedom from								
			Bioprosthesis (B)	Mechanical (M)	Overall (A)	B	M	A	Structural degeneration B	Structural degeneration M	Structural degeneration A	Nonstructural degeneration B	Nonstructural degeneration M	Nonstructural degeneration A	Tricuspid reoperation B	Tricuspid reoperation M	Tricuspid reoperation A
Nakano[98]	1979–1992	39		8%			55% @14y		100%			72%				100% @14y	
Nakano[103]	1978–1995	98	15%			77% @5y; 69% @10y and 18y			98% @5y 96% @18y			99% @5y 82% @10y 77% @18y*			97% @5y; 76% @10y; 63% @18y		
Ratnatunga[101]	1966–1997	425	19%	16%	17%	71% @1y; 62% @5y; 48% @10y	74% 58% 34%	72% 60% 43%							99% @1y; 98% @10y;	98% 97%	
Glower[102]	1972–1993	129			27% (14% 1st Operation)	56% @5y; 48% @10y; 31% @14y									96% @5y; 93% @10y; 49% @14y		

Ohata[105]	1984–1998	88	7%			88% @5y; 81% @10y; 69% 14y			100% @14y		†		88% @14y	
Van Nooton[93]	1967–1987	146			16%			74% @5y; 23% @10y						
Singh[96]	1981–1984	14		8%			50% @10y							
Munro[99]	1975–1992	94	15%	14%	14%				97% @5, 7y, and 10y	100%			97%	87%
Kaplan[94]	1980–2000	122			25%	55% @20y	68% @20y	65% @20y	90% @20y	97%‡ @20y				
Scully[95]	1975–1993	60			27%		50% @15y							

Thick fibrous pannus in 35% of survivors; freedom from nonstructural valve dysfunction at 18 y = 24%.

†*Thick pannus noted in reoperative case.*

‡*Freedom from deterioration, endocarditis, leakage, and thromboembolism 93% @20 y.*

in simultaneously explanted porcine valves. The tricuspid position had less structural tissue degeneration and calcification than the mitral position. The report described the presence of pannus formation on the ventricular side of the cusps in tricuspid porcine valves. The pannus interfered with cuspal pliability and function.[107]

Nakano's 2001 report of bioprosthetic tricuspid valves reported an 18-year freedom from reoperation of 63%.[103] The freedom from structural deterioration was 96%, and nonstructural dysfunction was 77%. Reoperation replacing previously placed bioprosthetic valves occurred in 12 of 58 survivors. In 6 of the 12 patients, the primary indication for reoperation was tricuspid dysfunction, and 7 of the 12 had pannus formation on the ventricular side of the cusps (Fig. 47-7). This rate of degeneration and the subclinically high incidence of pannus formation, often eventually leading to reoperation, are major concerns. Tricuspid bioprosthetic valves require echocardiographic follow-up. Possible anticoagulation of bioprosthetic valves in the tricuspid position can reduce the incidence of pannus formation. The reported data in the literature categorize this pannus formation as nonstructural degeneration; therefore, clinical surgeons should be aware of future reports following this potentially serious clinical problem.

In the tricuspid position it is always possible to place large bioprosthetic or mechanical valves. Prostheses with more than a 27 mm internal diameter do not have clinically significant gradients. Therefore, hemodynamic performance is rarely an issue for tricuspid valve replacement. The data demonstrate excellent results with modern bileaflet mechanical valves. Series comparing bioprosthetic and mechanical valves have been consistent in demonstrating equality during the period of follow-up. The development of thrombus on a bileaflet valve can be treated successfully with thrombolysis.

A recent review by Filsoufi and a meta-analysis of biologic or mechanical prostheses in the tricuspid position both conclude that there is no survival benefit of a bioprothesis over a mechanical valve[113-115] (see Fig. 47-7A,B). Some patients with mitral valve disease and TR undergoing surgery do not require surgical treatment of the tricuspid valve. Guidelines to identify these patients are poorly developed. Experience has shown that careful observation of the patient preoperatively is quite valuable. Absence of tricuspid valve regurgitation during periods of good medical control, absence of TR by transesophageal echocardiography (TEE) at the time of operation, minimal elevation of pulmonary vascular resistance, and absence of right atrial enlargement are helpful findings that permit the surgeon to replace the mitral valve confidently without performing an annuloplasty or replacement of the tricuspid valve. If left unrepaired, reassessment of the tricuspid valve by TEE after weaning from cardiopulmonary bypass is essential.

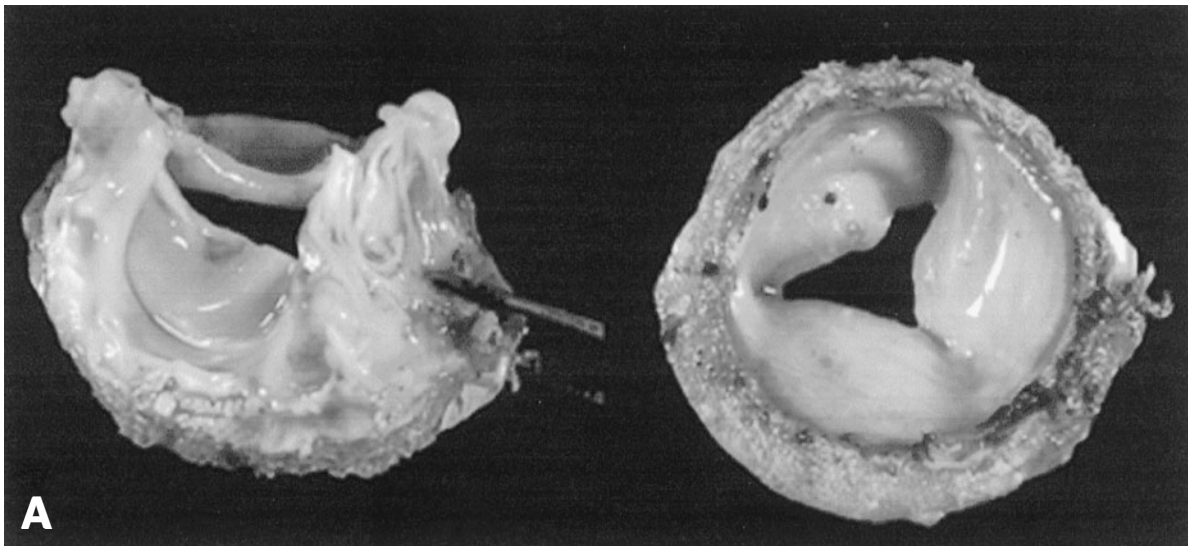
Temporary right ventricular dysfunction due to RCA air embolism often requires a brief return to cardiopulmonary bypass, repeat of air maneuvers, elevation of the blood pressure, TEE evaluation for residual intracavity air, and a search for the characteristic echogenic brightness in the myocardial distribution of the RCA confirming the suspicion of air embolism. Treatment should include 10 to 15 minutes of cardiopulmonary bypass support and reweaning from cardiopulmonary bypass, with inotropic support for right ventricular dysfunction and reassessment of the TR and cardiac function. If TR persists and elevated right atrial pressures greater than left atrial pressures are encountered with an underfilled, well-contracting left ventricle, tricuspid repair should be performed. A patent foramen ovale with interatrial shunting needs to be identified and closed surgically. Hemodynamically, when right atrial pressure is greater than left atrial pressure, the foramen may open, leading to systemic desaturation from a right-to-left shunt.

CONCLUSION

Clinical experience has demonstrated that up to 20% of patients undergoing mitral valve replacement receive a tricuspid annuloplasty, but less than 2% require replacement. The surgeon's clinical judgment and experience guide the approach to tricuspid valve surgery and ultimately lead to variability in reported clinical data. The accuracy of the judgments can be guided by assessment of the risk factors for persistent or progressive tricuspid valve regurgitation. They are related to unresolved or recurrent mitral valve pathology; the degree of preoperative tricuspid regurgitation or the misjudgment of its severity; failure of the pulmonary hypertension and pulmonary vascular resistance to resolve, resulting in persistent impairment in right ventricular function (often with right ventricular dilatation); and failure to recognize organic tricuspid valve disease.

Patients undergoing a tricuspid valve annuloplasty during a mitral valve replacement have more advanced disease than those having mitral valve replacement alone. This is evidenced by the elevation in operative mortality (approximately 12 versus 3%) and the progressive increased hazard of late death (5-year survival of 80 versus 70%) despite good valve function. However, these patients achieved good functional results (class 1–2). It is unknown what the survival and functional result would have been if tricuspid repair had not been performed in these patients, but one presumes that it would have been worse.

The durability of simple annuloplasty techniques such as bicuspidization and the DeVega technique has been good when employed only for mild to moderate degrees of functional TR with successful resolution of pulmonary hypertension after the mitral valve operation. Extensive experience with the tricuspid annuloplasty using the Duran, Carpentier-Edwards, or Cosgrove rings or bands resulted in an 85% freedom from moderate to severe TR at 6 years. The subsequent requirement for tricuspid reoperation is very low. Inadequate resolution of the mitral disease and persistent pulmonary hypertension



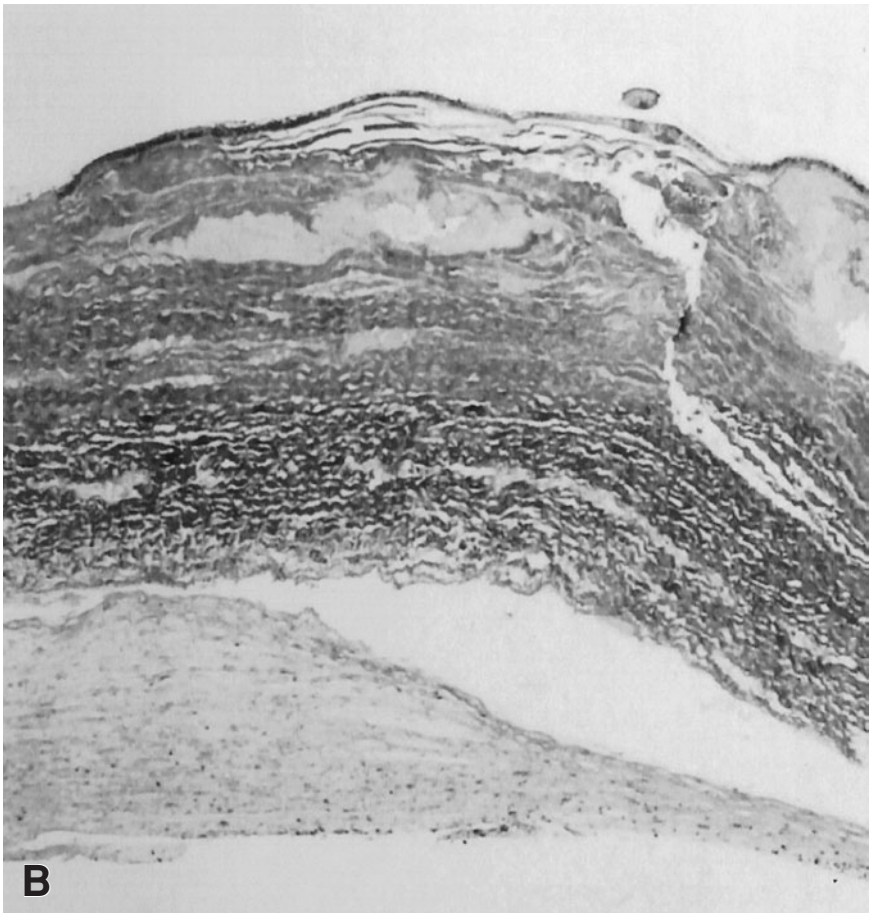


Figure 47-7. (A) Fibrous pannus observed 8 years after implantation of a Carpentier-Edwards pericardial valve. (B) Photomicrograph of a pericardial leaflet. The bottom of the leaflet has pannus, a dense fibrous tissue on the ventricular side. (*Reprinted with permission from the Society of Thoracic Surgeons and Nakano K, Ishibashi-Ueda H, Kobayashi J, et al: Tricuspid valve replacement with bioprostheses: Long-term results and causes of valve dysfunction. Ann Thorac Surg 2001; 71:105.*)

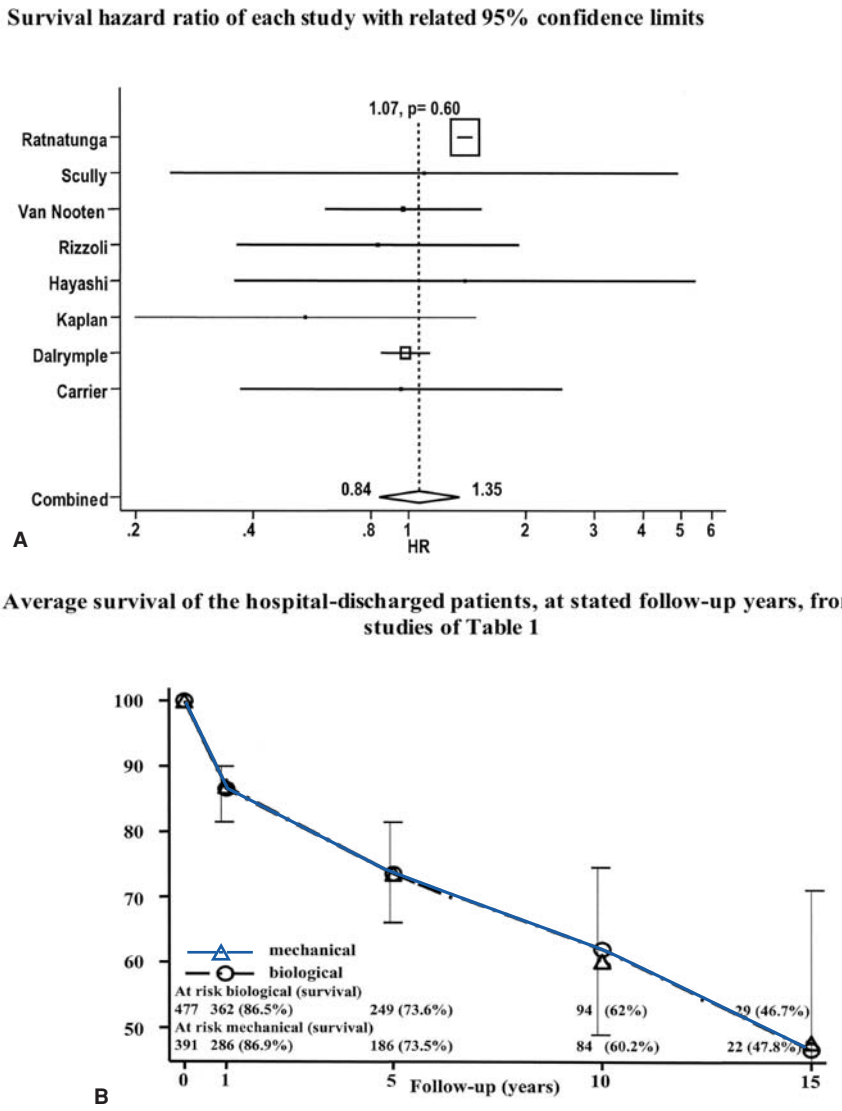


Figure 47-8. Meta-analysis of bioprosthetic vs mechanical valves replacing the tricuspid valve. (A) Survival hazard. (B) Survival curve of hospital survivors.

with right ventricular dilatation and dysfunction are the major predictors of poor late results.

Patients requiring tricuspid and mitral valve replacement have operative mortalities from 5 to 10% by current standards. Actuarial survival rates are 55% at 10 years (Fig. 47-8A,B). Advanced right ventricular failure or arrhythmia causes late death. Patients who need valve replacement for endocarditis comprise a unique subgroup with the additional risk for death owing to sepsis, reinfection, and the complications related to drug addiction.

Complete heart block can occur immediately postoperatively owing to damage to the conduction system during mitral and tricuspid valve surgery. This complication can be minimized intraoperatively by performing the tricuspid valve procedure on the perfused beating heart, as described earlier. Late heart block remains a persistent risk with a 25% actuarial incidence at 10 years for patients with mitral and tricuspid prostheses.[108] Late development of heart block rarely occurs after mitral valve replacement and tricuspid annuloplasty (Fig. 47-8A, B). The presence of two rigid prosthetic sewing rings can produce ongoing trauma and lead to AV node dysfunction over time.

The surgical treatment of tricuspid valve disease presents the surgeon with challenges requiring clinical and intraoperative judgment. Following the guidelines presented in this chapter for when to repair or replace the tricuspid valve should lead to optimal clinical outcome. The data support the safe use of mechanical bileaflet prostheses. A lingering concern is the pannus formation on the ventricular side of bioprosthetic cusps. This observation should be followed closely as future clinical series are reported.

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CHAPTER 48

Multiple Valve Disease

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Pathologic changes in the cardiac valves requiring surgical correction of more than one valve can result from rheumatic heart disease, degenerative valve diseases, infective endocarditis, and a number of miscellaneous causes. Further, valve dysfunction may be primary, i.e., a direct result of a disease process, or secondary, i.e., caused by cardiac enlargement and/or pulmonary hypertension. Surgical management is influenced both by the underlying cause of valve dysfunction and, when valves are involved secondarily, by the anticipated response to replacement or repair of the primary valve lesion. In addition, the consequences of various combinations of diseased valves on left and right ventricular geometry and function frequently are different from the remodeling as a result of single-valve disease. This chapter addresses pathophysiologic considerations in multivalvular heart disease, surgical techniques, and management of commonly encountered etiologies.

Repair of multiple lesions was necessary even in the early development of operative management of valvular heart disease (Table 48-1). The first triple-valve replacement during a single operation was reported in 1960, and simultaneous replacement of all four valves was reported in 1992.[1]

Experience from clinical practice indicates that multiple valve disease requiring surgical correction occurs in a few common combinations. As seen in Table 48-2, multiple procedures account for approximately 15% of all operations on cardiac valves; 80% of these operations involve the aortic and mitral positions. Replacement of the mitral and tricuspid valves (with or without aortic replacement) accounts for 20% of operations. Only rarely is the combination of aortic and tricuspid disease encountered.

PATHOPHYSIOLOGY OF MULTIPLE VALVE DISEASE

Valvular regurgitation may result from the pathologic process affecting the valve directly or may be secondary to alterations in ventricular morphology caused by other valve lesions; this secondary or functional regurgitation affects the atrioventricular valves. In some patients, secondary valvular regurgitation may be expected to improve with repair or replacement of the primarily diseased valve. In other patients, the secondary disease process may have advanced to the stage that valve function will not improve following correction of the primary lesion, and thus simultaneous surgical correction should be considered.

Primary Aortic Valve Disease with Secondary Mitral Regurgitation

Isolated aortic valve lesions can cause secondary regurgitation of the mitral valve and, rarely, of the tricuspid valve. Severe aortic valve stenosis with or without left ventricular dilatation frequently is associated with some degree of mitral valve regurgitation. In one series, 67% of patients with severe aortic valve stenosis had associated mitral valve leakage.[2]

When the mitral valve is structurally normal, its regurgitation would be expected to improve with relief of left ventricular outflow obstruction[3]; mild mitral valve regurgitation would be expected to resolve almost completely following aortic valve replacement. Improvement in mitral valve regurgitation results from both decreased intraventricular pressure and ventricular remodeling.[4] If mitral valve regurgitation is severe, some degree of persistent regurgitation is expected following aortic valve replacement, and mitral valve annuloplasty may be required. In contrast, with aortic valve stenosis and mitral valve regurgitation associated with a structurally abnormal mitral valve, repair or replacement of the mitral valve usually is necessary. A recent report alleges that moderate mitral regurgitation has an adverse impact on survival in elderly patients undergoing aortic valve replacement and suggests that those with intrinsic mitral valve disease should be considered for concurrent correction.[5]

Table 48–1.

History of Multiple Valve Operations

Event	Year	Institution
Staged mitral then tricuspid commissurotomy	1952	Doctor's Hospital, Philadelphia, PA[178]
Simultaneous mitral and tricuspid commissurotomy	1953	Cleveland, OH[179]
Simultaneous mitral commissurotomy and aortic valvuloplasty using cardiopulmonary bypass	1956	University of Minnesota, Minneapolis, MN[180]
Simultaneous mitral and aortic valve replacement	1961	St. Francis General Hospital, Pittsburgh, PA[140]
Simultaneous triple-valve replacement	1963	University of Oregon, Portland, OR
Simultaneous quadruple valve replacement	1992	Mayo Clinic, Rochester, MN[137]

Source: Modified with permission from Acker M, Hargrove WC, Stephenson LW: Multiple valve replacement. Cardiol Clin 1985; 3:425.

Thus determination of the morphology and pathophysiologic severity of each valve lesion is critically important in planning surgical management, and preoperative and intraoperative echocardiographic studies are necessary in all patients suspected of having multiple valve disease. Often, transthoracic echocardiography can define the etiology of mitral and tricuspid valvular regurgitation. When valve regurgitation is entirely secondary, the mitral valve leaflets will appear thin and freely mobile, without prolapsing segments. Mitral (and tricuspid) valve regurgitation secondary to rheumatic disease is readily identified when leaflets are thickened and chordae are shortened; fibrosis of these structures restricts leaflet mobility. Leaflet prolapse with or without ruptured chordae tendineae also may cause atrioventricular valve regurgitation.

Transesophageal echocardiography images the heart from a retrocardiac position, which avoids interference from

Table 48–2.

Prevalence of Multiple Cardiac Valve Replacement According to Institution

	University of Alabama	Mayo Clinic	Texas Heart Institute	University of Oregon	Percentage of all valve surgery (11,026 cases)	Percentage of multiple valve surgery (1662 cases)
Years involved	1967–1976	1963–1972	1962–1974	1960–1980		
Total number of all valve operations	2555	2166	4170	2135		
All multiple valve procedures	383 (15%)	437 (20%)	541 (13%)	301 (14%)	15 (1662)	100
M-A	298 (11.6%)	320 (14.7%)	459 (11%)	253 (11.8%)	12 (1330)	80
M-A-T	40 (1.6%)	55 (2.5%)	55 (2.5%)	48 (2.2%)	2 (198)	12
M-T	41 (1.6%)	58 (2.5%)	26 (0.6%)	—	1.5 (125)	8
A-T	4 (0.1%)	4 (0.2%)	1 (0.02%)	—	0.1 (9)	5

M = mitral valve; A = aortic valve; T = tricuspid valve.
Source: Modified with permission from Acker M, Hargrove WC, Stephenson LW: Multiple valve replacement. Cardiol Clin 1985; 3:425.

interposed ribs, lungs, and subcutaneous tissue. A high-frequency (5-MHz) transducer is employed, which yields better resolution than that of images obtained with routine transthoracic imaging with 2.25- to 3.5-MHz transducers.[6] Thus transesophageal echocardiography provides the best image of the mitral and tricuspid valves and may be obtained preoperatively. Intraoperative transesophageal Doppler echocardiography should be employed in all patients having valve repair or replacement, and the technique is especially important for assessment of response of mitral regurgitation to relief of left ventricular outflow obstruction.[7] In some cases, preoperative left ventriculography may help to quantify left atrioventricular valve leakage. Right ventricular angiocardiography also can be useful in determining the degree of tricuspid valve dysfunction, but it is rarely employed in current practice.[8]

Tricuspid Valve Regurgitation Secondary to Other Valvular Disease

Secondary tricuspid valve regurgitation commonly is associated with rheumatic mitral valve stenosis, and the exact cause is unknown.[9,10] Some authors believe that secondary tricuspid valve regurgitation is a result of pulmonary artery hypertension and right ventricular dilatation.[11] As with the mitral valve, tricuspid valve annular dilatation is asymmetric. Most enlargement occurs in the annulus subtended by the free wall of the right ventricle, and there is little dilation of the annulus adjacent to the septal leaflet of the tricuspid valve.[12,13]

Although pulmonary artery hypertension with secondary enlargement of the right ventricle and tricuspid valve annulus may be an important contributing factor in secondary tricuspid regurgitation, it is not the sole mechanism. For example, congenital heart lesions such as tetralogy of Fallot produce systemic pressure in the right ventricle, yet severe tricuspid valve regurgitation rarely is seen in these patients. Similarly, important tricuspid valve regurgitation is uncommon in children with ventricular septal defects who have enlargement of the right ventricle associated with variable degrees of pulmonary hypertension.

Furthermore, clinical experience suggests that other mechanisms must play a role in development of secondary tricuspid valve regurgitation. Patients who have had mitral valve replacement for rheumatic mitral valve stenosis may develop regurgitation of their native tricuspid valve years after initial operation, and many patients have only modest elevation of pulmonary artery pressure.[14,15]

It is useful to classify secondary mitral and tricuspid valve regurgitation as mild, moderate, and severe.[13] Usually, patients with mild tricuspid valve regurgitation do not have clinical signs and symptoms of right-sided heart failure. Also, mild tricuspid regurgitation demonstrated by preoperative echocardiography may appear even less severe in the operating room under general anesthesia. In most instances, mild secondary tricuspid regurgitation does not require intervention.

Patients with echocardiographic evidence of significant regurgitation who do not have symptoms or have their symptoms controlled by medical treatment can be classified as having moderate tricuspid regurgitation. These patients usually are managed with a DeVega suture annuloplasty or a partial-ring annuloplasty.[16] Patients with severe secondary tricuspid regurgitation and clinical evidence of right-sided heart failure (i.e., pulsatile liver, distended neck veins, and peripheral edema with or without ascites) are managed by concomitant ring annuloplasty or tricuspid valve replacement.

The degree of pulmonary hypertension may influence surgical management of secondary tricuspid valve regurgitation. Kaul and colleagues[17] grouped 86 patients with functional tricuspid regurgitation in association with rheumatic mitral valve disease according to the degree of pulmonary hypertension. One group had severe pulmonary hypertension (mean pulmonary pressure 78 mm Hg), and a second group had moderate pulmonary hypertension (mean pulmonary artery pressure 41 mm Hg). Patients with moderate pulmonary hypertension preoperatively had more advanced right-sided heart failure and right ventricular dilatation, and many of these patients continued to have tricuspid valve regurgitation following mitral valve surgery without tricuspid valve surgery. The patients with severe pulmonary hypertension all showed regression of tricuspid regurgitation, and 28% had complete resolution following mitral valve surgery without operation on the tricuspid valve.

Excluding hospital mortality, about 40% of patients undergoing tricuspid valve surgery have premature death.[8] It is also important to understand that mild to moderate (2+) regurgitation is a risk factor for late failure of tricuspid valve repair, and severe (4+) regurgitation preoperatively is a predictor of early residual regurgitation.[18] Finally, there is recent evidence to suggest that remodeling annuloplasty in the setting of of tricuspid annular dilatation (≥70 mm) at the time of mitral repair significantly decreases the risk of subsequent functional deterioration as compared with those not having annular correction.[19]

VALVE SELECTION FOR MULTIPLE VALVE REPLACEMENT

When multiple valve replacement is confined to the left ventricle, replacement valves should be chosen from the same class with respect to the need for anticoagulation and projected longevity. There are no theoretical or practical advantages to use of a tissue valve and a mechanical valve for mitral and aortic valve replacement, and studies show no reduction in the risk of thromboembolism, valve-related morbidity, or late death.[20,21] In addition, a lower reoperation rate is reported for patients with two mechanical valves in the left ventricle compared with patients with one mechanical and one tissue valve.[20]

For tricuspid valve replacement, alone or in conjunction with other valve procedures, use of a bioprosthesis may

have advantages in regard to minimizing risk of valve thrombosis.[22,23] Furthermore, there are few hemodynamic considerations in selecting a tricuspid prosthesis; the greater hemodynamic efficiency of mechanical valves compared with bioprostheses rarely is an issue in atrioventricular valve replacement, especially the tricuspid valve, in which the annulus diameter in adults is often 33 mm or more. In vitro studies demonstrate only minimal hemodynamic improvement with atrioventricular valves larger than 25 mm.[24]

SURGICAL METHODS

Aortic and Mitral Valve Replacement

Cannulation

Arterial inflow is established by cannulation of the distal ascending aorta near the pericardial reflection just to the left of the origin of the innominate artery (Fig. 48-1*A*). Venous cannulation is simplified by using a two-stage cannula in the right atrium for venous return. Individual cannulation of the superior and inferior venae cavae is reserved for operations that require right atrial or ventricular incisions (Fig. 48-2*A*).

Cardiopulmonary bypass is commenced at 2.4 L/m^2 per minute, and systemic hypothermia is induced according to the requirements of the operation. We prefer maintaining the systemic temperature near normal (35 to 37°C) for most operations, including multiple valve procedures. Provisions for intraoperative autotransfusion are used routinely, and antifibrinolytic drugs such as aprotinin or epsilon-aminocaproic acid (Amicar) may be useful, especially in reoperations, where pericardial adhesions may worsen bleeding.[25]

Cardioplegia

If the aortic valve is competent, myocardial protection during aortic cross-clamping is achieved by initial infusion of cold (4 to 8°C) blood cardioplegia through a tack vent placed in the aorta proximal to the clamp. The volume of cardioplegia needed to achieve diastolic arrest and uniform hypothermia depends on the heart size and the presence of aortic valve regurgitation. Generally, the initial volume of cardioplegia required for hearts with multiple valve disease is higher than that required for coronary revascularization because of myocardial hypertrophy. For patients without cardiac enlargement, we infuse approximately 10 mL/kg of body weight, whereas 15 mL/kg of body weight is used for patients with significant degrees of myocardial hypertrophy. Repeat infusions of 400 mL of cardioplegia are given directly into the coronary ostia at 20-minute intervals during aortic occlusion. We use custom-designed, soft-tipped coronary perfusion catheters to minimize the potential for trauma to the coronary ostia during intubation and infusion.[26]

If aortic valve regurgitation is moderate or severe, cardioplegia is infused directly into the coronary ostia. Initial aortotomy is facilitated by emptying the heart using suction on an aortic tack vent and temporarily reducing the cardiopulmonary bypass flow rate to maximize venous return. Some surgeons prefer retrograde infusion of cardioplegia,[27] and if this method is used, even larger volumes are necessary because of nonnutritive flow through the coronary venous system and variation in coronary venous anatomy.[28,29]

Procedure

After cardioplegia, the aortic valve is inspected through an oblique aortotomy extended into the noncoronary aortic sinus (see Fig. 48-1*B*). Aortic valve regurgitation caused by cuspal perforation or prolapse of a congenitally bicuspid valve often can be repaired,[30] but the decision for or against aortic valve repair should take into consideration whether or not a mitral valve prosthesis will be needed. For example, even though aortic valve repair might seem technically possible, prosthetic replacement may be the best option for a patient who requires mitral valve replacement and will be maintained on warfarin for long-term anticoagulation.

Severe calcification of the valve, whether it is bicuspid or tricuspid, necessitates replacement,[31] and the cusps therefore are excised and annular calcium débrided carefully. The aortic annulus then is calibrated; experience has shown that subsequent replacement of the mitral valve usually reduces the aortic annular diameter by shortening the circumference that is in continuity with the attachment of the anterior mitral valve leaflet. Therefore, we routinely identify (but do not break the sterile packaging of) two aortic prostheses: One corresponds to the calibrated dimension, and the other is the next size smaller. Final selection of the aortic prosthesis is made after mitral valve replacement or repair.

Although exposed first, the aortic valve usually is replaced after mitral valve repair or insertion of the mitral valve prosthesis. Sutures placed in the portion of the aortic valve annulus that is continuous with the anterior leaflet of the mitral valve pull the anterior leaflet superiorly toward the left ventricular outflow area and thus hinder exposure of this area as viewed through the left atriotomy.

If the aortic annulus is small, it can be enlarged with a patch of pericardium.[32] This technique increases annular diameter by 2 to 4 mm or more, and only rarely are more radical techniques necessary.[33–35] Another maneuver to accommodate as large a prosthesis as possible is to place the necessary sutures for the mitral valve repair or replacement but not secure the mitral prosthesis until the aortic valve is implanted. This eliminates downsizing of the aortic prosthesis but does not compromise insertion of sutures in the superior portion of the mitral valve annulus.

After removal of the aortic valve, the right atrial cannula is repositioned, and the mitral valve is exposed through an incision posterior to the interatrial groove (see Fig. 48-1*B*). The presence or absence of thrombi in the left atrium is noted, and the mitral valve is inspected. When there is rheumatic disease of the aortic valve, the mitral valve almost always will be involved to some extent. If aortic valve replacement is necessary, the surgeon should have a low threshold for replacing a diseased mitral valve because scarring and

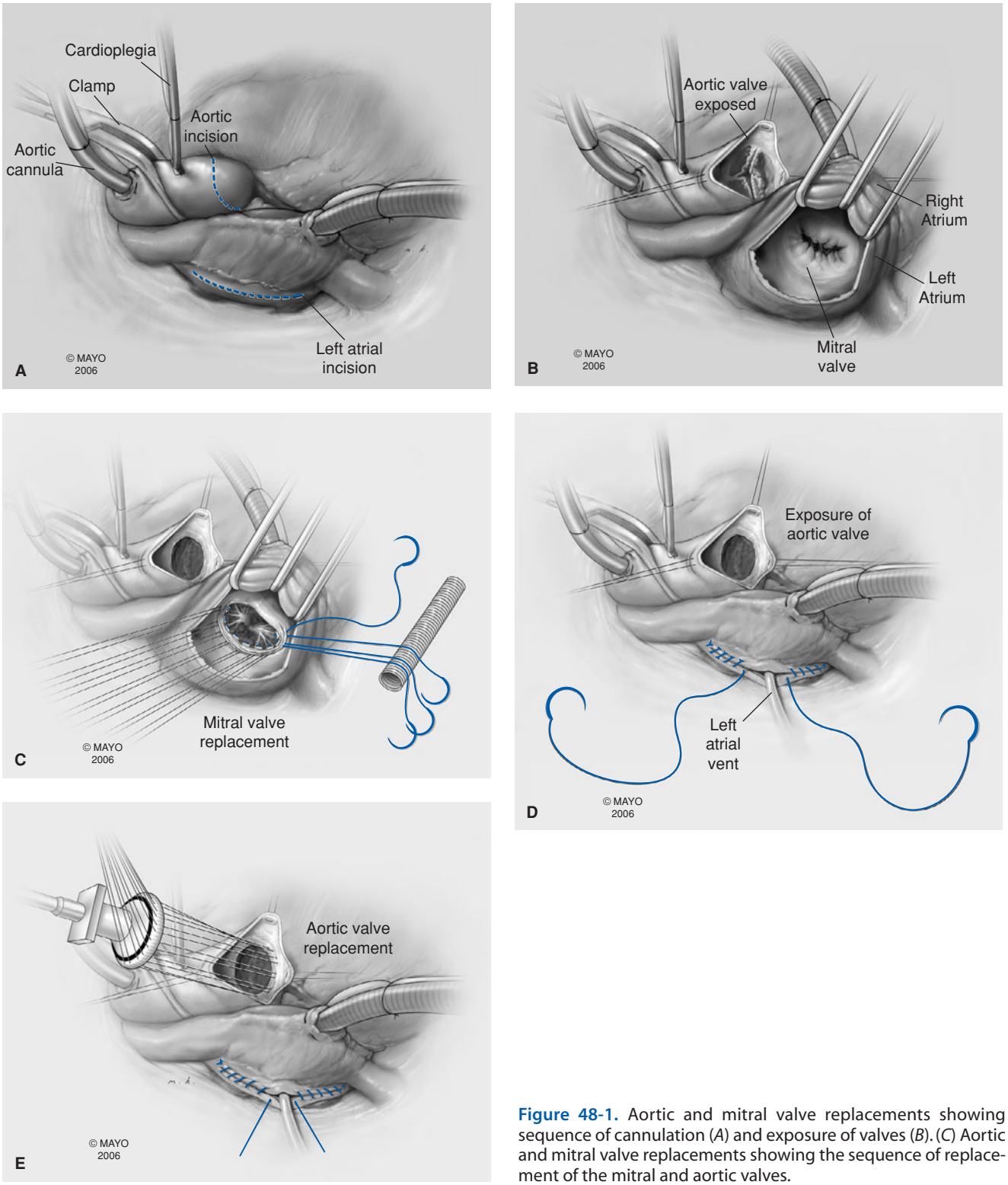

Figure 48-1. Aortic and mitral valve replacements showing sequence of cannulation (*A*) and exposure of valves (*B*). (*C*) Aortic and mitral valve replacements showing the sequence of replacement of the mitral and aortic valves.

fibrosis of the rheumatic process are progressive, and mitral valve repair (commissurotomy for stenosis or leaflet repair and annuloplasty for regurgitation) is less durable than repair for degenerative disease.[36–38] In contrast, when aortic valve replacement is necessary because of calcification of a bicuspid valve or because of senescent calcification, repair of mitral valve regurgitation owing to degenerative causes can be expected to give predictably good long-term results. Repair of the mitral valve is described in Chap. 37.

In preparation for replacement, the anterior leaflet of the mitral valve is excised, and when possible, a portion of the posterior leaflet with its chordal attachments is preserved

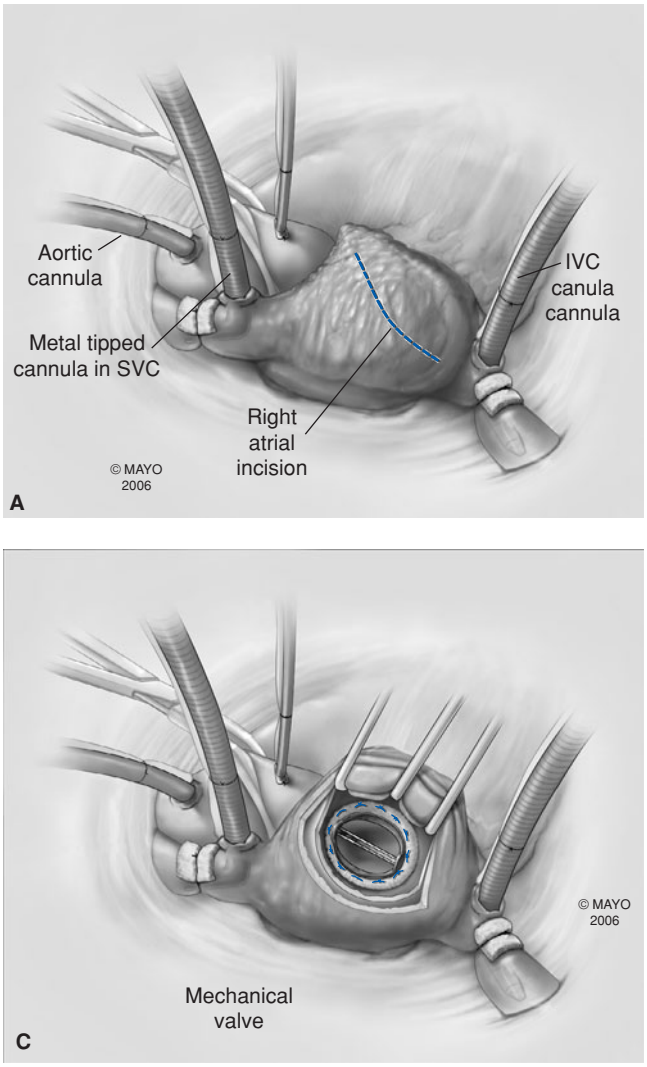

Figure 48-2. Combined mitral valve and tricuspid valve operation. The panels illustrate cannulation (*A*) and transseptal incision (*B*). (*C*) Combined mital valve and tricuspid valve operation: mitral replacement. (Superior vena cava snare not shown.)

to maintain left ventricular papillary muscle–annular continuity.[39–41] Some surgeons make a special effort to preserve the anterior leaflet and its chordal attachments, believing that this has a further beneficial effect on ventricular performance.[42] The mitral prosthesis is implanted using interrupted mattress sutures of 2-0 braided polyester reinforced with felt pledgets, which can be situated on the atrial or ventricular side of the valve annulus (see Fig. 48-1*C*). The leaflets of mechanical valves should be tested for free mobility following valve seating.

When atrial fibrillation is present preoperatively, we obliterate the left atrial appendage by oversewing its orifice from within the left atrium or by ligating it externally. The left atriotomy is closed from each end with running polypropylene sutures. Vent tubing is inserted through the partially closed left atriotomy and left in place while the aortic valve is being replaced (see Fig. 48-1*D*).

After appropriate exposure, the aortic prosthesis is sewn in place with interrupted 2-0 polyester mattress sutures backed with felt pledgets, and the aortotomy is closed, usually with two layers of 4-0 polypropylene. Any remaining air is evacuated from the heart with the usual maneuvers, and a tack vent in the ascending aorta is placed on suction as the aortic clamp is removed. The vent is removed from the left atrium, and closure of the left atriotomy is secured.

In patients with annuloaortic ectasia, the mitral valve sometimes can be visualized and replaced through the enlarged aortic annulus.[43]

Aortic Valve Replacement and Mitral Valve Repair

Intraoperative transesophageal echocardiography is useful in assessing the degree of mitral regurgitation and, importantly, in identifying the cause of valve leakage. When mitral valve regurgitation is only moderate and leaflet morphology is normal, we expect mitral valve function to improve following relief of severe aortic stenosis. In all other instances, the valve should be inspected directly to determine the need for repair or replacement.

Sternotomy, cannulation, and assessment of the aortic valve proceed as described previously. When there is no

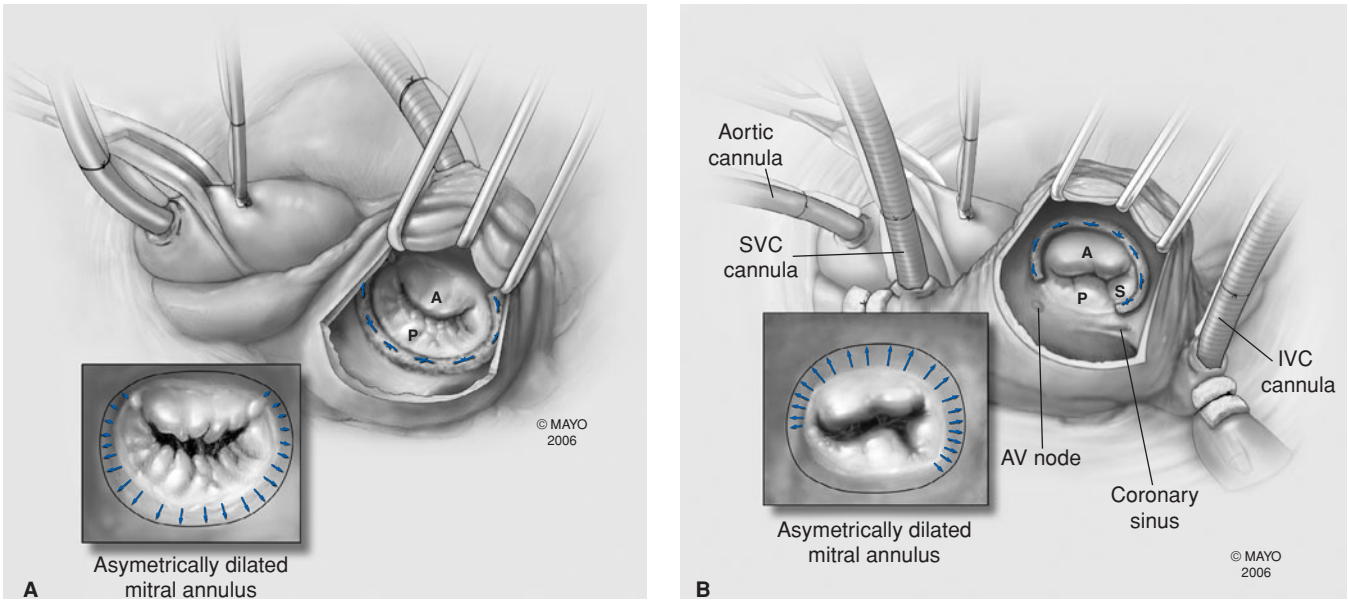

Figure 48-3. Mitral valve repair (*A*) and tricuspid valve repair (*B*) using a partial-ring annuloplasty. (Superior and inferior venae cavae snares not shown.)

indication of tricuspid valve disease and no other right atrial procedures are planned, venous return is obtained through a single two-staged cannula (Fig. 48-3*A*). Specific techniques of mitral valve repair depend on operative findings.[44] Localized prolapse of a portion of the posterior leaflet with or without ruptured chordae usually is managed by triangular excision of that segment and repair with continuous 4-0 polypropylene suture.[45] Ruptured chordae to the anterior leaflet are replaced with 4-0 or 5-0 polytetrafluoroethylene (PTFE) sutures inserted into papillary muscle and through the free edge of the prolapsing leaflet.[46]

Almost all leaflet repairs are supplemented with a posterior annuloplasty. Interrupted 2-0 braided polyester mattress sutures are placed along the posterior circumference of the annulus ending at the right and left fibrous trigones (see Fig. 48-3*A*). Sutures then are spaced evenly through a flexible 6.0- to 6.5-cm-long partial ring; this standard length can be obtained by using a flexible 63-mm posterior annuloplasty band.[47,45] Following annuloplasty, competence of the mitral valve is tested by filling the ventricle with saline or blood; the atrium then is closed, and the aortic valve prosthesis is sewn into place.

Mitral Valve Replacement and Tricuspid Valve Replacement or Repair

In most instances, tricuspid valve regurgitation is caused by annular dilatation.[48] The severity of tricuspid valve leakage can be determined by transesophageal echocardiography prior to bypass and by digital exploration of the right atrium just prior to venous cannulation. Under general anesthesia, changes in blood volume and cardiac output can cause significant fluctuation in the amount of regurgitation, and most often the severity of tricuspid valve leakage is lessened in the immediate prebypass period.

The patient's clinical condition must be correlated with echocardiographic findings and intraoperative assessment of the tricuspid valve. Patients with an enlarged, pulsatile liver, peripheral edema, and jugular venous distension are likely to require tricuspid valvuloplasty following mitral valve replacement or repair. Patients without the stigmata of right-sided heart failure usually have less severe valve leakage, and tricuspid valve function may improve without direct repair or replacement after left-sided valvular lesions are corrected.

The decision for repair or replacement of functional tricuspid valve regurgitation at the time of mitral valve replacement is important because the risk of subsequent reoperation is high. In our earlier experience, operative mortality was 25% in patients who required later reoperation for tricuspid valve regurgitation. Further, tricuspid regurgitation progresses in 10 to 15% of patients after replacement of rheumatic mitral valves.[49] Therefore, we maintain a liberal policy for annuloplasty or prosthetic replacement at initial operation.[50]

Procedure

For operations on the tricuspid valve, insertion of a Swan-Ganz catheter is optional; if one is used, the catheter is withdrawn from the right heart chambers during inspection and assessment of the tricuspid valve. We prefer direct cannulation of the inferior and superior venae cavae.[51] After commencement of cardiopulmonary bypass and cardioplegia, the cavae are snared around the venous cannulae, and the interatrial septum and tricuspid valve are exposed through a right atriotomy (see Fig. 48-2*A*). A decision for repair or replacement of the tricuspid valve is made, and the necessary prosthesis is identified.

When the tricupspid valve is also addressed, we tend to expose the mitral valve through an incision in the interatrial

septum, which crosses the fossa ovalis and can be extended superiorly (see Fig. 48-2*B*). Care should be taken during retraction to avoid tearing the septum inferiorly toward the coronary sinus and triangle of Koch. Alternatively, the mitral valve can be exposed through a standard left atriotomy posterior to the interatrial groove.

After repair or replacement of the mitral valve (see Fig. 48-2*C*), the septal or left atrial incision is closed, and the tricuspid valve is repaired or replaced. For tricuspid valve repair, we use either the DeVega method or ring annuloplasty.[11,16,52,53] Both techniques are based on the observation that the anterior and posterior valve portions of the tricuspid valve annulus are more prone to dilatation than the septal leaflet portion of the annulus, as described previously. When ring annuloplasty is indicated, we prefer a flexible device such as the Cosgrove-Edwards prosthesis[54] or a partial Duran ring (see Fig. 48-3*B*). The use of a partial ring avoids placement of sutures in the annulus near the penetrating bundle of His and reduces risk of injury to conduction tissue.

Tricuspid Valve Replacement and Pulmonary Valve Replacement for Carcinoid Heart Disease

If there is no involvement of the mitral and aortic valves,[55] tricuspid and pulmonary valve replacement usually can be performed without the need for aortic occlusion and cardioplegic arrest. It is important to exclude the presence of a patent foramen ovale to eliminate the risk of air entering the left atrium, and if a defect in the atrial septum is identified, it is closed using a brief period of aortic occlusion. In the past, our strategy for patients with carcinoid heart disease was to replace the tricuspid valve and excise the diseased pulmonary valve.

Subsequent experience has suggested that right ventricular function is better preserved with a competent pulmonary valve, so we now favor pulmonary valve replacement rather than valvectomy.[56] Tricuspid valve replacement always is indicated, and it is usually necessary only to remove the anterior leaflet. A recent review of 200 patients with carcinoid heart disease at our institution demonstrated that prognosis has improved in the current era and that valve replacement surgery was independently associated with prolonged survival.[57]

Carcinoid disease produces fibrosis and retraction of the leaflets, so anchoring sutures (interrupted mattress sutures of 2-0 braided polyester backed with felt pledgets) can be inserted into the remaining septal and posterior leaflets. We prefer to position the pledgets on the ventricular side of the valve annulus. If exposure is difficult, a brief period of aortic clamping and cardioplegic arrest is used during placement of sutures in the posterior and septal leaflets; the aortic cross-clamp is removed, and the heart is allowed to beat rhythmically. The remaining sutures are placed, and all sutures are secured with observation of the electrocardiogram. If atrioventricular block develops, the sutures in the area of the penetrating bundle of His are removed and reinserted in a more superficial location.

Pulmonary valve replacement is performed through a longitudinal incision across the valve annulus onto the outflow portion of the right ventricle. We prefer to insert the prosthetic valve using a continuous 3-0 polypropylene suture, anchoring the sewing ring to the native valve annulus for approximately two-thirds of the valve annulus and then anteriorly to a pericardial patch that is used routinely to augment the valve annulus and to facilitate closure of the pulmonary artery and right ventricle.

Triple-Valve Replacement

Operative preparation is similar to that described previously. Usually left-sided valvular lesions are corrected prior to tricuspid valve procedures. Again, if there is aortic valve regurgitation, the aortotomy is performed first, and cardioplegia is administered; simultaneously, we snare the cavae and open the right atrium. After excision of the aortic valve and calibration of the annulus, the interatrial septum is incised, and the mitral valve is repaired or replaced. Next, the aortic valve is implanted, and after closure of the aortotomy and septotomy, the tricuspid valvuloplasty or prosthetic replacement can be performed without aortic cross-clamping.[58]

RHEUMATIC HEART DISEASE AFFECTING MULTIPLE VALVES

As shown in Table 48-3, rheumatic valvulitis is a common cause of multiple valve disease. Autopsy studies show that almost all patients with rheumatic heart disease have some involvement of the mitral valve, although it is not always evident clinically.[59] The percentages of multiple valve involvement in two autopsy studies of patients with rheumatic heart disease are shown in Table 48-4.

Forty-seven percent of those studied had involvement of more than one valve. Mitral and aortic valve disease was the most common combination and was present in 34% of patients; the second most common combination was mitral, aortic, and tricuspid valve disease (9%). A recent report has suggested that all four valves might be involved with the rheumatic process.[60]

Long-term follow-up of children with rheumatic heart disease suggests that approximately 50% of patients have multivalvular involvement.[61,62] In a study of patients undergoing mitral valvotomy for rheumatic mitral stenosis (Table 48-5), 13% had clinical evidence of other rheumatic valve stenosis or regurgitation. Most of these patients had associated rheumatic aortic disease.[63]

Rheumatic heart disease can cause valve stenosis, regurgitation, or a combination of lesions. The percentages of 290 patients with specific valvular lesions from four studies of multiple valve disease are shown in Table 48-6. Mixed lesions producing stenosis and regurgitation were encountered most commonly in both aortic and mitral valves.

Table 48–3.

Reports of Operations for Multiple Valve Disease, Showing the High Incidence of Rheumatic Heart Disease

Study	Patients (no.)	Patients with rheumatic heart disease, % (no.)
Combined mitral and aortic replacement[170]	86	100 (86)
Combined mitral and aortic replacement[145]	92	100 (92)
Combined mitral and aortic replacement with tricuspid repair[51]	109	98 (107)
Triple valve replacement[172]	48	100 (48)
Combined mitral and aortic replacement[101]	54	85 (46)
Multiple valve procedures[150]	50	86 (43)
Triple valve replacement[22]	91	100 (91)
Combined mitral and aortic replacement[149]	65	80 (52)
Mitral replacement and tricuspid surgery[14]	32	81 (26)
Combined mitral and aortic replacement[181]	166	64 (106)
Mitral and aortic procedures[71]	124	100 (124)
Multiple valve procedures[182]	102	100 (102)
Combined mitral and aortic replacement[183]	33	82 (27)
Mitral and aortic regurgitation[91]	39	67 (26)
Mitral and aortic stenosis[84]	32	100 (32)
Mitral and aortic stenosis[82]	141	100 (141)

Rheumatic Mitral Stenosis with Rheumatic Aortic Regurgitation

Approximately 10% of patients with rheumatic mitral valve stenosis also have rheumatic aortic regurgitation.[64] Clinical and laboratory characteristics of patients with mitral stenosis and aortic regurgitation are summarized in Table 48-7.

Diagnosis, signs, and symptoms

PHYSICAL FINDINGS: An early blowing diastolic murmur is present along the left sternal border in about 75% of patients with rheumatic mitral stenosis.[65,66] This murmur can mimic a Graham Steell murmur of pulmonary valve regurgitation; however, this diastolic murmur usually originates from the aortic valve and represents mild aortic regurgitation.[67] In patients with aortic regurgitation, a late diastolic murmur can be either the murmur of mitral stenosis or the Austin Flint murmur caused by a regurgitant jet directed toward the anterior mitral leaflet.[68] Exercise or amyl nitrite inhalation intensifies the murmur of organic mitral stenosis while diminishing the murmur of aortic regurgitation and the Austin Flint murmur.[66] Doppler echocardiography differentiates mild aortic regurgitation and pulmonic regurgitation.[69] Occasionally, the murmur and peripheral signs of aortic regurgitation are absent because of mitral stenosis.[65,70]

ELECTROCARDIOGRAPHY: Electrocardiographic and roentgenographic evidence of eccentric left ventricular hypertrophy in patients with mitral stenosis is an important clue to associated aortic valve regurgitation. Also, atrial fibrillation early in the course of aortic regurgitation may be associated with mitral stenosis.[66,71]

ECHOCARDIOGRAPHY: Left ventricular hypertrophy and volume overload detected by echocardiography suggest severe aortic valve regurgitation because these findings normally are not associated with mitral stenosis.[66] Diastolic fluttering

Table 48–4.

Results of Autopsy Series (1910–1937) Showing Multiple Valve Involvement in 996 Patients with Rheumatic Heart Disease

Valve lesion at autopsy	Clawson[184]	Cooke and White[185]	Percentage of 996 patients studied
All combinations	321	147	47
M-A	221	100	32
M-A-T	52	35	9
M-T	31	7	4
M-A-T-P	14	5	2
A-T	2	0	0.2
A-M-P	1	0	0.1

M = mitral valve; A = aortic valve; T = tricuspid valve; P = pulmonary valve.
Source: Modified with permission from Acker M, Hargrove WC, Stephenson LW: Multiple valve replacement. Cardiol Clin 1985; 3:425.

of the anterior leaflet of the mitral valve and the ventricular septum is an additional finding suggesting aortic valve regurgitation in patients with mitral stenosis.[66,72] In the presence of aortic valve regurgitation, the Doppler determination of mitral valve area is overestimated when pressure half-time measurements are used.[73]

CATHETERIZATION DATA: With current echocardiographic methods, cardiac catheterization to determine the severity of valvular heart disease is rarely indicated; however, hemodynamic profiles of such patients have been studied thoroughly. Characteristically, the left ventricular diastolic pressure is elevated in about 35% of patients with mitral stenosis and aortic regurgitation. This can cause the transmitral gradient at rest to be small even when significant stenosis of the mitral valve is present.[43,74] In patients with isolated aortic valve regurgitation, the left ventricular diastolic pressure is elevated more frequently than in patients with concomitant mitral stenosis and aortic regurgitation.[48] Aortography may underestimate the severity of aortic regurgitation in patients with associated mitral stenosis because low cardiac output and low stroke volume produce a concomitant reduction in regurgitant volume.[40]

Table 48–5.

Patients with Rheumatic Mitral Stenosis Undergoing Valvotomy with Clinical Evidence of Multiple Valve Disease

Valve lesion at surgery	No.	Percentage of 1000 patients with rheumatic mitral stenosis
All combinations	127	12.7
M-A	121	12.1
M-T	6	0.6

M = mitral valve; A = aortic valve; T = tricuspid valve.
Does not include patients with tricuspid regurgitation.
Source: Modified with permission from Ellis LB, Harken DE, Black H: A clinical study of 1000 consecutive cases of mitral stenosis two to nine years after mitral valvuloplasty. Circulation 1959; 19:803.

Pathophysiology

In patients with mitral valve stenosis and aortic valve regurgitation, decreased cardiac output minimizes the classic signs of aortic regurgitation (i.e., waterhammer pulse, head bobbing, or visibly pulsating capillaries). Also, concomitant mitral stenosis reduces left ventricular volume overload, which is a characteristic of isolated aortic regurgitation.[74] The underfilling of the left ventricle characteristic of mitral stenosis is offset by overfilling secondary to aortic valve regurgitation. Pulmonary artery hypertension characteristic of mitral stenosis usually is present.

Operative decision making

Patients with rheumatic mitral stenosis and rheumatic aortic regurgitation of more than a mild degree usually require replacement of both valves. Aortic valve repair is possible using techniques such as cuspal extension with glutaraldehyde-treated bovine or autologous pericardium[75] or the

Table 48–6.

Hemodynamic Classification in Patients Undergoing Multiple Valve Surgery for Rheumatic Valvular Disease

	Combined mitral and aortic surgery[71]	Triple-valve replacement[172]	Combined mitral and aortic replacement[183]	Triple-valve replacement[22]	Totals
Number in study	124	48	27	91	290
MS	53% (66)	19% (9)	30% (8)	22% (20)	35.5% (103/290)
MR	47% (58)	10% (5)	52% (14)	12% (11)	30.3% (88/290)
MS/MR	—	71% (34)	19% (5)	66% (169)	34.1% (99/290)
AS	53% (66)	10% (5)	44% (12)	10% (9)	31.7% (92/290)
AR	47% (58)	35% (17)	41% (11)	33% (30)	40% (116/290)
AS/AR	—	54% (26)	15% (4)	57% (52)	28.3% (82/290)

MS = mitral stenosis; MR = mitral regurgitation; AS = aortic stenosis; AR = aortic regurgitation.

Trussler technique.[76] Although early results with cuspal extension have been good, inexorable progression of valve fibrosis may necessitate later prosthetic replacement for many patients.[77]

Preoperative transthoracic and intraoperative transesophageal echocardiography aids in assessing function of the aortic valve in patients requiring surgery for mitral stenosis. At operation, the degree of ventricular filling and amount of aortic root distension with infusion of cardioplegia are clues to important aortic valve regurgitation. As stated previously, if mitral valve replacement is necessary, serious consideration should be given to replacement of the aortic valve when there is moderate or worse leakage owing to rheumatic valvulitis.

Great care should be exercised to avoid ventricular distention if ventricular fibrillation occurs prior to aortic clamping. If ventricular fibrillation develops, distension of the heart can be prevented by inserting a left ventricular vent and by compressing the heart manually. Also, even mild or moderate degrees of aortic regurgitation can complicate cardioplegia delivery through the proximal aorta.

Table 48–7.

Characteristics of Patients with Combined Mitral Stenosis and Aortic Regurgitation

Mitral stenosis and aortic regurgitation	Terzaki[71]
Number of patients	26
Symptom of dyspnea	100% (26)
Electrocardiographic evidence of LVH	62% (16)
Roentgenographic evidence of LVH	54% (14)
Symptom of angina	23% (6)
Aortic diastolic pressure >70 mm Hg	46% (12)
Elevated LVEDP	38% (10)

LVH = left ventricular hypertrophy; LVEDP = left ventricular end-diastolic pressure.

Rheumatic Mitral Stenosis with Rheumatic Aortic Stenosis

Diagnosis, signs, and symptoms

PHYSICAL FINDINGS: When rheumatic valve disease produces the combination of mitral valve stenosis and aortic stenosis, the signs and symptoms of both lesions can be present; however, those of mitral stenosis (e.g., dyspnea) tend to predominate, and the signs and symptoms of aortic stenosis (e.g., syncope and angina) occur less frequently. Table 48-8 outlines the clinical characteristics of patients in four studies of combined mitral and aortic stenosis. Dyspnea, the most frequently observed symptom, was present in 95% of patients, and angina and syncope were observed in 29% and 25% of patients, respectively. Mitral valve stenosis even may mask the signs and symptoms of aortic stenosis, making the

Table 48–8.

Clinical Characteristics of Patients with Combined Mitral and Aortic Stenosis

Mitral stenosis and aortic stenosis	Uricchio[82]	Katznelson[80]	Terzaki[71]	Honey[84]	Totals
Number of patients	141	22	40	35	198
Dyspnea	94% (132)	100% (22)	—	97% (34)	95% (188/198)
Fatigue	87% (122)	—	—	—	87% (122/141)
Edema	60% (85)	—	73% (29)	—	63% (114/181)
Palpitations	—	64% (14)	58% (23)	—	60% (37/62)
Orthopnea	—	55% (12)	—	63% (22)	60% (34/57)
Atrial fibrillation	47% (66)	68% (15)	65% (26)	—	53% (107/203)
PND	36% (51)	55% (12)	—	40% (14)	39% (77/198)
Hemoptysis	32% (45)	32% (7)	—	60% (21)	37% (73/198)
Angina	23% (32)	23% (5)	68% (27)	17% (6)	29% (70/238)
Vertigo, dizziness, or syncope	25% (35)	32% (7)	25% (10)	23% (8)	25% (60/238)
Emboli	20% (27)	27% (6)	—	17% (6)	20% (39/198)

PND = paroxysmal nocturnal dyspnea.
Number of patients in parentheses.

clinical recognition of aortic stenosis difficult in patients with combined disease.[78]

In addition, auscultatory findings may be confusing if the elevated end-diastolic pressure caused by aortic stenosis minimizes the opening snap of mitral stenosis.[78–80] Clinical signs of aortic stenosis, i.e., delayed carotid upstroke, systolic thrill, and ejection murmur, may be less prominent in patients with coexisting mitral valve stenosis than in those with isolated aortic valve stenosis.[79] Some clinical features raising suspicion of multiple valve involvement in patients with mitral stenosis or aortic stenosis are shown in Tables 48-9 and 48-10.

Radiographic findings in patients with combined rheumatic mitral and aortic valve stenosis are summarized in Table 48-11. Left atrial enlargement is observed in 85% of patients, and dilatation of the proximal ascending aorta, common in patients with congenitally bicuspid valves, is

Table 48–9.

Features Raising Suspicion of Mitral Stenosis in a Patient with Known Aortic Stenosis[80]

ECG	Atrial fibrillation, P-mitrale
Chest roentgenogram	Left atrial enlargement, right ventricular enlargement, or calcification of mitral valve

Table 48–10.

Features Raising Suspicion of Aortic Stenosis in a Patient with Known Mitral Valve Disease[66]

Symptoms	Angina or syncope
Physical findings	Delayed carotid upstroke Prolonged ejection murmur
ECG	Left ventricular hypertrophy in presence of mitral stenosis
Chest roentgenogram	Aortic valve calcification Poststenotic aortic root dilation

Table 48–11.

Frequency of Radiographic Findings in Patients with Combined Aortic and Mitral Stenosis

	Honey[84]	Katznelson[80]	Terzaki[71]	Zitnik[78]	Total
Number of patients	35	22	40	10	107
Left atrial enlargement^{2+}	—	64% (14)	100% (40)	70% (7)	85% (61/72)
LVH^{2+}	9% (3)	59% (13)	76% (31)	60% (6)	50% (53/107)
Mitral valve calcification	—	36% (8)	38% (15)	50% (5)	39% (28/72)
Aortic valve calcification	6% (2)	55% (12)	43% (17)	30% (3)	32% (34/107)
Aortic dilation	11% (4)	32% (7)	—	40% (4)	22% (15/67)

Number of patients in parentheses.

relatively infrequent (22%). Calcification of the mitral or aortic valves is identified in approximately 35% of patients.

ELECTROCARDIOGRAPHY: Atrial fibrillation is not common in patients with isolated aortic valve stenosis but is observed in 52% of patients with combined disease (Table 48-12). Approximately one-third of patients will exhibit electrocardiographic evidence of left ventricular hypertrophy, and right ventricular hypertrophy occurs in 18% of patients. Atrial enlargement manifested by P-mitrale is observed in 32% of patients.

ECHOCARDIOGRAPHY: Echocardiography provides definitive information on valve structure, function, and hemodynamics. In patients with combined mitral and aortic stenosis, estimation or measurement of valve area may be more reliable than the pressure gradient because cardiac output may be low, and atrial fibrillation produces variable stroke volume from one cardiac cycle to the next. Severity of mitral valve stenosis is determined by directly measuring the mitral valve orifice on the short-axis view of two-dimensional echocardiography. This method is reliable and reproducible, and there is excellent correlation between mitral valve area measured from a two-dimensional echocardiogram and the area measured directly from a pathologic specimen.[81]

Pathophysiology

In contrast to isolated mitral stenosis, in which ventricular function frequently is preserved, the combination of mitral and aortic stenosis is associated with ventricular hypertrophy and diastolic dysfunction. The pressure load from the aortic stenosis causes a concentric hypertrophy with a small, noncompliant ventricular cavity.[71] Mitral stenosis compromises the ventricle's ability to maintain cardiac output (in contrast to isolated aortic stenosis, in which cardiac output is maintained).[80,82] The decrease in cardiac output minimizes the signs and symptoms of aortic stenosis and may make the diagnosis

Table 48–12.

Frequency of Electrocardiographic Findings in Patients with Combined Aortic and Mitral Stenosis

	Honey[84]	Katznelson[80]	Uricchio[82]	Terzaki[71]	Zitnik[78]	Total
Number of patients	35	22	144	40	10	251
Atrial fibrillation	21	15	66	26	3	52% (131/251)
LVH	13	12	26	34	3	35% (88/251)
P-mitrale or left atrial hypertrophy	—	6	—	10	7	32% (23/72)
RVH	11	1	21	9	4	18% (46/251)

LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy.

of aortic stenosis difficult.[83] Other hemodynamic parameters are similar to those of isolated mitral stenosis, e.g., elevation of left atrial and pulmonary arterial pressures.[82,84]

Operative decision making

Although mitral valve stenosis sometimes can be treated effectively with valvuloplasty, commissurotomy for rheumatic aortic stenosis is indicated rarely. Thus, for patients with both aortic and mitral valve stenoses caused by rheumatic heart disease, we favor prosthetic replacement with mechanical prostheses if patients can manage long-term anticoagulation. If aortic valve stenosis is only mild and the decision is made not to replace the aortic valve at the time of mitral valve replacement, then the patient should be followed carefully because over 50% will develop moderate to severe disease by 15 years postoperatively.[85] The combination of aortic stenosis and mitral stenosis may present unique problems for the surgeon. First, concentric hypertrophy of the left ventricle may displace the mitral valve orifice anteriorly, producing poor exposure through a standard atriotomy; several maneuvers and alternative incisions are described for patients in whom mitral valve exposure is difficult.[83,86–90] Also, the small left ventricular cavity may impinge on struts of a stent-mounted bioprosthesis. There is also the potential for left ventricular outflow obstruction from high-profile prostheses in the mitral position in patients with aortic and mitral valve stenoses and small left ventricular cavity size.

Rheumatic Mitral Regurgitation with Rheumatic Aortic Regurgitation

Diagnosis, signs, and symptoms

PHYSICAL FINDINGS: When mitral regurgitation and aortic regurgitation are both present, the cardinal signs of either lesion may be masked by the other,[71] and when the clinical features of aortic regurgitation predominate, it may be difficult to determine whether coexisting mitral regurgitation requires surgical treatment.[71] The clinical characteristics of patients with combined mitral and aortic regurgitation are summarized in Table 48-13. Dyspnea and congestive heart failure are most common, whereas angina, syncope, and evidence of emboli occur less frequently.

Mitral valve regurgitation produces a characteristic systolic blowing murmur and also may be associated with a diastolic flow murmur. Aortic valve regurgitation produces a characteristic diastolic murmur and also may cause a systolic flow murmur. The combination of two simultaneous murmurs during both diastole and systole may confuse clinical diagnosis. Most patients have a long, pansystolic murmur heard best at the apex, often with a diastolic rumble and decreased intensity of aortic closure. In general, when aortic regurgitation is the dominant lesion, the early diastolic rumble is prominent; when mitral regurgitation prevails, the aortic diastolic murmur is less intense.[91–93] However, the severity of the two lesions does not always correlate with the relative intensity of murmurs.[71] Additionally, a prominent S_3 gallop can be heard, whereas an S_4 is unusual.[94]

Combined aortic and mitral regurgitation also results in significant left ventricular enlargement,[92] which is evident on both electrocardiogram[71,91] and chest x-ray.[71,91,93,94] Characteristic electrocardiographic findings are summarized in Table 48-14. On chest x-ray, nearly all patients have cardiomegaly and left atrial enlargement.[71,91] Calcification of the mitral or aortic valve is relatively uncommon.[71]

ECHOCARDIOGRAPHY: Mitral valve motion and diastolic orifice configuration may be altered in aortic regurgitation with a decrease in the opening amplitude of the anterior leaflet and an abnormal mitral orifice configuration with diastolic

Table 48–13.

Clinical Characteristics of Patients with Combined Mitral and Aortic Regurgitation Owing to Rheumatic Valvular Disease

Mitral and aortic regurgitation	Shine[91]	Terzaki[71]	Total
Number of patients	39	32	71
Dyspnea	—	100% (32)	100% (32/32)
CHF	90% (35)	38% (12)	66% (47/71)
Angina	28% (11)	25% (8)	27% (19/71)
Syncope	8% (3)	19% (6)	13% (9/71)
Emboli	5% (2)	—	5% (2/39)

CHF = congestive heart failure.
Number of patients in parentheses.

Table 48–14.

Frequency of Electrocardiographic Findings in Patients with Combined Aortic and Mitral Regurgitation

Electrocardiographic finding	Shine[91]	Terzaki[71]	Total
Number of patients	39	32	71
LVH	79% (31)	81% (26)	80% (57/71)
Left atrial enlargement	—	69% (22)	69% (22/32)
Atrial fibrillation	59% (23)	68% (22)	63% (45/71)
LBBB	5% (2)	—	5% (2/39)

LVH = left ventricular hypertrophy; LBBB = left bundle branch block. Number of patients in parentheses.

leaflet oscillation.[94] The mitral valve orifice image is deformed because restriction in anterior leaflet excursion is most pronounced in the center of the leaflet, where peak vertical separation normally occurs. This restriction causes the anterior leaflet to appear flattened rather than convex anteriorly, and in severe cases, it actually may be concave toward the left ventricular outflow tract.[94]

CATHETERIZATION DATA: Most patients have elevated right atrial and pulmonary arterial capillary wedge pressure. There is usually a prominent *v* wave in the pulmonary capillary wedge tracing. Approximately 75% of patients have an elevated left ventricular end-diastolic pressure.[64,71]

Pathophysiology

The combination of mitral and aortic valve regurgitation produces severe volume overload of the left ventricle. The reduction of impedance to ejection allows the ventricle to empty further, reducing ventricular wall tension with a resulting increase in the velocity of shortening.[95] Chronic volume overload increases stroke volume and distension of the left ventricle so that a larger stroke volume can be achieved with less myocardial fiber shortening than in normal hearts.[71] Patients who respond to increased volume load by left ventricular dilatation appear to tolerate surgical correction better than patients with left ventricular hypertrophy owing to an increased pressure load.[71]

Patients with aortic valve regurgitation have augmented stroke volume to maintain an adequate cardiac output, but when mitral regurgitation coexists, part of the augmented stroke regurgitates into the left atrium and pulmonary veins. For this reason, when aortic regurgitation is severe, concomitant mitral regurgitation greatly reduces systemic cardiac output and can produce severe pulmonary congestion.[96]

Operative decision making

As stated previously, aortic valves involved with rheumatic disease usually require replacement. When the mitral valve also has rheumatic involvement, we replace the mitral valve at the time of aortic valve operation. After the aortic valve is excised, the mitral valve is inspected visually if it is suspected of being diseased or if the degree of regurgitation is severe.

MYXOMATOUS AND PROLAPSING VALVE DISEASE AFFECTING MULTIPLE VALVES

Myxomatous degeneration is the most common etiology of mitral regurgitation requiring surgical correction in North America, and myxomatous aortic valve disease with annular dilatation is perhaps the most common cause of aortic regurgitation.[97–99] Most cases of isolated mitral or aortic valve prolapse are not associated with known connective tissue disorders. However, the coexistence of both mitral and aortic valvular prolapse together frequently can be seen in patients with connective tissue diseases such as Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and others.[96]

Aortic valve regurgitation in patients with Marfan syndrome is caused by progressive enlargement of the sinus portion of the aorta and the aortic valve annulus, i.e., annuloaortic ectasia.[100,101] The principal causes of mitral regurgitation in patients with Marfan syndrome are mitral annular dilatation, floppy or prolapsing leaflets, and mitral annular calcification.[101] The pathologic lesion in Marfan syndrome is cystic medial necrosis, which is characterized by degeneration of elastic fibers and infrequent cysts.[101] Alterations in the synthesis and cellular secretion of fibrillin are responsible for the phenotypic characteristics of many patients with Marfan syndrome.[102] Some patients have myxomatous cardiovascular lesions and annuloaortic ectasia without the other clinical characteristics of Marfan syndrome.

Two-dimensional echocardiographic studies show that the frequency of aortic valve prolapse in patients with mitral valve prolapse varies between 3% and 24%[103,104] (Table 48-15). In one necropsy study, the frequency of mitral regurgitation in Marfan patients with aortic aneurysms (most with aortic regurgitation) was 54% (7 of 13).[101] About 17% of patients who undergo surgery for myxomatous aortic valve require surgical correction of mitral regurgitation (Table 48-16).

Although multiple valve involvement with myxomatous degeneration usually manifests as mitral regurgitation in combination with aortic regurgitation, in some cases, all four valves may be involved.[107] It is not clear whether the underlying pathology of isolated mitral valve prolapse is the same as the cardiovascular lesions that occur in Marfan syndrome and other multiple-floppy-valve syndromes.[108,109]

Table 48–15.

Incidence of Echocardiographic Evidence of Aortic Valve Prolapse in Patients with Mitral Valve Prolapse

	Ogawa[104]	Rippe[103]	Mardelli[186]	Total
Number of patients with MVP	50	400	75	525
Aortic valve prolapse	24% (12)	3% (11)	20% (15)	7% (38/525)
Aortic regurgitation	16% (8)	1% (4)	—	3% (12/450)
Aortic and mitral valve replacement	2% (1)	—	—	2% (1/50)

MVP = mitral valve prolapse.
Number of patients in parentheses.

Diagnosis, Signs, and Symptoms

Signs and symptoms of aortic and mitral valve regurgitation are reviewed in the section on rheumatic valvular disease. In addition to complete evaluation of the aortic and mitral valves and proximal aorta, patients with Marfan syndrome should have assessment of the descending aorta for aneurysm or chronic dissection.

Operative Decision Making

If annuloaortic ectasia is not present, patients with mitral and aortic valve regurgitation caused by myxomatous degeneration are candidates for repair of both valves. The aortic valve is inspected initially, and the decision for repair or prosthetic replacement is made depending on cuspal morphology. If tissue is sturdy and there is little prolapse or prolapse is limited to one cusp, repair can be undertaken with commissural narrowing and cusp resuspension. Often, aortic valve regurgitation is central, and simply narrowing the annulus by commissural plication restores valvular competence. Outcome of repair of both mitral and aortic valves has been good in terms of patient survival and freedom from valve-related complications, but reoperation is necessary in 35% of patients 10 years after the initial procedure; patients with most severe aortic valve regurgitation have an increased risk of late reoperation.[110] If tissue is attenuated, or if multiple cusps have severe prolapse, the valve is replaced.

In most instances, patients with Marfan syndrome and aortic regurgitation require composite replacement of the aortic valve and ascending aorta.[111] Occasionally, moderate aortic regurgitation can be repaired at the time of aortic replacement by suspending the aortic valve inside a tube graft or remodeling the sinus portion of the aorta.[112] Even if the aortic valve is replaced with a composite graft and mechanical valve, the surgeon should favor repair of associated mitral regurgitation.[113] Gillinov and colleagues reported that valvuloplasty is possible in approximately 80% of patients with mitral regurgitation and Marfan syndrome and that 5 years postoperatively, 88% of patients are free of significant mitral valve insufficiency.[114]

Myxomatous Mitral Regurgitation with Tricuspid Regurgitation

Myxomatous degeneration also may involve the tricuspid valve, and presentation of mitral and tricuspid valve regurgitation owing to degenerative disease is not uncommon. In

Table 48–16.

Frequency of Mitral Valve Procedures in Patients Undergoing Aortic Valve Repair or Replacement for Myxomatous Degeneration, Prolapse, or Root Dilation

	David[187]	Gott[188]	Shigenobu[97]	Agozzino[100]	Bellitti[99]	Total
All aortic surgery	18	270	13	69	25	395
Number requiring concomitant mitral surgery	3 (17%)	36 (13%)	5 (38%)	16 (23%)	3 (12%)	73 (16%)

one study, 54% of patients with mitral valve prolapse also had tricuspid valve prolapse; however, most of these patients did not have significant regurgitation.[96] As with tricuspid regurgitation associated with rheumatic mitral disease, preoperative and intraoperative echocardiography is important in evaluating tricuspid disease in patients with myxomatous mitral regurgitation. In contrast to rheumatic disease, myxomatous mitral and tricuspid regurgitation almost always lends itself to valve repair.

SENILE CALCIFIC AORTIC VALVE DISEASE WITH MULTIPLE VALVE INVOLVEMENT

Unlike aortic stenosis caused by rheumatic disease, in which associated mitral valve disease is common, senile calcific aortic stenosis usually presents as an isolated lesion. Although the combination of mitral valve disease and senile calcific aortic stenosis is uncommon, senile aortic calcification is a frequent cause of aortic valve stenosis.[98] The incidence of senile calcific aortic disease has increased steadily in the last 20 years. Therefore, although mitral valve disease associated with calcific aortic stenosis is less common than that seen with rheumatic disease of the aortic valve, as the incidence of calcific aortic stenosis increases, so does the likelihood of encountering patients with disease of both valves.

Patterns of Multiple Valve Involvement with Calcific Aortic Stenosis

Calcific aortic stenosis with infective endocarditis of the mitral valve

Stenotic aortic valves frequently are sites of infective endocarditis. As discussed in the section on endocarditis, the mitral valve may become involved with infective endocarditis by common abscess, by verrucous extension, or from a jet lesion, and infection may cause mitral valve aneurysm, perforation, and/or chordae disruption.[115] Management of these patients usually requires aortic valve replacement and assessment of the mitral valve at the time of operation. Vegetations of the mitral valve sometimes can be removed and perforations patched if the remaining tissue is sturdy and appears healthy.

Calcific aortic stenosis with functional mitral valve disease

Senile calcification of the aortic valve may lead to mixed stenosis and regurgitation,[98] and the volume load from regurgitation may lead to left ventricular dilatation and secondary mitral regurgitation of an otherwise normal mitral valve.[98] Mitral regurgitation secondary to aortic valvular disease is discussed in the section on pathophysiology of multiple valve disease.

Calcific aortic stenosis with calcification of the mitral valve

Degenerative calcification is an age-related process usually affecting the aortic and mitral valves. In a study of patients older than 75 years of age, one-third had degenerative aortic or mitral calcification.[96] About 25 to 50% of patients with calcific aortic stenosis have calcification of the mitral valve annulus. Generally, patients with associated mitral annular calcification are older, have more severe aortic stenosis, and are more often female when compared with patients with aortic stenosis without mitral annular calcification.[106] Mills reported 17 patients undergoing mitral valve replacement for valvular disease related to severe annular calcification. Four of these patients also had concomitant aortic valve replacement.[116] Mitral annular calcification may exist in the setting of rheumatic or myxomatous disease.[117] These patients may have increased incidence of conduction defects,[118] aortic outflow murmurs, coronary artery disease,[119] and stroke.[120] Mitral repair or replacement is facilitated in some circumstances by removal of the annular calcium bar and pericardial reconstruction.[121]

Diagnosis, Signs, and Symptoms

Physical findings

Auscultatory findings in aortic stenosis and mitral regurgitation consist of two systolic murmurs that can be distinguished by location of maximum intensity and radiation. Characteristically, aortic stenosis produces a crescendo-decrescendo murmur at the base, and mitral regurgitation produces a holosystolic murmur at the apex. Occasionally, a prolonged ejection murmur of aortic stenosis may simulate a holosystolic murmur at the apex, and the murmur of severe mitral regurgitation may radiate toward the base and may take on a crescendo-decrescendo pattern simulating an ejection murmur.[66,69]

Electrocardiography

Atrial fibrillation is uncommon in isolated aortic stenosis, and its presence is a clue to associated mitral valve disease.[66] Both aortic stenosis and mitral regurgitation produce left ventricular hypertrophy and left atrial enlargement.

Echocardiography

Echocardiography is essential to delineate mitral valve morphology, determining whether there is prolapse (from either chordal elongation or rupture), annular dilatation, or other abnormalities and also to assess the severity of aortic valve stenosis. Transesophageal echocardiography (either preoperatively or intraoperatively) is preferred at our institution to evaluate the mitral valve completely and accurately.

INFECTIVE ENDOCARDITIS AFFECTING MULTIPLE VALVES

As with infection of a single valve, multiple valve infective endocarditis may occur in valves that are normal, previously diseased, or prosthetic. Infective endocarditis requiring multiple valvular procedures occurs in about 10 to 25% of all

Table 48–17.

Locations and Combinations of Valvular Infective Endocarditis

	NVE	PVE	Total
Number of patients	131	47	178
Aortic	51% (68)	68% (32)	56% (100)
Mitral	27% (36)	23% (11)	26% (47)
Multiple	24% (31)	9% (4)	20% (35)
Aortic and mitral	18% (24)	9% (4)	16% (28)
Tricuspid	3% (4)	0% (0)	2% (4)
Mitral and tricuspid	1% (2)	0% (0)	1% (2)
Aortic, mitral, and tricuspid	1% (1)	0% (0)	0.6% (1)

NVE = native valve endocarditis; PVE = prosthetic valve endocarditis.
Number of patients in parentheses.
Source: Modified with permission from Karp RB: Role of surgery in infective endocarditis (review). Cardiovasc Clin 1987; 17:141.

patients having operation and usually involves the mitral and aortic valves[12,117,122–123] (Tables 48-17 and 48-18). Conduction defects on electrocardiogram may be a clue to abscess involvement of both the aortic and mitral annulus.[130]

About 1 to 5% of patients who require surgery for multiple valve endocarditis have biventricular involvement, and most instances of tricuspid valve infections are due to intravenous drug use.[127,131] Patients with multiple valve infective endocarditis more frequently have congestive heart failure as an indication for surgery and are more likely to have intracardiac abscess when compared with patients with single-valve infective endocarditis.[127]

Table 48–18.

Incidence of Multiple Valve Replacement for Native-Valve Infective Endocarditis from 1961–1974 at the Mayo Clinic

	No. of patients	Percent
Valve replacement for IE	138	
Aortic	99	71% (99/138)
Mitral	16	12% (16/138)
Multiple	23	17% (23/138)

IE = infective endocarditis.
Source: Modified with permission from Wilson WR, Danielson GK, Giuliani ER, et al: Cardiac valve replacement in congestive heart failure due to infective endocarditis. Mayo Clin Proc 1979; 54:223.

Aortic Regurgitant Jet Lesion of the Mitral Valve

Perforation of the anterior leaflet of the mitral valve may occur from the regurgitant jet of aortic valve endocarditis, and the diagnosis can be made from transesophageal echocardiography.[132] Often, the perforation in the mitral valve can be débrided and repaired with a patch of pericardium or prosthetic material.

Prosthetic Valve Endocarditis

Risk of prosthetic valve endocarditis is greatest approximately 4 to 6 weeks postoperatively and decreases to a stable rate by about 1 year after operation.[133,134] *Staphylococcus epidermidis* and *Staphylococcus aureus* account for 20 to 30% of cases, respectively.[135] Transesophageal echocardiography can identify vegetations caused by infection as well as prosthetic valve dysfunction and associated abscess cavities.[135] In general, management of patients with endocarditis affecting multiple valves is similar to management of patients with infection of one valve. There are, however, some special considerations. When aortic valve endocarditis is complicated by abscess formation, infections may extend into the mitral annulus and necessitate concomitant mitral valve replacement; this occurs in approximately 12% of patients with aortic root abscess[136] and is especially prevalent when there is involvement of the aorticomitral junction or subannular interventricular septum.[127,136] Surgical reconstruction of the

intervalvular fibrous body during simultaneous aortic and mitral valve replacement is a technically challenging operation reserved for situations where extirpation of endocarditis results in aortomitral discontinuity. The improved survival and durability of this technique in the recent era have been described by David and colleagues.[137]

Tricuspid Valve with Left-Sided Valve Replacement

When the tricuspid valve is excised at the time of left-sided valve replacement, there remains a question of whether the tricuspid valve needs to be replaced. Simple excision of the tricuspid valve seems appropriate only in the absence of pulmonary hypertension and left-sided failure. A prosthetic left-sided valve is intrinsically stenotic, and many patients with tricuspid valve endocarditis can have pulmonary hypertension secondary to septic pulmonary emboli. Silverman found that patients who had tricuspid valve excision alone with left-sided valve replacement required perioperative inotropic support, and management of their postoperative congestive heart failure was more difficult than that of the patients who had tricuspid valve replacement.[127]

Results

Early mortality following surgery for multiple valve endocarditis is in the range of 20 to 30%, and Table 48-19 compares New York Heart Association (NYHA) class-matched groups that had multiple valve procedures for infective endocarditis and for other reasons.

CARCINOID HEART DISEASE AFFECTING MULTIPLE VALVES

Valvular heart disease develops in about 50% of patients with carcinoid tumors; patients with primary carcinoid tumor in the small intestine are more likely to have carcinoid heart disease than those with carcinoid tumors in other locations.[1] In most cases, the tricuspid and pulmonary valves are involved. We have offered valvular surgery to patients with severe symptoms of right-sided heart failure caused by carcinoid heart disease whose systemic carcinoid symptoms are controlled by octreotide and/or hepatic dearterialization.[138] Patients who are being considered for complete resection of hepatic metastases after control of the primary tumor are also candidates for extirpation of cardiac disease and valve replacement. A recent review of 200 patients with carcinoid heart disease from our institution revealed that survival has improved over the past decade. Multivariate analysis indicated that valve replacement surgery was associated with a risk reduction of 0.48.[57]

Diagnosis, Signs, and Symptoms

Jugular venous distension with *v* waves (from tricuspid regurgitation) and *a* waves (from tricuspid stenosis) can be evident. Right ventricular enlargement can produce a pericardial lift. Most patients have murmurs from the tricuspid and pulmonary valves.[138] Patients often demonstrate ascites and liver enlargement as a result of either right-sided heart failure or hepatic metastases or both. Therefore, these findings are not necessarily indicative of severe tricuspid valve regurgitation.

The electrocardiogram of patients with carcinoid heart disease often shows low voltage (85%), right bundle-branch block (42%), and evidence of right atrial enlargement (35%).[1,138] The chest x-ray characteristically shows cardiomegaly (69%), pleural effusions (58%), and pleural thickening (35%).[138]

Echocardiography

Echocardiographic findings of carcinoid heart disease include thickening and reduced motion of the tricuspid valve leaflets; the pulmonic valve cusps may be thickened and retracted. Fusion of the pulmonary valve commissures results in a stiff fibrotic ring that may cause a stricture in the

Table 48–19.

Comparison of Early Outcome Between Patients Having Multiple Valve Surgery for Infective Endocarditis and Patients Having Multiple Valve Surgery for other Reasons[8,108]

	Class II	Class III	Class IV
Multiple valve procedures for infective endocarditis	20% (15)	33% (3)	20% (5)
Multiple valve procedures for other causes	16% (25)	12% (25)	36% (25)

Operative mortality is expressed as percentage, and numbers of patients are in parentheses.

Table 48–20.

A Comparison of Venous Drainage, Presence of Liver Metastases, and Carcinoid Plaque Location in Relation to Location of Primary Carcinoid Tumor[136]

Tumor location	Venous drainage	Liver metastases	Plaque location
Gut	Portal	Yes	Right-sided
Ovary	Systemic	No	Right-sided
Bronchial	Pulmonary	No	Left-sided.

entire pulmonary orifice. Pulmonary regurgitation and stenosis both may be present.[139]

Invasive Studies

Cardiac catheterization is not necessary unless ischemic symptoms or a history of myocardial infarction suggests coronary artery disease.

Pathophysiology

Carcinoid heart disease results from deposition of plaques on the endocardium of the valves and atria; this usually occurs on the right side of the heart. However, plaques can develop on the mitral and aortic valves when there is carcinoid tumor in the lungs or in the presence of intracardiac shunting that bypasses the lungs. Valves are damaged by exposure to circulating substances released from carcinoid tumors such as serotonin and bradykinin. Both these components are inactivated by the lungs and the liver; the relationship between tumor location and the location of cardiac lesions is summarized in Table 48-20.[140]

The plaques usually deposit on the downstream side of the cardiac valves, causing adherence of the leaflet to the underlying structures and producing functional regurgitation. Carcinoid plaque deposition also may constrict the valve annulus and produce stenosis.[1]

The dominant functional lesion of carcinoid heart disease is tricuspid valve regurgitation; the valve is fixed in a semiopen position so that some degree of stenosis is present. Fibrosis and plaque deposition also affect the pulmonary valve, causing mixed stenosis and regurgitation, which increases the degree of tricuspid regurgitation.[1]

Operative Decision Making

Timing of operation

The primary indications for surgery are increasing symptoms of congestive failure with objective evidence of valvular disease.[141] Again, it should be noted that some of the signs of right-sided heart failure, such as peripheral edema, ascites, and hepatomegaly, can be caused by the primary disease. Another indication for operation may be progressive right ventricular enlargement in the absence of symptoms. In a small series of carcinoid patients, right ventricular size and function did not correlate with operative or late mortality.[138] Currently, we employ exercise testing to provide an objective assessment of the functional status and a guideline to the timing of cardiac surgery. If the primary cause for debilitation is right-sided heart failure, it is reasonable to offer valve replacement even though the prognosis may be guarded.[141]

Tricuspid valve operation

The tricuspid valve always requires replacement, and in our earlier experience, we used mechanical prostheses because of the possibility of carcinoid plaque formation on a bioprosthesis. However, review of our patients and those reported previously shows little difference in patient survival with mechanical or tissue valves. Bioprostheses are selected for patients who have liver dysfunction that would complicate anticoagulation with Coumadin and for patients who will undergo subsequent hepatic resection or hepatic artery embolization.

Pulmonary valve options

As stated previously, we now advise valve replacement rather than excision when the pulmonary valve is involved.

Management of the carcinoid syndrome during and early after operation is critically important, and this has been simplified greatly by treatment with long-acting octreotide; this is supplemented intraoperatively with intravenous administration of short-acting octreotide when there is evidence of flushing and vasodilatation.[142] Preoperative steroids and antihistamines also can be used to prevent adverse effects from tumor-released mediators.[142,143] We usually give octreotide, 500 μg intravenously, prior to induction of anesthesia, with additional intravenous doses given as needed at the onset and termination of cardiopulmonary bypass. Postoperatively, octreotide is continued, and the dose is adjusted according to the severity of the flushing and vasodilatation.

Table 48–21.

Rare Causes of Multiple Valve Disease Requiring Surgery

Disease	Valves replaced or repaired
Methysergide/ergotamine toxicity [96]	Aortic and mitral
Radiation injury[136, 189]	Mitral and tricuspid
Q-fever endocarditis[190]	Aortic and mitral
Ectodermal anhydrotic dysplasia[191]	Aortic and mitral
Maroteaux-Lamy syndrome (mucopoly-saccharidosis type VI)[192]	Aortic and mitral
Werner syndrome (adult progeria)[193]	Aortic and mitral
Blunt trauma[194]	Mitral and tricuspid
Lymphoma[195]	Aortic and mitral
Relapsing polychondritis[196]	Aortic and mitral
Systemic lupus erythematosus[197]	Mitral and tricuspid
Secondary hyperparathyroidism[198]	Aortic and mitral
Urticarial vasculitis syndrome (HUVS) with Jaccoud hands deformity[199]	Aortic and mitral

Aprotinin, a kallikrein inhibitor, may mitigate the effects of substances released by carcinoid tumors during anesthesia and reduce intraoperative and postoperative bleeding.[142]

RARE CAUSES OF MULTIPLE VALVE DISEASE

Table 48-21 lists some rare causes of multiple heart valve disease that require surgical correction.

RESULTS OF MULTIPLE VALVE SURGERY

Long- and Short-Term Mortality

Survival following multiple valve surgery has improved along with refinements in myocardial protection; for example, mortality for multiple valve operations performed using normothermic ischemic arrest was approximately 40%[144]; the use of cardioplegic arrest reduced operative risk by three-quarters.[71,144,145] In recent reports,[146] operative mortality (30-day mortality or hospital mortality) ranges from about 6 to 17% (Table 48-22, part A). The 5-year actuarial survival is 60 to 88% (see Table 48-22, part B), and the 10-year actuarial survival is 43 to 81% (see Table 48-22, part C). Risk factors identified for morbidity and mortality following multiple valve surgery include advanced NYHA class,[147–149] advanced age,[147–150,151] current or prior myocardial revascularization,[150] ejection fraction,[147] presence of coronary artery disease,[147,148] aortic stenosis,[152] elevated pulmonary artery pressure,[150] tricuspid regurgitation,[152] and diabetes mellitus.[150]

Clearly, operative mortality is influenced by patient selection,[149] and comparisons between studies are of limited value.[149] Causes of death following multiple valve surgery are low cardiac output,[23,149,152,153–155] myocardial infarction,[154] technical failure,[155] multiple-organ failure,[23] ventricular rupture,[101,150,153] and mechanical obstruction of the prosthetic leaflet.[101,154]

Comparisons of late survival between patients having multiple valve versus single-valve replacement are inconsistent. Some studies show poorer survival[148] after multiple valve replacement, and others report no significant difference in survival.[23,145,148,155–160] The discrepancy in these results may be because the majority of deaths in many reports are secondary to progression of coronary artery disease and noncardiac causes rather than valve-related issues.[145,148] The presence of coronary artery disease and concomitant coronary artery surgery increases mortality following multiple valve surgery.[150,161,162]

Some causes of early death following multiple valve surgery are perhaps less common today owing to changes in practice. In a necropsy study from 1963 to 1985 of patients who died early following double-valve replacement, prosthetic valve dysfunction secondary to mechanical interference was evident in almost 50%, and ventricular rupture had occurred in 15% of patients.[101] Most of these patients received Starr-Edwards caged-ball prosthetic valves. Mechanical failure of low-profile tilting-disk prostheses that are in current use is rare, and early valve-related death with this type of prosthesis is very unusual.[23,148,149,163] The current practice of preserving the posterior leaflet and chordal attachments of the mitral valve during prosthetic replacement may decrease the chance of ventricular disruption.[164]

Thromboembolism

Thromboembolic rates following multiple valve replacement are shown in Table 48-22, part D, and range from 1 to 7% per patient-year for double-valve replacement. Ten years postoperatively, freedom from thromboembolic events ranges from 77 to 89% (see Table 48-22, part E). Although the data presented in Table 48-22, part D, along with other sources,[165] do not indicate significant differences between single and multiple valve replacement, some reports suggest that both mechanical[166] and bioprosthetic[167] valves have an increased

Table 48–22.

Summary of Morbidity and Mortality Following Multiple Valve Surgery

	DVR	MVR	AVR	*P* value	Valve type	Reference
A. Operative mortality (percent)	5.6				Various*	Teoh[148]
	5.9	4.3	2	—	SJM	Horstkotte[164]
	6.3	5.2	3.1	—	SJM	Smith[158]
	6.5				SJM	Armenti[145]
	7.2	4.7	3.9	—	SJM	Aoyagi[129]
	8.2	4.3	2.4	—	SJM	Ibrahim[200]
	10				Hancock II	David[201]
	10.5				C-E	Jamieson[202]
	10.8	11.3	7.8	—	Sorin Disc	Milano[203]
	10.8				Various*	Galloway[146]
	11.5	13.0	4.9	$p < .001$	SJM	Khan[144]
	11.6	7.5	5.1	—	C-E	Bernal[155]
	15.3				Various	Donahoo[149]
	17.5				Various*	Mattila[150]
B. 5-year actuarial survival (percent)	88	88	91	N.S.	SJM	Aoyagi[129]
	86	86	94	MVR or DVR< AVR $p < .05$	< SJM	Smith[158]
	86				SJM	Khan[144]
	78				Various*	Galloway[146]
	75				C-E	Bernal[155]
	73				Hancock II	David[201]
	70				C-E	Jamieson[202]
	62				MIPB	Lemieux[204]
	61	65	75	DVR < MVR or AVR $p < .01$	SJM	Khan[144]
	60				SJM	Armenti[145]
	****	****	****	DVR < AVR or MVR $p < .006$	B-S	Alvarez[152]
C. 10-year actuarial survival (percent)	81	80	81	N.S.	SJM	Aoyagi[129]
	72	78	85	—	SJM	Horstkotte[164]
	60	59	71	N.S.	SJM	Ibrahim[200]
	55	63	65	—	B-S	Orszulak[205]
	43	42	43	N.S.	SJM	Khan[144]
D. Thromboembolism (percent per patient-year)	0.3	0.3	0.6	—	SJM	Smith[158]
	0.79	1.6	1.3	—	SJM	Nakano[206]
	1.3	1.1	1.0	N.S.	SJM	Aoyagi[129]
	2.1				Various*	Mattila[150]
	2.1	1.2	1.3	N.S.	Sorin Disc	Milano[203]
	3.2	2.4	2.5	N.S.	SJM	Khan[144]
	4.5				Various*	Mullany[51]
	4.6				SJM	Armenti[145]
	4.6	4.3	2.1	—	B-S	Orszulak[205]
	5.0	4.4	2.4	—	SJM	Ibrahim[200]
	6.6	5.1	3.7	—	SJM	Horstkotte[164]

Table 48–22.

Summary of Morbidity and Mortality Following Multiple Valve Surgery *(continued)*

	DVR	MVR	AVR	*P* value	Valve type	Reference
E. 10-year freedom from thromboembolism (percent)	89	92	91	—	C-E pericardial	Pelletier[207]
	89	89	94	N.S.	SJM	Aoyagi[129]
	89	83	—	—	C-E	van Doorn[208]
	86	88	80	—	Hancock II	David[201]
	77	83	76	N.S.	SJM	Khan[144]
	77	79	87	—	B-S	Orszulak[205]
	ξ	ξ	ξ	N.S.	B-S	Alvarez[152]
F. Anticoagulation-related hemorrhage (percent per patient-year)	0.1	0.2	0.1	—	SJM	Nakano[206]
	0.5	0.3	0.4	—	SJM	Aoyagi[129]
	0.9	0.9	0.9	N.S.	Sorin Disc	Milano[203]
	1.2				SJM	Armenti[145]
	1.2	0.7	0.2	—	SJM†	Horstkotte[164]
	2.3	1.2	2.0	N.S.	SJM	Khan[144]
	4.5	2.1	1.2	—	SJM‡	Horstkotte[164]
	ξ	ξ	ξ	DVR > AVR or MVR $p < .05$	B-S	Alvarez[152]
G. Endocarditis (percent per patient-year)	0.2	0.06	0.21	—	St. Jude	Nakano[206]
	0.3	0.03	0.4	—	St. Jude	Aoyagi[129]
	2.1				Various*	Mattila[150]
	2.5				SJM	Armenti[145]
	ξ	ξ	ξ	DVR > AVR or MVR $p < .05$	B-S	Alvarez[152]
H. 8-, 10-, and 15-year freedom from structural deterioration for bioprostheses (percent)	77	79	87	—	C-E pericardial	Pelletier[207]
	59.6	70.8		—	C-E	van Doorn[208]
	44	33	62	$p < .03$	C-E	Bernal[165]
	38	58	80	DVR < MVR , AVR p < .05	MP	Pomar[161]

Comparisons to isolated aortic and mitral valve procedures from the same series are included when available. If statistical analysis between the results of multiple and single valve procedures was reported, the p values are included. If a series was limited to a single valve type, it is listed.

**Includes some patients with concomitant tricuspid procedures.*

†dR INR 1.75 = 2.75.

‡INR 4 = 6.

ξ Results reported graphically.

DVR = double valve replacement; AVR = isolated aortic valve replacement; MVR = isolated mitral valve replacement; N.S. = not statistically significant; SJM = St. Jude Medical; C-E = Carpentier-Edwards; B-S = Björk-Shiley; MP = Mitroflow pericardial; MIPB = Medtronic intact porcine bioprosthesis.

risk of thromboembolism in the mitral position. This risk is present early (90 days after operation) in patients undergoing multiple valve replacement that includes a bioprosthetic mitral valve.[167]

Anticoagulation-Related Hemorrhage

Rates of anticoagulant-related hemorrhage following multiple valve replacement, as with single-valve surgery, depend on target international normalization ratio (INR).[168] Risks of hemorrhage are reported to be 0.1 to 4.5% per patient-year following multiple valve surgery (see Table 48-22, part F). Alvarez reported a significantly higher rate of anticoagulant-related hemorrhage following multiple valve replacement than following single-valve replacement.[152]

Prosthetic Valve Infective Endocarditis

Rates of infective endocarditis following multiple valve surgery range from 0.2 to 2.5% per patient-year, as shown in Table 48-22, part G. In comparison with isolated valve surgery, Alvarez reports that prosthesis infection is more frequent following double valve replacement than following either isolated aortic ($p < .05$) or mitral valve replacement ($p < .001$).[152]

Table 48–23.

Results of Triple Valve Surgery by Author

	Coll[209]	Gersh[22]	Galloway[146]	Brown[166]	Mullany[51]	Kara[171]
Years studied	1970–1984	1962–1984	1976–1985		1965–1984	1972–1983
Number of patients	37	91	61	40	109	107
Type of procedure	Triple valve replacement	Triple valve replacement	Triple valve procedure	Triple valve replacement	Double valve replacement with tricuspid repair	Triple valve procedure
Valve type		Various (mostly S-E)	Various	Various	Various (60% S-E)	S-E, Björk, or St. Jude
Operative mortality	5%	24%	23%		21%	20%
Actuarial 5-year survival	75%	55%	62%	78%	70%	53%
Thromboembolism rate		12.3% pt-y		32% at 5 years combined with hemorrhage	4.5% pt-y	
Prosthetic infective endocardit is rate		6%			3%	
Hemorrhage rate		22%		17%		
Significant risk factors		Age, NYHA Class IV			Age, NYHA Class IV	Higher NYHA class, emergent operation, tricuspid replacement

S-E = Starr-Edwards; NYHA = New York Heart Association functional class.

Valve Performance

Rates of bioprosthetic structural deterioration relate to valve position; tissue valves appear to fail earlier in the mitral position than in the aortic position. When multiple valve replacements include the mitral valve, the rates of deterioration are similar[169] or even worse than[165] isolated mitral valve replacement (see Table 48-22, part H).

COMPARISON OF BIOPROSTHETIC VALVES TO MECHANICAL VALVES

Comparisons of outcomes of patients with two or more mechanical prostheses with those of patients with two or more bioprostheses show similar rates of thromboembolism,[20,170] but freedom from operation favors those with multiple mechanical valves.[20,170,171] As might be expected, anticoagulation-related hemorrhage is less in patients with two bioprosthetic valves,[170,172] but there is no clear advantage of one prosthesis over the other in terms of early and late mortality.[20,170,172]

Results of Tricuspid Valve Procedures with Other Valve Procedures

Results of mitral and tricuspid valve surgeries

Reported operative mortality following mitral valve replacement and tricuspid valve repair or replacement is approximately 12 to 15%,[173] and 65% to 75% of patients are alive 5 years postoperatively.[150,173] Outlook for patients with lesser

degrees of tricuspid regurgitation at the time of mitral valve replacement is good; 5-year actuarial survival for patients with tricuspid regurgitation who do not have tricuspid valve repair or replacement is 80 to 84%, and 10-year survival is 62 to 77%.[174]

Triple-valve replacement

The operative mortality following triple-valve replacement is higher than that for double-valve replacement and ranges from 5 to 25%.[22,150] As with double-valve replacement, advanced age and higher NYHA class are associated risk factors for early mortality.[22,175] Causes of perioperative death are similar to those following double-valve replacement and include low cardiac output, multiorgan failure, hemorrhage, and dysrhythmia.[22]

Five-year actuarial survival after triple-valve replacement is 53 to 78%, and 10- and 15-year survivals are 40% and 25%, respectively (Table 48-23).

Considering only perioperative survivors of triple-valve replacement, late survival is comparable with that of patients undergoing isolated valve replacement.[22,176] Reports of thromboembolic rates following triple-valve replacement range from 5 to 12% per patient-year (see Table 48-23).

Double-valve replacement and tricuspid annuloplasty

Operative mortality for patients undergoing double-valve replacement with tricuspid valve repair is about 25%,[51] and the 10- and 15-year survival rates are 35% and 27%, generally comparable with those of patients having triple-valve replacement.[51] Rates of thromboembolism in this group are reported to be 5% per patient-year.[51]

Other Results

The operative mortality for double re-replacement is about 10 to 20%.[148,177] Incidence of postoperative ventricular arrhythmias is higher in patients having combined valve surgery than in those having single-valve surgery.[178] Hemolysis may be more common with multiple valve disease or following multiple valve replacement.[179,180]

The incidence of perivalvular leak following multiple valve surgery is about 4% per patient-year and may be more frequent following multiple valve surgery than following single-valve surgery.[154,156]

When multiple valve surgery is combined with myocardial revascularization, the morbidity and mortality are 12 to 24%.[161,181] Early death in this group of patients is associated with prolonged perfusion time, the need for postoperative inotropic support, and high blood loss.[181]

CONCLUSION

The challenges of multiple valve replacement and repair include not only the technical maneuvers of operation but also the identification of associated valve lesions and correct judgment in surgical management. Echocardiography is the essential tool in preoperative diagnosis, and surgeons should become as familiar and facile with interpretation of ultrasound assessment of cardiac valves as with analysis of coronary angiograms. Finally, the various etiologies of multiple valve disease occur in certain combinations, and understanding the pathophysiology and pathologic anatomy is necessary to select the best procedure and to optimize early and late operative results.

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CHAPTER 49

Reoperative Valve Surgery

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The number of patients undergoing reoperation for valvular heart disease is increasing and will continue to increase as the general population ages.[1] These reoperations most commonly involve structural deterioration of a bioprosthesis and progression of native-valve disease after nonvalve surgery. In fact, structural failure of a biologic valve should be considered part of the natural evolution of tissue valves and should be fully appreciated by both the surgeon and the patient prior to implantation.[2] Reoperations are technically more difficult than primary operations because of adhesions around the heart with an associated risk of reentry, the presence of more advanced cardiac pathology, and the existence of more frequent comorbidities such as pulmonary hypertension. Perhaps most important, reoperative replacement operations often are performed in functionally compromised patients who tolerate complications poorly or who have little reserve.[3] As a consequence of these and other factors, reoperative valve surgery historically has been associated with a considerably higher operative mortality than primary valve surgery, particularly in patients who have had multiple prior replacements.[4] In the modern era, however, with use of alternative surgical approaches and advanced perioperative care, there has been significant improvement in outcomes.[5–9]

Reductions in operative risk and postoperative morbidity after reoperative valve surgery have been made in the past few years through advances in myocardial protection, as well as alternative perfusion strategies such as the proper use of deep hypothermic cardiac arrest.[10] In addition, use of peripheral cannulation techniques to institute cardiopulmonary bypass has become a relatively standard practice in reoperative cases.[11–13] Early institution of cardiopulmonary bypass prior to reentry is known to prevent injury to the distended right ventricle or patent coronary artery bypass grafts during reoperative sternotomy. In addition, this technique reduces myocardial oxygen consumption by decreasing myocardial distension.[4]

Successful replacement of the degenerate cardiac valve usually results in gratifying symptomatic and hemodynamic improvement. Maintenance of this improved state, however, depends on persistence of prosthetic valve function. In this regard, improvements in valve design have mitigated but not eliminated primary bioprosthetic failure.[14–16] As such, the risk of re-replacement for bioprosthetic failure remains a significant factor to be considered in the selection of valve type for implantation.[17]

MECHANICAL VERSUS BIOLOGIC VALVES

The most appropriate valve substitute for an individual patient remains a source of much controversy. This choice should be adapted to each individual patient depending on age, life expectancy, valve size, and cardiac as well as noncardiac comorbidities.[18] Some studies comparing the long-term outcome between biologic and mechanical aortic valve prostheses have yielded similar results with regard to overall valve-related complications.[19–23] However, most recent large studies have documented that anticoagulant-related bleeding with mechanical valves must be balanced against life expectation and the risk of biologic valve re-replacement.[24–27] Bioprosthetic valves are known to undergo a time-dependent process of structural deterioration that results in a freedom of reoperation of 80% at 15 years.[20] Consequently, structural degeneration of a bioprosthesis is the most frequent indication for reoperation in patients with tissue valves.[19,28]

Despite this, recently improved durability of tissue valves, as well as the availability of stentless valves and homografts, has led to surgeons placing bioprostheses in progressively younger age groups.[18,29–32] Contributing to this trend, many patients do not accept the risk of anticoagulant-related hemorrhage associated with mechanical valves: major events 0.5% per patient-year and minor events 2 to 4% per patient-year.[33]

Mechanical prostheses usually are selected for younger recipients because of their proven durability over time. However, the risk of anticoagulant-related bleeding, as well as thromboembolic events (TEs), in these valves is not trivial and depends on valve design, structural materials, and host-related interactions.[33] In a 12-year comparison of Bjork-Shiley versus porcine valves, Bloomfield and colleagues documented severe bleeding complications in 18.6% versus 7.1%, respectively.[34] Moreover, while endocarditis, dehiscence, perivalvular leak, and pannus formation are associated with both biologic and mechanical valves, acute prosthetic thrombosis is exclusively a complication of mechanical valves.[35,36] In considering mechanical valve durability, these associated risks cannot be ignored and must be weighed against the anticipated rate of tissue-valve failure and the need for reoperation.

RISK FACTORS IN REOPERATIVE VALVE SURGERY (TABLE 49-1)

In evaluating patients for reoperative valve surgery, certain factors are associated with added risk. For example, Husebye and colleagues, in a review of their 20-year experience[17] with reoperative valve surgery, found specific issues to carry higher risk. Overall operative mortality was 7% ($n = 14$ patients) for the second and 14% ($n = 69$ patients) for the third reoperation. Operative mortality for the first reoperation ($n = 530$ patients) was 5.9% in the aortic position and 19.6% in the mitral position. In the aortic position, operative mortality was 2.4% for New York Heart Association (NYHA) class I, 1.6% for NYHA class II, 6.3% for NYHA class III, and 20.8% for NYHA class IV, emphasizing the significance of early referral. Regarding the urgency of surgery, the mortality for elective mitral valve reoperations was 1.4%; for urgent procedures, 8%; and for emergency procedures, 37.5%. Based on these findings, the authors have recommended that referral for reoperation be made when valve dysfunction is first noted, i.e., prior to a significant decrement in myocardial function.[17] Similarly, Jones and colleagues reviewed their experience with first heart valve reoperations in 671 patients between 1969 and 1998.[6] Their overall operative mortality for first-time heart valve reoperation was 8.6%, similar to the results published by Lytle[37] (10.9%), Cohn[4] (10.1%), Akins[38] (7.3%), Pansini[2] (9.6%), and Tyers[39] (11.0%). In the Jones and colleagues series, mortality increased from 3.0% for reoperation on a new valve site to 10.6% for prosthetic valve dysfunction or periprosthetic leak; mortality was highest (29.4%) for associated endocarditis or valve thrombosis. Concomitant coronary artery bypass grafting carried a higher associated mortality (15.4%) than when it was not required (8.2%). Among the 336 patients requiring re-replacement of prosthetic valves, mortality was 26.1% for re-replacement of a mechanical valve compared with 8.6% for re-replacement of a tissue valve. The authors concluded through multivariable analysis that significant predictors of mortality were year of reoperation, patient age, indication, concomitant coronary artery bypass grafting, and the replacement of a mechanical valve rather than a tissue valve.[6]

REOPERATIVE AORTIC VALVE SURGERY

Historical Points

Historically, aortic valve surgery typically involved the placement of a mechanical valve. In the past, there were only a few generally accepted indications to use a bioprosthesis for

Table 49–1.

Risk Factors for Reoperative Valve Surgery

Advanced age
Impaired ejection fraction (EF), congestive heart failure (CHF), or advanced preoperative functional class (NYHA)
Urgency of operation or unstable status preoperatively
Preoperative shock
Concomitant coronary artery bypass graft (CABG) or the presence of previous bypass grafts
Prosthetic valve endocarditis
Surgery for perivalvular leaks, valve thrombosis, or prosthetic dysfunction
Renal dysfunction
Chronic abstructive pulmonary disease (COPD)

primary, isolated aortic valve replacement: (1) the presence of well-established contraindications to continuous anticoagulation, (2) the inability to monitor prothrombin levels adequately, and (3) patients whose survival was limited and more dependent on non-valve–related issues.[18,28] In recent years, however, the use of biologic valves in the aortic position has become more common.[25,26]

As mentioned earlier, reoperations are technically demanding, and many patients present in a poor functional state that further increases their mortality, in some series up to 19%.[34,40,41] Generally speaking, optimal planning for reoperation prior to deterioration to NYHA class III–IV levels and before unfavorable comorbid conditions have arisen is imperative to ensure good outcomes.[42] Following these guidelines in the modern era, elective re-replacement of malfunctioning aortic bioprostheses can be performed with results similar to those of the primary operation.[18,24,43] The Mayo Clinic, for example, recently reviewed its experience with 162 reoperative aortic valve replacements (AVRs). Early mortality for reoperative AVR was not statistically different from that for primary AVR.[44] In light of recent lower operative mortality in reoperative valve surgery, a more conservative approach toward issues such as "prophylactic" AVR in patients with asymptomatic mild to moderate aortic stenosis at the time of coronary artery bypass grafting (CABG) also may be more appropriate.[45]

In evaluating the reoperative patient, the presence of concomitant coronary artery disease and pulmonary hypertension has been shown consistently to be independent risk factors.[18] Patients with these risk factors therefore need careful surveillance once the probability of bioprosthetic dysfunction begins increasing (i.e., 6 to 10 years after implantation).[16] Regarding valve surveillance and timing of reoperation, the following variables are relevant to the clinical management of patients with an aortic bioprosthesis: a history of endocarditis prior to the first operation, perioperative infectious complications, coronary artery disease acquired after the first operation, an increase in pulmonary artery pressure, and a decrease in left ventricular function during the interoperative interval.[18] Proper timing of the reoperation therefore is paramount because duration of clinical signs with a dysfunctional aortic bioprosthesis may be misleading. This is further supported by the fact that the need for emergency reoperation is the most ominous risk factor and consistently yields a high early mortality rate of 25 to 44%.[46]

Approaches and Techniques

Conventional resternotomy

The evolution of cardiac surgery through the last few decades has led to the popularization of various surgical approaches. Thoracotomy, for example, once was used extensively to gain access to mediastinal structures. Then median sternotomy became the standard approach. In reoperative cases, however, repeating the sternotomy carries definite risks. Prior to proceeding with a resternotomy, the relationship between certain anterior mediastinal structures (e.g., the right ventricle and the aorta) and the posterior aspect of the sternum must be assessed carefully.[47] This generally can be visualized on chest radiograph or more accurately with a computed tomographic (CT) scan. Recently, it has been shown that multidetector computed tomographic (MDCT) scanning, in combination with retrospective electrocardiographic gating, can be used as a noninvasive way to assess not only the heart's location in relation to the sternum but also graft location and patency.[48–50]

Exposure of the femoral vessels and preparation for emergency femoral-femoral cardiopulmonary bypass should be considered prior to resternotomy. In cases of heightened concern for right ventricle–graft injury or in cases in which a left internal mammary artery (LIMA) graft is patent, the surgeon should consider the use of cardiopulmonary bypass prior to chest reentry. Sternal wires from the previous operation should be undone carefully but left in place as a safeguard during initial sternal division. An oscillating (not reciprocating) bone saw can be used to divide the anterior sternal table. Most authors recommend dividing the posterior table using a combination of scissors and anterolateral rake retraction.[50–52] Following this, bilateral pleural spaces should be entered inferiorly, followed by careful dissection of other mediastinal structures. The pericardial dissection plane can be developed by starting at the cardiophrenic angle and advancing slowly cephalad and laterally on the surface of the right side of the heart. Cephalad dissection should start with freeing the innominate vein prior to spreading the retractor to avoid its injury. Further dissection then is carried down to the superior vena cava, being careful to note the location of the right phrenic nerve. An area of consistently dense adhesions is the right atrial appendage, and caution should be used here. In addition, great care should be taken to avoid "deadventializing" the aorta. The area where the aorta apposes the pulmonary artery is another site of potential injury.

Repairing small ventricular or atrial lacerations should not be attempted before releasing the tension of the surrounding adhesions. Repair of great vessel injuries or severe right ventricle injuries is best done under cardiopulmonary bypass.[51] Active hemorrhage during a second sternotomy usually is due to adherence of the heart or great vessels to the posterior sternum. Prevention of this ominous complication by interposition of pericardium or other mediastinal tissue at the time of the first operation has been suggested but has debatable relevance.[50] The incidence of resternotomy hemorrhage is between 2% and 6% per patient reoperation.[53–55] In a report of 552 patients who had undergone reoperative prosthetic valve surgery, 23 patients (4%) had complications related directly to sternal opening.[17] Of these, 5 patients had entry into the right atrium, 7 patients had lacerated right ventricles, 9 patients had injuries to the aorta, and 2 patients had a previously placed coronary artery graft divided. Nineteen of the 23 complications occurred during a first reoperation. Overall, there were 2 operative deaths related to resternotomy. The first death involved division of a

previously placed coronary artery graft during reentry. The second death was due to laceration of the aorta with subsequent exsanguination.[17] Of note, prior use of a right internal mammary artery (RIMA) graft can be particularly challenging because it frequently crosses the midline, and extreme caution must be used in first dissecting out this vessel.

Macanus and colleagues reviewed their experience with 100 patients undergoing repeat median sternotomy.[54] Eighty-one patients had one repeat sternotomy, whereas the others had undergone multiple sternotomies. All had had a previous valve procedure and were reoperated on for progressive rheumatic valvular disease or for complications related to the prosthesis. Complications included operative hemorrhage in 8 patients, postoperative hemorrhage in 2, seroma in 4, and dehiscence, wound infection, and hematoma in 1 patient each. There was one operative death directly related to resternotomy hemorrhage.[54] When major hemorrhage does occur on sternal entry, attempts at resternotomy should be abandoned, and the chest should be reapproximated by pushing toward the midline. The patient should be heparinized immediately while obtaining femoral arterial and venous cannulation. Blood loss from the resternotomy should be aspirated with cardiotomy suction and returned to the pump. Once bypass has been established, core cooling should be commenced with anticipation of the need for circulatory arrest. Once cool, flow rates can be reduced, and the remaining sternal division can be completed, followed by direct repair of the underlying injury.[50] Anticipating the possibility of this scenario, we frequently expose peripheral cannulation sites prior to beginning a resternotomy. In cases of heightened concern for right ventricle or graft injury, or in patients with a patent LIMA to left anterior descending (LAD) artery graft, cardiopulmonary bypass and cardiac decompression may be initiated *prior* to sternal reentry. After safe sternal entry, the patient may be weaned from bypass for further dissection of adhesions to avoid prolonged pump times.

Minimally invasive reoperative AVR

Reoperative procedures are challenging owing to diffuse mediastinal and pericardial adhesions. A large incision that increases the operative exposure also has been associated with a higher risk of injury to cardiac structures and coronary artery bypass grafts and results in greater bleeding with its associated transfusion requirements.[56–59] A smaller incision with a limited sternotomy, on the other hand, reduces the area of pericardiolysis, thus mitigating these effects. The intact lower sternum that remains also preserves the integrity of the caudal chest wall, thereby enhancing sternal stability and promoting earlier extubation.[60,61] *Minimally invasive* valve procedures gradually have become more accepted as new technologies and instrumentation have been developed.[60] Reoperative procedures in which there is risk for graft injury are an area where minimally invasive strategies may be of direct benefit.[62,63] Our surgical approach in reoperative AVR is shown in Fig. 49-1.[60] In our series of patients, peripheral cannulation sites were exposed

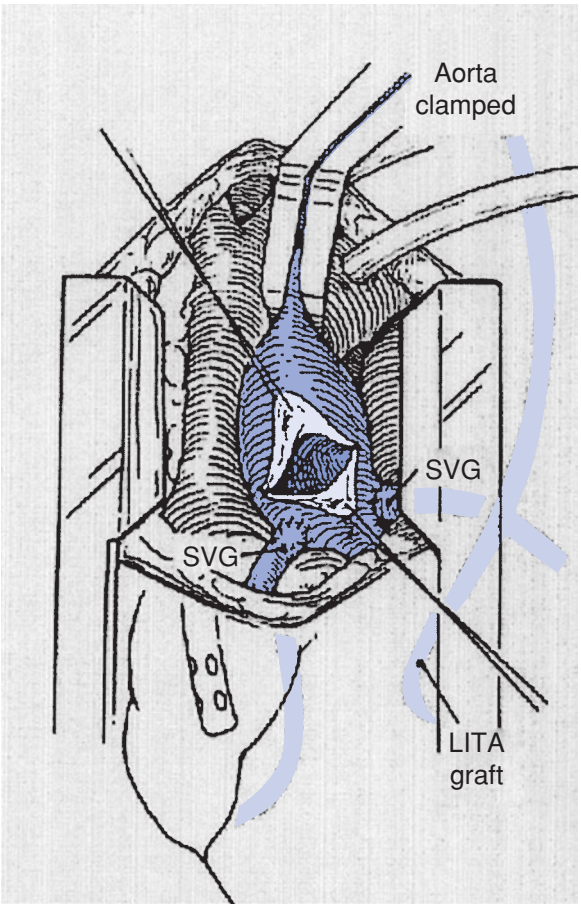

Figure 49-1. Partial upper resternotomy for reoperative AVR. The previous sternotomy incision is exposed to the third or fourth intercostal space depending on the position of the aortic valve, as documented by TEE. After dissection of the ascending aorta, paying particular attention to the position of coronary artery bypass grafts and their proximal anastomoses, cannulation is carried out. In this figure, the ascending aorta and innominate vein are cannulated. Frequently, however, other cannulation sites are required owing to space limitations in the chest. The ascending aorta is cross-clamped, and the aortic valve re-replacement is conducted in a standard fashion. (*Used with permission from Byrne JG, Karavas AN, Adams DH, et al: Partial upper re-sternotomy for aortic valve replacement or re-replacement after previous cardiac surgery. Eur J Cardiothorac Surg 2000; 18(3):282.*

or cannulated prior to beginning the partial upper resternotomy. An external defibrillator was placed on the patient prior to draping for anticipated defibrillation as necessary. Transesophageal echocardiography (TEE) was used in every patient. A partial upper resternotomy was carried out to the third or fourth intercostal space depending on the estimated position of the aortic valve as documented by chest x-ray (CXR)/TEE and then was "T'd to the right."[64] The oscillating saw was used to divide the anterior sternal table, whereas the straight Mayo scissors, under direct visualization, was used to divide the posterior sternal table. In the setting of a patent LIMA-LAD graft or other anterior coronary artery bypass grafts, patients were placed on cardiopulmonary bypass prior to partial resternotomy. Mediastinal dissection was limited to only the ascending aorta as was necessary for

clamping and aortotomy. The right atrium was dissected only if it was cannulated. Although intrathoracic cannulation was preferred, we frequently used peripheral cannulation to avoid clutter in the chest. Retrograde cardioplegia, if necessary, was delivered via a transjugular coronary sinus catheter or with right atrial placement under TEE guidance. Vacuum assistance of venous drainage was used in the majority of patients. Once on cardiopulmonary bypass, all patients were systemically cooled to 20 to 25°C. Patients with patent LIMA-LAD grafts were cooled routinely to 20°C for additional myocardial protection and in so doing avoided the need and potential hazard of dissecting out the LIMA for clamping in an attempt to avoid cardioplegia washout. If flow from the patent LIMA-LAD graft led to significant blood flow out of the coronary ostium and obscured the operative field, pump flows were turned down temporarily to allow visualization. Venting was accomplished by placing a pediatric vent through the aortic annulus. The aortic valve surgery then was performed based on patient indications. While closing the aortotomy, intracardiac air was removed by insufflating the lungs and decreasing flows on cardiopulmonary bypass. Carbon dioxide was used and flooded the operative field. Patients also were tilted from side to side to help with deairing, and the ascending aortic vent was left open until separation from cardiopulmonary bypass. Temporary epicardial pacing wires were placed on the anterior surface of the right ventricle while the heart was decompressed and before the aortic cross-clamp was removed. Two 32F right-angled submammary chest tubes then were placed through the right pleural space, one angled medially into the mediastinum and one angled posterior into the pleural space. Decannulation and closure then were performed in the standard manner.

With our increasing experience in minimally invasive reoperative AVR, we have refined our technique as an alternative to conventional full resternotomy.[60] In so doing, we have ascertained the technical details of the partial upper resternotomy approach (Table 49-2). By following these guidelines, we have yet to convert any patient to a full resternotomy. Lateral CXR and/or TEE is helpful in locating the level of the aortic valve and determining the proximity of the aorta to the posterior aspect of the sternum.[64] If necessary, additional information can be obtained with CT scanning or magnetic resonance imaging (MRI) preoperatively. Also,

Table 49–2.

Thirteen Technical Details for Successful Aortic Valve Replacement After Previous Cardiac Surgery by Use of Partial Upper Resternotomy

1. Routine exposure of peripheral cannulation sites prior to partial upper resternotomy
2. Placement of Zoll (Zoll, Inc., Burlington, MA) defibrillator pads prior to prepping
3. Use of intraoperative transesophageal echocardiography for air removal and inspection of valve
4. In patients with patent left internal mammary artery to left anterior descending coronary artery (LIMA-LAD) graft, peripheral cannulation and cardiopulmonary bypass (CPB) established prior to partial upper resternotomy
5. Mediastinal dissection limited to ascending aorta for clamping and aortotomy and atrium (RA), only if RA is cannulated
6. Use of peripheral cannulation to avoid clutter in the chest
7. Use of vacuum assistance on CPB
8. Use of retrograde cardioplegia (CP) delivered by transjugular retrograde CP catheter in addition to antegrade CP
9. Use of aprotinin unless absolute contraindication
10. Cooling to at least 25°C in all patients primarily for myocardial protection; if a patent LIMA-LAD graft is present, cooling to 20°C without isolation and clamping LIMA graft
11. If visualization is poor due to LIMA-LAD collaterals flowing from coronary ostia, temporary low flows on CPB to improve visualization
12. Venting with a pediatric vent placed through the aortic annulus
13. Placement of temporary pacing wires on the right ventricular free wall before aortic clamp removal

Source: Reproduced with permission from Byrne J, Karavas A, Adams D, et al: Partial upper re-sternotomy for aortic valve replacement or re-replacement after previous cardiac surgery. Eur J Cardiothorac Surg 2000; 18:282.

extension of the sternal incision laterally on both sides through the intercostal spaces helps to later reapproximate the sternum. We have tried to limit mediastinal and pericardial dissection primarily to the aorta, believing that this is the principal reason for decreased bleeding and transfusion requirements postoperatively.[60,63,65,66] The right ventricle, which often is attached to the sternum, does not need to be dissected. Also, injuries to patent but atherosclerotic vein grafts can be reduced with this "no touch" technique.[67]

Arterial and venous cannulation sites can vary considerably, reflecting the individual choice of the operating surgeon and the sufficiency of intrathoracic space. Possible cannulation sites, other than standard ones, include the axillary artery, inominate vein, and percutaneous femoral vein.[68,69] Innominate vein or percutaneous femoral vein cannulation, as well as the use of TEE to place the retrograde cardioplegia catheter, has been extremely helpful in minimizing dissection of the right atrium. At present, we consider this approach to be useful for isolated, elective reoperative aortic valve surgery.[60]

Reoperative AVR after homograft/root/allograft

AVR with homografts and autografts was performed increasingly because of excellent freedom from thromboembolism, resistance to infection, and reasonable hemodynamic performance.[29] While improved durability of current tissue valves has slowed this trend, autografts and, to a lesser degree, homografts remain popular in younger patients owing to durability and, in the case of autografts, the potential for growth.[32,70] Consequently, many patients will require aortic valve re-replacement for structural degeneration of their homograft or autograft valve.[71] It is expected that about one-third of patients younger than 40 years of age will require aortic valve re-replacement within 12 years of homograft placement. This is due primarily to calcification and structural valve degeneration. As such, the issue of homograft or autograft durability is particularly pertinent in this subgroup of younger patients who are expected to live beyond 15 years from time of operation.[70]

The incidence of patients with homografts or autografts in need of a second valve operation is expected to increase owing to the aforementioned recent popularity and availability of these conduits. Also, there is varied opinion as to the optimal surgical method of primary homograft AVR, with increased rates of aortic insufficiency in patients with the subcoronary implantation technique. Importantly, the selected technique of primary homograft operation may have relevance at reoperation because calcification or aneurysmal dilatation of the homograft may pose surgical challenges at reoperation. Despite these challenges, Sundt and others[31,72,73] have documented the feasibility of aortic valve re-replacement after full-root replacement with a homograft. In our own series of 18 patients, full-root, mini-root, and subcoronary techniques all were amenable to valve re-replacement.[29]

How to best approach the reoperative root scenario and which valve to reimplant, however, have been debated. At one extreme, Hasnet and colleagues documented the results of 144 patients who underwent a *second* aortic homograft replacement with a hospital mortality rate of only 3.5%.[71] Although Kumar and colleagues, in a multivariate analysis of reoperative aortic valve surgery, did not show that a previous homograft added significant risk,[74] the technical aspects of reoperative AVR in this patient population consistently have been found to be challenging owing to the heavy calcific degeneration that invariably occurs. With this in mind, and owing to the typical absence of the need for a second root operation, we and others[75] believe that a more simplified approach to reoperative aortic valve surgery in patients with previously placed homografts may be optimal. Our approach has been to perform aortic valve re-replacement using a mechanical valve or, less commonly, a stented xenograft while reserving a second homograft and root operation for specific indications such as endocarditis, associated root pathology, or a very young patient with contraindications to a mechanical valve.

Homograft re-replacement nonetheless is performed but is much less common, and hospital mortality varies widely across many centers, ranging between 2.5% and 50%.[31,72,73] David and colleagues, for example, recently reviewed their experience with root operations in 165 patients who previously had undergone cardiac surgery. Of these, 28 had a previous root operation. Overall, 12 operative (7%) and 20 late deaths (12%) occurred.[76] Variations in sample size, valve selection, surgical techniques, and patient factors, as well as the experience of the surgeons, may account for these wide differences.

REOPERATIVE MITRAL VALVE SURGERY

Historical Points

Fundamental to a flawless surgical procedure is excellent and consistent exposure of the mitral valve.[77] Historically, the mitral valve has been exposed through a variety of surgical approaches, including median sternotomy, right thoracotomy, left thoracotomy, and transverse sternotomy.[78] The median sternotomy and right thoracotomy will be discussed in detail below; however, a brief description of the other approaches is warranted.

The *left* thoracotomy has been used in recent years to gain access to the mitral valve in situations in which a right thoracotomy is precluded (e.g., mastectomy/radiation or pleurodesis). This incision is made through the fourth intercostal space, and the left pleural cavity is entered in the standard fashion.[78] Surgery is performed under fibrillatory arrest or with beating-heart technique. Of importance, the mitral valve orientation is noted to be upside down with this approach, with the posterior annulus found anteriorly.[79] Thompson and colleagues recently reported their experience with the beating-heart left thoracotomy approach for reoperative mitral valve surgery. Of the 125 patients undergoing this technique, 86% were in NYHA class III or IV, and 28%

had undergone two or more sternotomies. Thirty-day mortality was 6.4% with low complication rates.[80] While occasionally useful, this approach provides limited access to the other cardiac chambers as well as poor visibility. This left-sided approach is rarely needed and typically reserved for patients in whom reoperative sternotomy or right thoracotomy is considered unacceptable. A bilateral anterior thoracotomy (i.e., transverse sternotomy) carried out through the fourth intercostal space also has been described.[78,81] Rarely used today, this incision transects the sternum transversely, requiring ligation of both internal mammary arteries.

Regardless of the actual approach, once cardiopulmonary bypass has been established and the heart exposed, there are several incisions that can be employed to view the underlying mitral valve. The standard left atriotomy begins with blunt dissection of the interatrial groove (i.e., Waterston's groove), allowing the right atrium to be retracted medially and anteriorly (Fig. 49-2) The right superior pulmonary vein at its junction with the left atrium then is exposed, and the left atrium is opened at the midpoint between the right superior pulmonary vein insertion and the interatrial groove. This incision is extended longitudinally both superiorly and inferiorly to give enough exposure of the mitral valve. Care must be taken to avoid inadvertent injury to the posterior wall of the left atrium, and when closing, one must avoid including the posterior wall of the right pulmonary vein. The right atrial transeptal approach has become more popular in recent years, especially in reoperative valve surgery. After opening the right atrium, the interatrial septum is incised starting at the fossa ovalis and moving vertically upward for a few centimeters (Figs. 49-3 and 49-4). This technique is especially helpful in reoperative surgery because it minimizes the amount of dissection required. Superior biatrial atriotomy, left ventriculotomy, and aortotomy all have been well described[15,59,77,78,82,83] as approaches to the mitral valve; each one has varying advantages and disadvantages.

Approaches and Techniques

Resternotomy

Resternotomy is still the most common approach in reoperative mitral valve surgery. In many cases, this incision provides full and adequate exposure. This is especially true when concomitant procedures are necessary. However, reoperative median sternotomy has known risks, including injury to or embolism from prior grafts, sternal dehiscence, excessive hemorrhage, and inadvertent cardiac injury.[84] Patients with valvular heart disease may be especially prone to these complications because atrial dilatation can result in significant cardiomegaly, atrial thinning, and adherence of the heart to the posterior sternum. As discussed previously, patients undergoing prosthetic valve reoperation have a 4% incidence of complications directly related to sternal reentry that can result directly in intraoperative death.[17,37] Resternotomy also

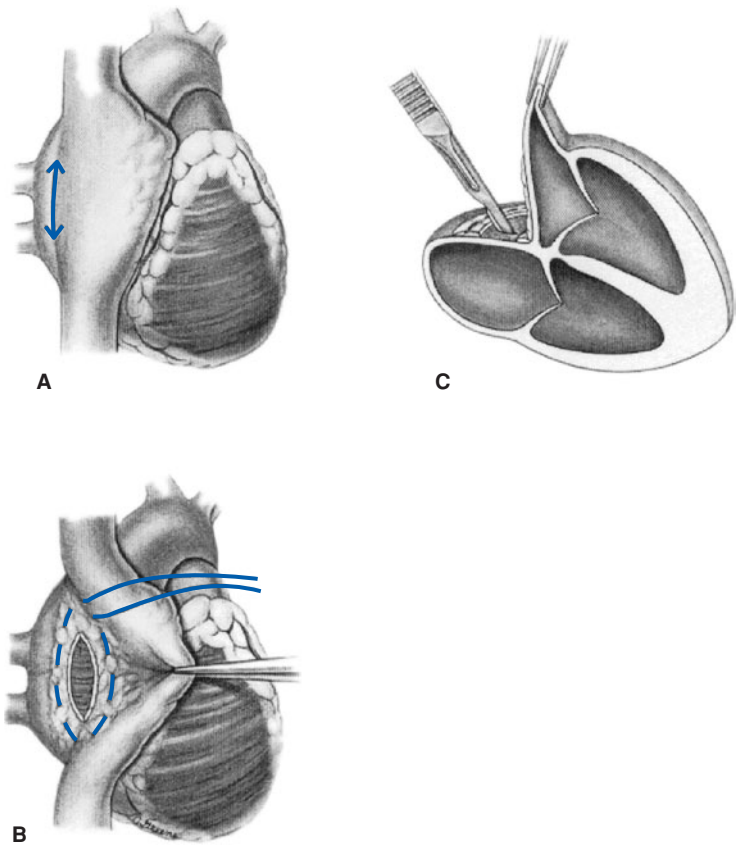

Figure 49-2. Sondergaard's groove approach. The left atrium enlarges to the right, increasing visualization from the right thoracotomy approach. The interatrial groove (Sondergaard's groove) is dissected approximately 1 cm deep, down to the left atrial wall. The purse-string suture is placed in the nondissected area. This prevents tearing of the dissected left atrial wall when the suture is tied down. Sagittal view shows location of the mitral valve in relation to the atriotomy. (*Used with permission from De DH, Pessella AT: Closed mitral commissurotomy utilizing right thoracotomy approach. Asian Cardiovasc Thorac Ann 2000; 8:192.*)

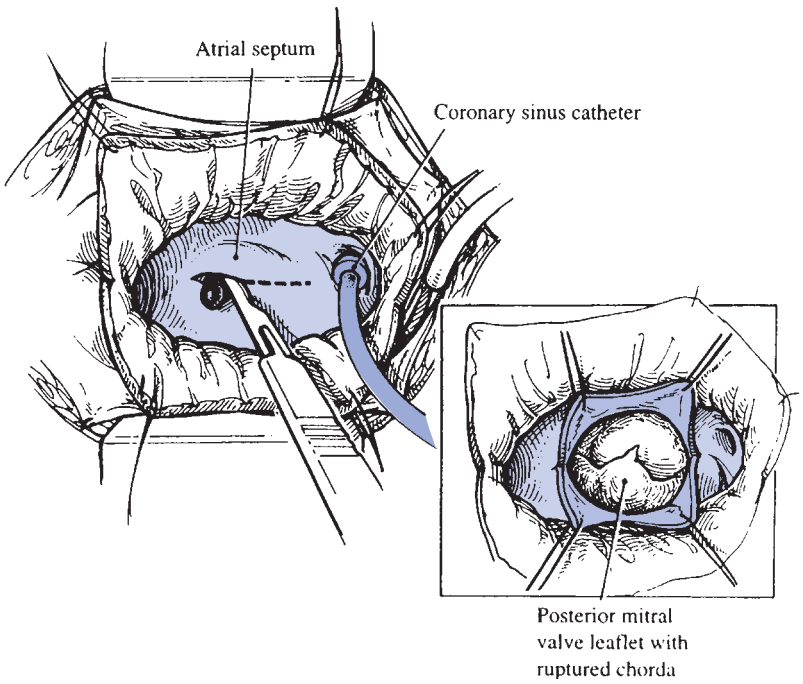

Figure 49-3. Atrial incision through the fossa ovalis. When the right atrium is incised, an incision is made in the atrial septum through the fossa ovalis. Retraction sutures on both the right atrium and the atrial septum of 2-0 silk then are used to elevate the septum and to keep the left atrium open. The mitral valve then will be exposed (*inset*). (*Used with permission from Byrne JG, Mitchell ME, Adams DH, et al: Minimally invasive direct access mitral valve surgery. Semin Thorac Cardiovasc Surg 1999; 11(3):212.*)

has been noted to be particularly hazardous in the presence of patent internal mammary grafts. Injury to a patent LIMA graft has an associated mortality rate approaching 50%.[50,64] Furthermore, manipulation of patent but diseased saphenous vein grafts can result in embolization into the native coronary circulation with resulting morbidity and mortality.[85,86] Patients with previous aortic valve replacements can have difficult exposure of the mitral valve owing to anterior fixation and probably are best served by an anterolateral thoracotomy approach. In general, in the setting of reoperative surgery, the resternotomy is likely to be the most dangerous part of the operation.[87] In this situation, we also have employed techniques that avoid resternotomy, such as right thoracotomy.

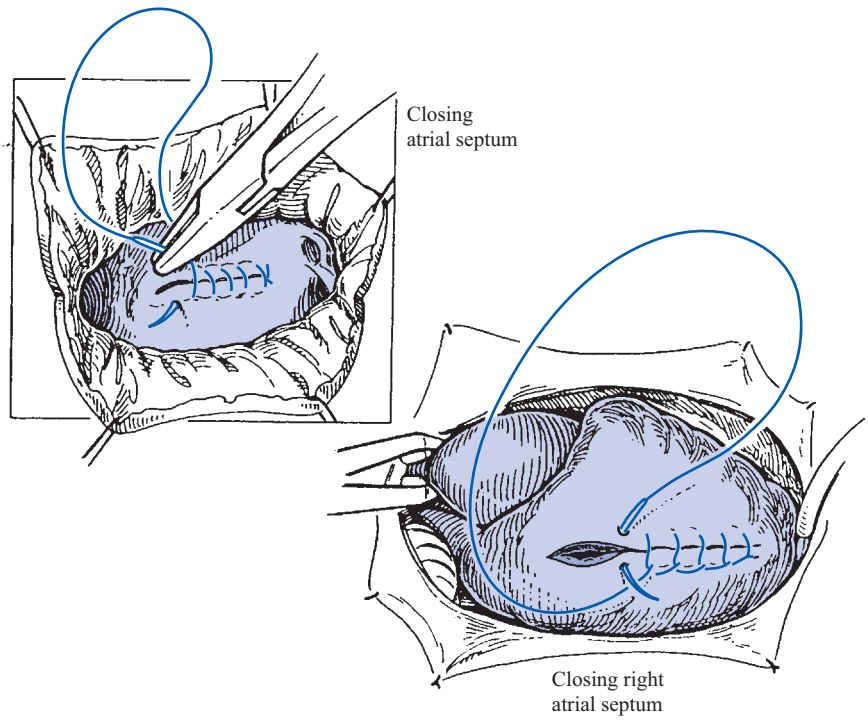

Figure 49-4. Closure. In the transeptal approach, the atrial septum is approximated with running 4-0 Prolene sutures and is left open until the aortic cross-clamp is removed and the air is evacuated. The left ventricle should be filled with fluid before removal of the cross-clamp to help dislodgment of intraventricular air. Once the cross-clamp has been removed, air is evacuated vigorously from the left atrium through the septum or the left atrium itself, and the sutures are tied. The right atrium is then closed with running 4-0 Prolene sutures in two layers. TEE has been very important in helping to monitor the clearing of air from the intracardiac structures. We consider it mandatory in the minimally invasive technique, in which access to the entire cardiac structure is limited. (*Used with permission from Byrne JG, Mitchell ME, Adams DH, et al: Minimally invasive direct access mitral valve surgery. Semin Thorac Cardiovasc Surg 1999; 11(3):212.)*

Right thoracotomy

The right anterolateral thoracotomy approach was one of the first surgical approaches to the mitral valve, and it has become a safe alternative to resternotomy for mitral valve replacement[10,50,88–89] (see Fig. 49-3). This approach provides excellent exposure of the valves (mitral and tricuspid) with minimal need for dissection within the pericardium. In our recent experience with this approach,[87,93–96] all patients had double-lumen endotracheal tubes placed, and operations were performed in the right lateral thoracotomy position. We routinely prepared and draped the right groin to allow femoral cannulation, if necessary. Preoperative and intraoperative Doppler TEE was performed in all patients, as well as standard intraoperative cardiac monitoring and thermodilution Swan-Ganz catheterization. A right thoracotomy was made, and the chest was entered through the bed of the fourth or fifth rib. Adhesions of the right lung to the chest wall or pericardium were divided by electrocautery. The pericardium was entered anterior to the phrenic nerve. Arterial cannulation was performed via the ascending aorta with the use of a flexible aortic cannula or, alternatively, through the groin. Bicaval venous cannulation was carried out with a 28F (DLP) cannula in the superior vena cava and a 32F (USCI) flexible cannula in the inferior vena cava. Patients then were cooled to 20 to 25°C. Fibrillatory arrest occurred spontaneously in the majority of patients. If care is used to avoid left ventricular ejection by keeping the left ventricle empty (i.e., maintaining laminar, nonpulsatile arterial line tracing), a beating-heart technique also may be used. In the absence of aortic insufficiency, aortic cross-clamping usually was not required. Regurgitant flow through the aortic valve occasionally required temporary low pump flow at appropriate temperatures to avoid cerebral injury. The mitral valve then was approached through the left atrium directly by dissection of the intra-atrial (Sundergaard's) groove (see Fig. 49-2) or through the right atrium via the atrial septum (see Fig. 49-4). As the valve procedure was completed, rewarming was initiated (Fig. 49-5). Carbon dioxide (CO_2) can flood into the field and be infused directly into the left atrium and left ventricle to reduce the time spent de-airing. In addition, perfusing blood via a cannula (e.g., the left ventricular vent) positioned across the mitral valve and into the left ventricle will serve to displace residual air. An aortic root vent kept on suction in the ascending aorta is used to remove any ejected air. Patients then were placed in the Trendelenburg position and de-airing ascertained under 2D TEE guidance. When core temperatures reached 37°C, the patient was weaned from cardiopulmonary bypass. Temporary atrial and ventricular pacing wires were placed and exteriorized through the chest wall. Closure then was routine. At the conclusion of the procedure, patients were returned to the supine position and reintubated with a single-lumen endotracheal tube for postoperative ventilation. The use of a small right anterior thoracotomy, femorofemoral bypass, and deep hypothermia has increased since our initial report in 1989.[97] Reduced blood use and decreased risk of LIMA or cardiac structural injury

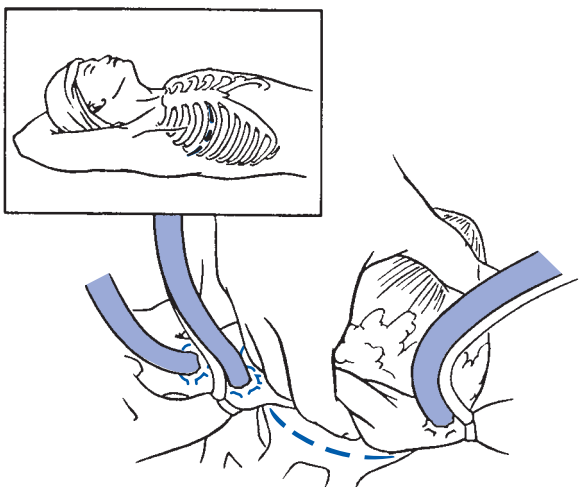

Figure 49-5. Right anterolateral thoracotomy through the fourth intercostal space and standard left atriotomy. (*Used with permission from Balasundaram SG, Duran C: Surgical approaches to the mitral valve. J Card Surg 1990; 5(3):163.*)

during sternal reentry make it a desirable approach for many complicated mitral reoperations. Deep hypothermia (~20°C) and low-flow femorofemoral bypass perfusion, without the necessity of aortic cross-clamping, provide adequate myocardial protection.[98] Cardiopulmonary bypass times, blood loss, blood product usage, and LIMA injury rates have been lower in reoperative patients undergoing right thoracotomy than in those with resternotomy.[37,80,83,90,98,99]

Certain issues must be considered before the right thoracotomy approach is entertained. Patients who require simultaneous coronary artery bypass grafting generally will require a median sternotomy, although isolated right-sided grafting may be performed with a thoracotomy. Simultaneous replacement of the aortic valve is difficult from a thoracotomy approach and generally should be performed through a resternotomy. Significant aortic insufficiency can make effective perfusion on cardiopulmonary bypass difficult because, after opening the left atrium, blood will be returned to the pump via the cardiotomy suction. Unless the ascending aorta is clamped, effective end-organ perfusion will not be achieved. Also, in the setting of aortic insufficiency (AI), exposure of the mitral valve may be difficult owing to this regurgitant flow into the surgical field. Left ventricular distension and myocardial stretch injury also can occur with fibrillatory arrest in patients with and occasionally without AI. Patients with greater than minimal aortic insufficiency therefore should either be excluded from a right thoracotomy approach or expected to require aortic cross-clamping either with traditional clamping or rarely with balloon occlusion. Significant right pleural disease, especially scarring in the right hemithorax, previously has been a relative contraindication to a right thoracotomy, although our series includes two patients with a previous right thoracotomy who did not represent an overwhelming challenge.[84]

Holman and colleagues[100] reported their experience in 84 patients undergoing reoperative mitral valve surgery via right thoracotomy. Myocardial management included ventricular fibrillation in 10 patients, a beating-heart procedure in 58 patients, and hypothermic blood cardioplegia in 16 patients. The mean duration of cardiopulmonary bypass was 63 ± 56 minutes. There were no perioperative strokes, and the operative risk for patients who received cardioplegic arrest was significantly greater than in the other two groups ($p = .007$). The authors concluded that procedures on the beating or fibrillating heart were feasible in most patients and are at least as safe as surgery using cardioplegic arrest.[100]

Minimally invasive/port access right-sided techniques

A final approach to the reoperative mitral valve is with minimally invasive or port access techniques. From January 2000 to July 2005, 517 patients underwent a simplified port access mitral valve procedure performed by one author (MRP) at St. Thomas Hospital in Nashville, TN. Of these 517 patients, 110 (21%) had a previous sternotomy, with 58 (11%) having a previous mitral valve procedure. All 110 operations were done with a 5-cm anterolateral thoracotomy incision through the fourth or fifth interspace under hypothermic fibrillatory arrest. Standard single-lumen endotracheal intubation was used. Cardiopulmonary bypass was instituted via femoral cannulation and vacuum-assisted venous return. Twenty-three patients (21%) had an ejection fraction of less than 30%, and 7 (6%) had an ejection frcation of less than 20%. There were no operative deaths. Skin-to-skin operative times averaged 3 hours and 18 minutes. Thirty-two percent of the patients were discharged in 5 days or less and 68% in 7 days or less (Dr. Michael R. Petracek, personal series, unpublished data). By not cross-clamping, the need for cardioplegia is eliminated, and there is minimal myocardial ischemia. The only dissection is at Waterston's groove; therefore, bleeding is decreased.

Some authors have noted that the distance to the mitral valve with the right thoracotomy approach at times can be limiting. Broaching this issue, Chitwood and colleagues recently reported use of a minithoracotomy aided by the voice-activated robotic camera AESOP.[101] Vleissus also reported 22 patients who underwent a "minimally invasive" right thoracotomy approach to the atrioventricular valves.[69] The procedures performed included mitral valve repair ($n = 12$), mitral valve replacement ($n = 5$), prosthetic mitral valve re-replacement ($n = 4$), repair of a perivalvular leak ($n = 3$), tricuspid valve repair ($n = 5$), and closure of an atrial septal defect ($n = 7$). Mean bypass time was 109 minutes with a mean fibrillatory time of 62 minutes. Operative mortality in this group was 0%, and none of the patients experienced a wound complication. At follow-up, all reoperative patients thought that their recovery from this approach was more rapid and less painful than their original sternotomy.[102] Burfeind and colleagues recently reviewed Duke University's experience with the port access technique.[103] In their series of 60 patients, a 6-cm right anterolateral thoracotomy was used with standard port access technique. Forty-five percent of patients underwent cardiac arrest with the endoclamp technique, whereas ventricular fibrillation was used in 55% of patients. Femoral cannulation was used in all patients. When compared with concurrent cohorts of patients undergoing reoperative sternotomy or right anterolateral thoracotomy, patients undergoing the port access technique had lower mortality and decreased transfusion requirements but significantly longer cardiopulmonary bypass times. While similar results have been found by other groups, one should be mindful of the potential hazards of the port access technique, namely, endoclamp migration.[104–107]

Additional techniques of reoperative mitral surgery

A less common indication for reoperative mitral valve surgery but one that can be challenging is periprosthetic leak. The incidence of perivalular leak for both mechanical and biologic valves is about 0 to 1.5% per patient-year. Of note, perivalvular leak is slightly more common with mechanical than with tissue valves-possibly owing to differences in suture technique for each and sewing ring characteristics. The regurgitant flow across the perivalvular area frequently leads to hemolysis and, through denuding of the endocardium, endocarditis. The antibacteriocidic Silzone coating on St. Jude prostheses has been shown recently to have a particular predilection for this complication.[108]

In evaluating patients with a periprosthetic leak, an assessment of valve function is important. If the valve itself is competent, direct repair of the leak avoids the hazards of valve replacement. While pledgeted suturing may be attempted for smaller leaks, fibrotic tethering of surrounding tissue and the size of the defect may require a bovine or autologous pericardial patch. In cases of significant dehiscence or associated valvular dysfunction, removal of the valve is necessary. Replacement in this situation, however, is prone to leak recurrence because the annulus is partially intact, often calcified, and otherwise less than ideal for suture placement. In these cases, a bovine pericardial skirt can be fashioned and sewn to the sewing ring of the valve. Annular sutures then are placed in a typical fashion through the sewing ring, and the valve is seated. A running suture then can be used to sew this skirt to the left atrium (Fig. 49-6).

An additional risk of reoperative mitral valve replacement is atrioventricular disruption. Care must be used in removing the original valve sewing ring because it is frequently "socked in," and inadvertent removal of excessive annular tissue may occur. Any evidence of disruption of the posterior annulus necessitates patch repair with pericardium (autologous or bovine) prior to placement of annular sutures.[109] When faced with less than ideal annular tissue, and in an attempt to ensure stability, bites must not be overly aggressive in depth. Left circumflex injury can occur and will lead to significant morbidity and mortality (Fig. 49-7). When removal of the old sewing ring will result in severe annular disruption, the ring may be left in place and used as a "neoannulus" for suturing.

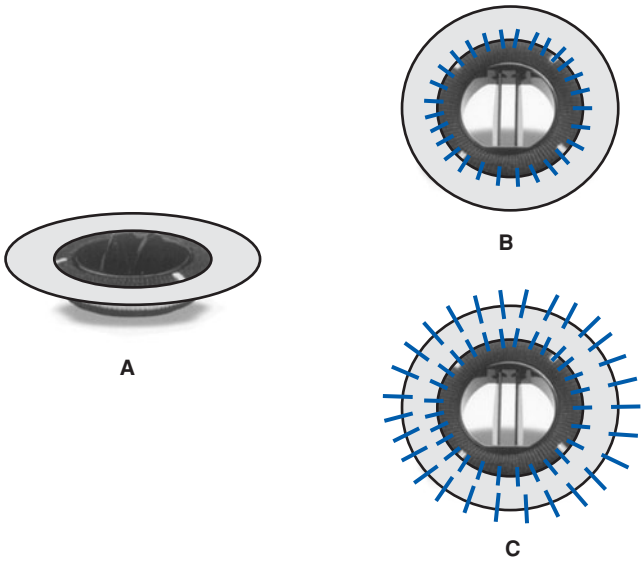

Figure 49-6. Pericardial skirt. Bovine pericardium can be fashioned as a skirt (*A*) and sewn to the sewing ring of the mitral prosthesis (*B*). Standard annular valve sutures are then taken through the sewing ring, the valve is seated, and the skirt is sewn to the left atrium with running technique (*C*). (Carbomedics mechanical valve shown.)

The benefits of preservation of the subvalvular apparatus have been clearly demonstrated during first-time mitral valve replacement.[110] Aside from improved contractile function, disruption of the posterior mitral annulus is avoided. David and colleagues found that preservation of the subvalvular apparatus is also important in reoperative patients.[111] Of 513 reoperative mitral valve replacements, preservation of the posterior subvalvular apparatus was accomplished in 103 (21%) patients, with anterior and posterior preservation occurring in 31 patients (6%). Gore-Tex neochordal construction was performed in 135 reoperative mitral valve replacement patients (26%). Perioperative mortality occurred in 3.6% of redo patients with a preserved subvalvular apparatus (native tissue and/or Gore-Tex reconstruction) versus 13.3% of redo patients without preservation ($p < .001$). Attempts at preservation of the subvalvular apparatus in reoperative patients therefore should be made.

REOPERATIVE TRICUSPID VALVE SURGERY

The need for reoperative tricuspid valve surgery most frequently occurs in high-risk patients. In a recent series of tricuspid valve replacements (TVR) by Filsoufi and colleagues,[112] 72% ($n = 58$) were reoperations. The overall operative mortality in this group was 22% ($n = 18$). Risk factors for mortality included urgent/emergent status, age greater than 50 years, functional etiology, and elevated pulmonary artery pressure. Of the 60 survivors, 26 (43%) died during follow-up. The authors concluded that patients requiring TVR are at high risk, frequently at end-stage functional class. As such, serious consideration of the risks should occur prior to embarking on such procedures.

Tricuspid valve endocarditis is most commonly the result of seeding of the tricuspid valve leaflets during sustained bacteremia.[114] Continued sepsis despite antibiotic therapy, heart failure owing to tricuspid insufficiency, and recurrent multiple pulmonary emboli are indications to intervene surgically in tricuspid valve endocarditis. Complete excision of the tricuspid valve (without subsequent replacement) was first advocated by Arbulu and colleagues.[115] From an infectious disease standpoint, this surgical approach has the obvious advantage of complete extirpation of the infected tissue and avoids placement of any prosthetic material. Although it is tolerated initially, the extirpation procedure inevitably leads to late-onset right-sided failure in the majority of patients.[115,116,117] In a 20-year follow-up of the originally reported series of 55 patients with intractable right-sided endocarditis who underwent tricuspid valvectomy without replacement, 2 patients (4%) died in the

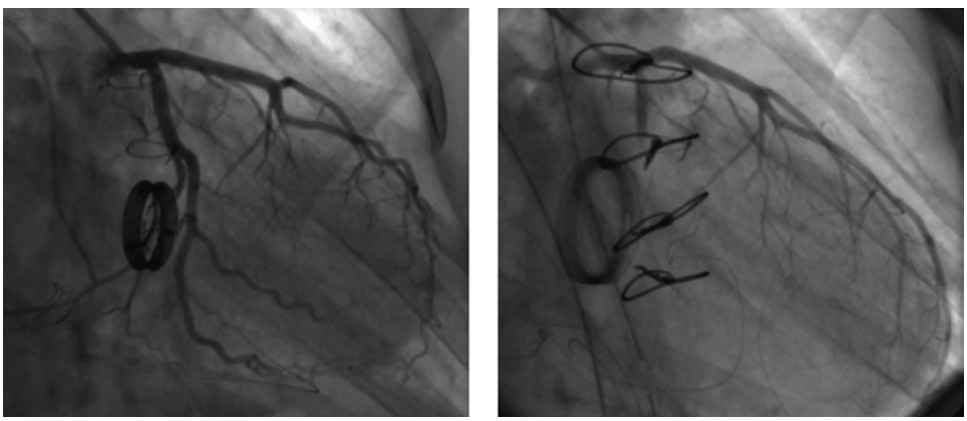

Figure 49-7. Left circumflex artery injury. Preoperative (*left*) and postoperative (*right*) angiograms demonstrating excessive depth of annular sutures leading to left circumflex occlusion.

Table 49–3.

Technical Considerations for Reoperative Valve Surgery
Consider reoperation prior to decline in functional status (NYHA class). Assess RV/aortic proximity to sternum preoperatively with CXR or CT scan
Consider alternate approaches (especially with patent bypass grafts) Right thoracotomy for reoperative MVR Mini-sternotomy for reoperative AVR
Consider alternate cannulation techniques to gain safe entry, e.g., groin, axillary
Address the LIMA-LAD graft if present Dissect it out and clamp it, or Cool and ignore it
Consider ease of implantation in valve choice, e.g., mechanical in homograft
Use "no-touch" technique of bypass grafts
Use a conservative myocardial protection strategy Antegrade and retrograde Systemic cooling Glutamate-aspartate Warm induction/final dose ("hot shot")
If using hypothermic fibrillatory arrest, beware of AI leading to LV distension and/or obscuring operative field
Place external defibrillator pads
Consider the use of antifibrinolytic agents, e.g., aprotinin, amicar

postoperative period owing to right-sided failure. Six patients (11%) required prosthetic valve insertion 2 days to 13 years later for medically refractory right-sided heart failure. Of those who underwent reoperation ($n = 6$), 4 (66%) died. As such, severe hepatic congestion and the need for reoperative valve replacement have made this approach (without replacement) untenable to some practitioners. An alternative treatment option is to perform valvectomy followed by delayed valve replacement 3 to 9 months later.[118,119]

THE HYBRID APPROACH

Recently, hybrid approaches that combine percutaneous intervention (PCI) and valve surgery have been advocated for high-risk reoperative patients. In Byrne's[117] series of 26 patients undergoing initial PCI of culprit lesions followed by valve surgery (*staged hybrid* approach), almost half (46%) the patients underwent reoperation. In this way, surgical time and complexity were minimized. As a consequence, a marked reduction in mortality was observed (3.8%) compared with the predicted mortality calculated by STS algorithms (22%, range 3.5 to 63.5%). These results and those of other similar reports have led to popularization of the hybrid approach to reoperative valve surgery, as well as prompting the creation of hybrid operating rooms (combined catheter laboratory and operating room) throughout the United States.

CONCLUSION

The most common indication for valve re-replacement is structural valve degeneration of a bioprosthesis.[4] After 8 to 10 years of follow-up, biologic valves begin to deteriorate structurally, especially in young patients and in the mitral position, which exposes the valve to higher pressure gradients than seen by the aortic valve. Close follow-up therefore should be encouraged in these patients to avoid missing early degeneration. When patients have been allowed to degenerate into higher NYHA classes, the mortality of reoperative surgery is affected directly (see Table 49-3).

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CHAPTER 50

Valvular and Ischemic Heart Disease

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In recent years, there has been a great deal of progress in coronary artery surgery, nonsurgical treatment of coronary artery disease, and the surgical treatment of valvular heart disease. As thoroughly described in previous chapters, surgery on the beating heart has become commonplace. Interventional therapies for coronary artery obstruction have extended to multivessel disease and continue to change the number and the nature of patients referred for bypass surgery. The options for treatment of valvular disease have continued to expand with advances in techniques for repair of aortic and mitral valves, as well as increases in the choices of valve type for replacement. Other areas of rapidly growing interest are surgical treatment of atrial arrhythmias and the surgical approach to the failing ventricle in dilated ischemic cardiomyopathy. Some of these topics will be discussed in subsequent chapters. All are issues that the surgeon must consider when planning strategy for the treatment of the patient with combined valvular and coronary artery disease. More patients are now presenting with increasingly complex pathology. It is less often that the surgeon sees a patient with simple aortic stenosis and proximal coronary artery disease. Rather, that patient now may have been managed with more aggressive medical therapy or even catheter interventions, and is referred at an older age and is sicker, with more diffuse disease, arrhythmias, and worsening ventricular function. As a result those patients who present for surgery have a higher-risk profile than was previously the case, and require a more flexible and thoughtful approach.

The interaction between the pathophysiologies of valvular heart disease and coronary artery disease is complex. Valvular heart disease alters ventricular function. Coronary artery disease may have an additional impact because of its potential to affect ventricular morphology and physiology. In addition to decreases in contractile strength, regional myocardial infarction may lead to distortion of ventricular shape with resulting effects not only on ventricular function, but also on mitral valve performance. In patients with valvular heart disease, coronary obstructions may be symptomatic or asymptomatic, but the decision to intervene surgically is often made regardless of the presence of symptoms and in order to have a positive effect on the pathophysiology of both diseases.

Under most circumstances, surgeons attempt to treat both valvular and coronary artery diseases simultaneously. At the least, this makes for a longer and more complicated operation with longer myocardial ischemia times. Because of this, combined coronary artery and valve operations usually have a higher risk for early and late mortality than operations for valvular heart disease alone (Fig. 50-1). The increased complexity increases the need for careful preoperative assessment of myocardial function and an understanding of the impact of the changing afterload and preload associated with valve surgery on ventricular function. Therefore, in adult patients with combined valvular and ischemic heart disease, the assessment of intrinsic left ventricular function assumes paramount importance. Clinical signs and symptoms of left ventricular failure should be sought. In addition to history, physical examination, and routine lab tests, preoperative echocardiography is mandatory. Transesophageal echocardiography allows for accurate planning when operative repair is considered. It is also important to distinguish heart failure due to valvular disease from reversible or irreversible myocardial dysfunction due to coronary ischemia. Dobutamine stress echocardiography may be useful in eliciting ventricular size and shape changes that occur under stress and any resultant exacerbation of underlying valve pathology. At cardiac catheterization, left ventricular end-diastolic pressure and pulmonary pressures give additional information about left and right ventricular function and supplement noninvasive evaluation of valve function and coronary anatomy. In centers where it is available, positron emission tomography (PET) scans help detect areas of viable myocardium with reversible ischemia and ischemic dysfunction, as distinguished from

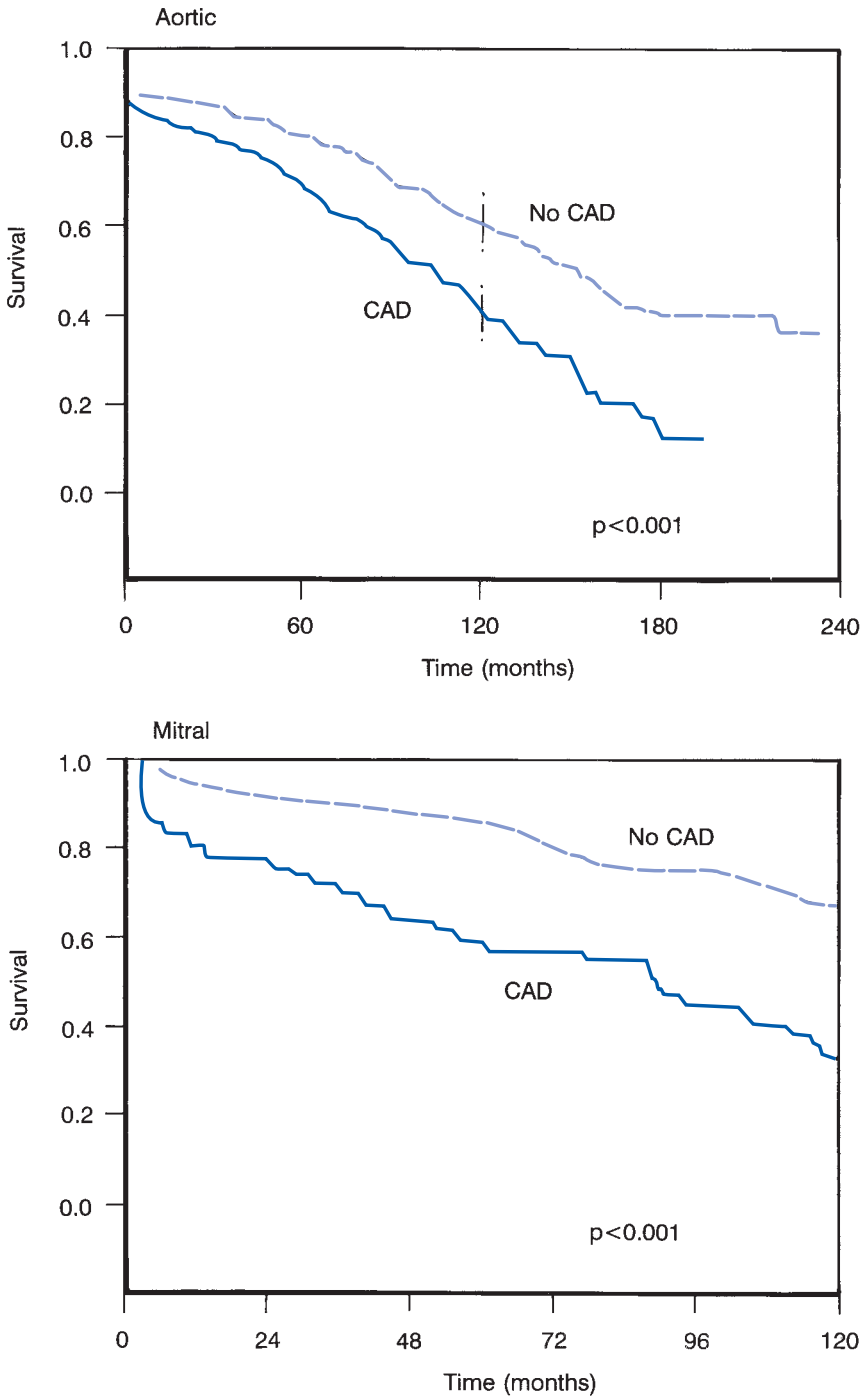

Figure 50-1. Survival after aortic or mitral valve replacement in patients with and without coronary artery disease (CAD). In both cases, long-term survival is significantly worse in patients with coronary disease. (*Adapted with permission from Jones EL, Weintraub WS, Craver JM, et al: Interaction of age and coronary disease after valve replacement: Implications for valve selection. Ann Thorac Surg 1994; 58:378.*)

irreversibly scarred muscle. These assessments are important prior to embarking on combined valve and coronary artery surgery, for they are crucial in estimating operative risk and planning the operative approach.

The assessment of valve pathology is covered in detail in previous chapters on isolated valvular heart disease. As has been noted earlier, coronary angiography is not necessarily required in all patients with valvular pathology who are about to undergo valve surgery. However, given the prevalence of coronary artery disease in aging Western populations, a high index of suspicion leads to the generalized use of coronary angiography in all patients over 40 years of age, and in select younger patients as well.

With present technology and techniques, myocardial revascularization can be added to any valve operation. For the most part, all that is needed is a rational approach, more time, and good myocardial protection. Because of the wide pathophysiologic spectrum of valvular and coronary artery diseases, several frequently encountered valve and coronary artery combinations are considered in this chapter, including (1) aortic stenosis with coronary artery disease (CAD), (2) aortic regurgitation plus CAD, (3) mitral regurgitation plus

CAD, (4) mitral stenosis plus CAD, (5) aortic stenosis and mitral regurgitation plus CAD, and (6) aortic regurgitation and mitral regurgitation plus CAD. Of course, patients may have combined lesions of stenosis and insufficiency, but to avoid unproductive complexity, and because one lesion usually dominates, the somewhat arbitrary categorization noted above will be maintained during the ensuing discussion. For each entity, the clinical presentation, the pathophysiology of the disease state and its correction, the operative and management approach, and short- and long-term results are discussed.

AORTIC STENOSIS AND CORONARY ARTERY DISEASE

Aortic stenosis is one of the more frequently encountered valvular lesions in adult populations. Since degenerative calcific aortic stenosis is most common in patients in their 60s, 70s, and 80s,[1,2] and since congenitally bicuspid valves that become stenotic are more frequent in men who are susceptible to CAD at an earlier age,[3] it is not surprising that the combination of aortic stenosis and CAD is encountered frequently. This disease combination is usually gratifying to treat because the response to surgical relief of aortic stenosis and coronary artery obstructions is significant, immediate, and relatively durable.

Clinical Presentation

Patients with aortic stenosis are asymptomatic initially, but eventually present with angina pectoris, congestive heart failure, syncope, or some combination of these. When significant coronary artery obstructions are present in addition to valvular obstruction, angina pectoris is almost always present. However, angina pectoris can occur in the absence of significant coronary artery obstructions. It is relatively easy to identify symptoms of myocardial ischemia or congestive heart failure in these patients. Neurologic symptoms may be more difficult to elicit, and careful questioning regarding transient symptomatology is required. Symptoms suggestive of carotid artery obstruction should be sought. Specific studies of the carotid arteries may be necessary, especially since the murmur of aortic stenosis may radiate into the carotids and obscure the detection of bruits.

Prominent findings on physical examination include the typical crescendo/decrescendo systolic murmur heard in the aortic area. Signs of congestive heart failure with rales and edema may be present. The electrocardiogram may show left ventricular strain. If the patient suffered recent or old myocardial infarction, electrocardiographic abnormalities typical of infarction also may be present. The echocardiogram typically shows calcified and immobile aortic valve leaflets producing a constricted aortic orifice with the resultant hypertrophied left ventricle. All patients with angina pectoris and all patients with aortic valve disease who are over 40 years of age should have coronary angiography to define coronary anatomy. Right- and left-sided heart catheterization should be performed simultaneously so that complete evaluation of myocardial performance, including measurement of left ventricular end-diastolic pressure and the pulmonary artery pressure, can be obtained. The transaortic valvular gradient also can be determined at catheterization.

The preoperative evaluation of patients with aortic stenosis, coronary artery disease, and poor ventricular function is complicated. Patients with poor ventricular function often generate relatively low transaortic valve gradients. This renders the calculation of valve area and the assessment of critical aortic stenosis less accurate. The morphology of the valve with immobile leaflets and heavy calcification as seen on echocardiography is often an important confirmatory sign that critical aortic stenosis is present. Even in the presence of a small gradient, if echocardiographic signs of significant valve stenosis are present, and if left ventricular intracavitary pressure exceeds 120 mm Hg in systole, mortality rates are acceptable, and response to valve replacement surgery is usually good. A poorly contractile, thinned-out ventricle with low transvalvular gradient and low intracavitary systolic pressure usually suggests that the operation is of high risk and may be of limited or no benefit. A poorly contractile ventricle with normal or increased wall thickness may recover contractile force if a substantial amount of reversibly ischemic myocardium is present and if the degree of aortic stenosis is significant. In addition to ventricular function, other important determinants of the risks and advisability of surgery include patient age, presence of previous cardiac operations, and overall organ function, especially renal function.

The optimal management of a patient with coronary artery disease and mild or moderate aortic stenosis presently remains a matter of some controversy. The dilemma is whether to subject a patient to the lifelong limitations of a valve replacement procedure which may not be necessary, or the prospect of a repeat cardiac operation, perhaps in only a few years, should the aortic stenosis progress.

There is now evidence that favors valve replacement in patients with moderate aortic stenosis who are referred for surgical myocardial revascularization.[4–6] In one study,[4] survival rates at both 1 year and 8 years were superior for patients who underwent valve replacement for moderate aortic stenosis (gradient >30 mm Hg or gradient <40 mm Hg with valve area between 1.0 and 1.5 cm^2). One-year survival was 90% in those having valve replacement compared to 85% in patients having coronary artery bypass graft (CABG) alone. Similarly, 8-year survival (55% versus 39%) was statistically significantly better ($p < .001$).

The rate of progression of aortic stenosis may also provide an indication for valve replacement even without hemodynamically critical disease.[6] For slow progression (<3 mm Hg per year), isolated CABG is preferred for patients with valve gradients <50 mm Hg. In contrast, rapid progression (more than 10 mm Hg per year) favors valve replacement at the time of CABG surgery. One possible exception is in octogenarians with valve gradients <25 mm Hg. Of course, other

individual patient characteristics (life expectancy and other significant comorbidity) may influence the decision as to whether to replace the aortic valve at the time of revascularization surgery.

Pathophysiology

Aortic stenosis produces high ventricular afterload, which ultimately is the source of all the symptoms and signs of aortic stenosis. Most patients with aortic stenosis have hypertrophied and thick-walled left ventricles. Contractile function is initially good, and ejection fraction may be maintained. In later stages of the disease, the ventricle begins to fail with enlargement and global diminution of contractile function. At any stage of the disease, the presence of critical coronary artery obstruction can cause regional wall motion abnormalities. Significant three-vessel CAD of long-standing duration may itself lead to global ventricular dysfunction.

In patients with critical aortic stenosis and good ventricular function, the increased left ventricular afterload is immediately reduced by valve replacement. Since most patients with aortic stenosis have hypertrophied and thick-walled ventricles, intraoperative subendocardial ischemia is more difficult to avoid during aortic cross-clamping. Although revascularization should not decrease left ventricular contractility and may increase it, some myocardial stunning with a temporary decrease in global and regional left ventricular contractility inevitably results from the surgical procedure.[7–10] This, of course, assumes more important pathophysiologic significance in patients with poor ventricular function preoperatively.

Postoperatively, patients may have dramatic improvement in symptoms. Relief of left ventricular outflow obstruction immediately leads to enhanced cardiac output and perfusion of vital organs. In addition, left ventricular function improves both immediately and over time after relief of outflow obstruction and as remodeling ensues. Correction of myocardial ischemia can lead to recruitment of formerly hibernating myocardium[10] with further enhancement of ventricular function.[3]

Operative Management

Monitoring for surgery of the aortic valve and coronary arteries includes catheters and measurements that have become standard for most cardiac surgical operations. These include arterial lines (usually in the radial artery for blood pressure and blood gases) and a pulmonary artery catheter for measurement of pulmonary artery pressures, and cardiac output by thermodilution, with optical sensors for continuous estimation of mixed venous oxygen saturation. While the pulmonary artery catheter has a balloon at its tip, occlusion wedge pressure is rarely measured in the perioperative period because of the danger of pulmonary artery rupture. Particularly useful information is provided by continuous measurement of mixed venous oxygen saturation.

The perfusion setup is standard and similar to that for isolated coronary artery bypass (Fig. 50-2). A single aortic cannula is ordinarily placed in the distal ascending aorta. A single two-stage venous cannula is placed via the right atrial appendage with its tip positioned in the inferior vena cava. After establishment of cardiopulmonary bypass, the patient is usually cooled to 32 to 34°C, during which time a left ventricular vent is positioned via the right superior pulmonary vein. With the heart well emptied, the aortic cross-clamp is applied during a temporary reduction in pump flow. Thereafter, the heart is arrested with cold (4°C) potassium blood cardioplegia and topical irrigation is applied with iced saline solution. After the aorta is opened, the endocardium is intermittently irrigated with iced saline solution to enhance myocardial cooling.

A combination of antegrade and retrograde cardioplegia is optimal. The initial dose of cardioplegia usually is given both ways, half antegrade and half retrograde. Approximately 15 mL/kg is given as the initial dose. Subsequent doses of cardioplegia are given retrograde throughout the operation. This is particularly convenient because retrograde cardioplegia can be given even after the aortic root is opened without significantly disrupting the flow of the operation. Cardioplegia may also be given antegrade via radial and vein grafts after they are attached. This is especially important if a graft has been placed in the right coronary system, as retrograde cardioplegia may not fully protect the right ventricle.

The left internal mammary artery is almost always used to graft the left anterior descending artery when it has a significant obstruction. In general, reversed greater saphenous veins and radial arteries are used for other bypass grafts. The reasoning behind the choice of valve prosthesis is nearly identical to that used in the treatment of isolated valvular heart disease. Any type of prosthesis may be used. However, several issues must be considered. The indications for all types of tissue valves are stronger, as these patients' life expectancies are often shorter. However, these sicker patients may not tolerate well the longer clamp times necessary for the more complex implantation of nonstented tissue valves.

The multiple steps in the combined operation follow a logical sequence. After establishment of cardiopulmonary bypass and insertion of the left ventricular vent, the aorta is clamped and the heart arrested with antegrade and retrograde cold blood cardioplegia and topical hypothermia with iced saline. The first step in the operation is performance of the distal radial artery and saphenous vein bypass grafts. When these are complete, the ventricles may be wrapped in a cooling pad, after which the aorta is opened and aortic valve replacement is carried out using the prosthesis of choice. The aorta is closed completely at this point. The distal anastomosis of the internal mammary artery graft is then made. Following completion of this, air is evacuated from the heart and the aortic cross-clamp is released. A partially occluding clamp is applied to the aorta, and proximal anastomoses are performed when necessary. Alternatively, the proximal anastomoses can be performed with the aortic cross-clamp still in place. While this prolongs the ischemia time, it avoids

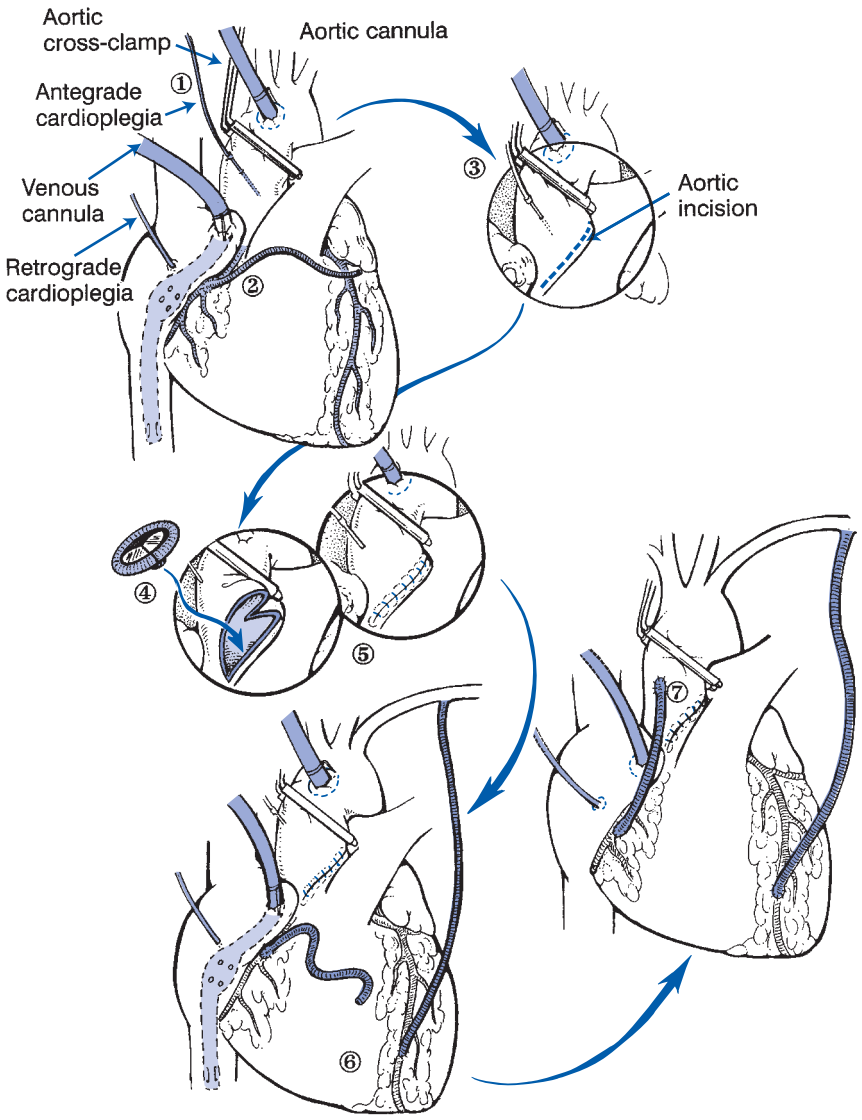

Figure 50-2. Operative sequence for aortic valve replacement and coronary artery bypass grafting. (1) The aorta is cross-clamped and cardioplegia administered antegrade and retrograde. (2) Distal graft anastomoses are performed. (3) The aortotomy is made with an oblique incision into the noncoronary sinus of Valsalva. (4) Aortic valve replacement is carried out using the prosthesis of choice. (5) The aortotomy is closed. (6) The distal mammary artery anastomosis is performed. (7) The proximal graft anastomoses are done. In this case, the proximal anastomoses are done with the aortic cross-clamp in place.

application of a second clamp to the aorta with the potential for disruption of atheromatous debris or injury to the aortic suture line. This consideration is particularly important in patients undergoing reoperations, since the presence of previous bypass grafts can make application of a partially occluding clamp on the aorta difficult. Coordinated sinus rhythm is established after temporary atrial and ventricular pacing wires are positioned. After de-airing is confirmed by transesophageal echocardiography, the left ventricular vent is removed. Of note, atrial-ventricular sequential activation is particularly important to optimize hemodynamic performance in patients with aortic stenosis, because as much as 30% of the cardiac output may be derived from atrial kick as a result of the hypertrophied and noncompliant ventricle that is typical of the patient with aortic stenosis.

Weaning from cardiopulmonary bypass is performed gradually with stepwise diminution of pump flow and increased left ventricular filling. Simultaneous monitoring of the appearance of the heart, pulmonary artery and systemic blood pressures, and mixed venous oxygen saturation is done during weaning. In patients with hypertrophied ventricles, it may be important to keep the left ventricle filled to prevent excessive left ventricular outflow tract obstruction in systole and to provide adequate preload in the noncompliant heart.

In patients with particularly severe ventricular dysfunction who do not wean from bypass, the intra-aortic balloon pump may be used. Two to three attempts to wean from cardiopulmonary bypass using inotropic drugs should be made over a period of 20 to 30 minutes. If weaning from cardiopulmonary bypass is not successful at this point, an intra-aortic balloon pump should be inserted. In some patients, a ventricular assist device is required. Persistent attempts to wean from bypass without mechanical support may be counterproductive because complications from prolonged cardiopulmonary bypass may ensue beyond 30 minutes of elapsed time. As the hypertrophied heart recovers following the ischemic insult, inotropic and mechanical support often

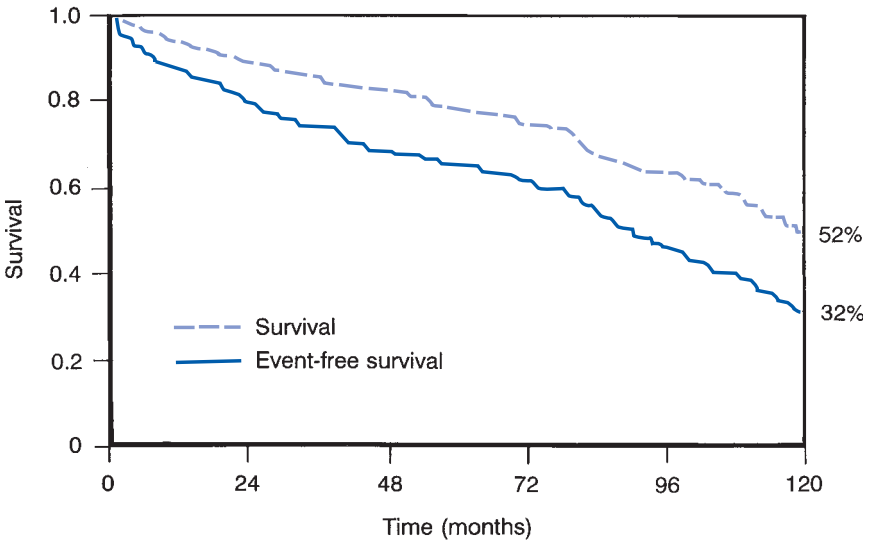

Figure 50-3. Long-term survival and event-free survival after aortic valve replacement and coronary artery bypass grafting in 471 patients. (*Adapted with permission from Lytle BW, Cosgrove DM, Gill CC, et al: Aortic valve replacement combined with myocardial revascularization. J Thorac Cardiovasc Surg 1988; 95:402.*)

can be weaned rapidly. In patients with more impaired ventricular function, weaning, of necessity, occurs more gradually and may take days.

Results

Early hospital mortality after aortic valve replacement and CABG ranges from approximately 2 to 10%.[3,11] Higher mortality is observed in patients with more severe symptoms of heart failure and impaired ventricular function preoperatively. The most frequent causes of operative death are low-output cardiac failure, myocardial infarction, and arrhythmia. Incremental risk factors for hospital death include patient age, functional class, and several measures of ventricular function. In a number of studies, late survival has ranged from 60 to 80% at 5 years and from 50 to 75% at 8 years postoperatively (Fig. 50-3).[12–17] By multivariate analysis, variables leading to reduced late survival include older age, cardiac enlargement, and more severe preoperative clinical symptoms. The use of a mechanical prosthesis at valve replacement has been associated with lower long-term survival and lower long-term event-free survival (Fig. 50-4). As discussed earlier, choice of valve type is a complex issue in combined valve–coronary artery surgery. This is a decision that cannot be made without consultation with the patient. A frank discussion of the advantages and drawbacks of each approach continues to be an important component of the preoperative evaluation and planning for this type of surgery.

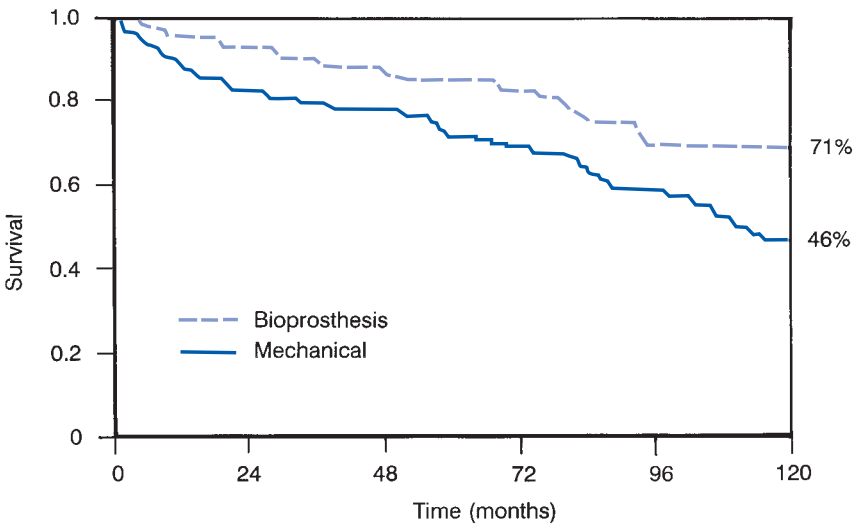

Figure 50-4. Long-term survival advantage for patients undergoing aortic valve replacement and coronary artery bypass grafting using a bioprosthesis (n = 218) versus a mechanical valve (n = 253). *(Adapted with permission from Lytle BW, Cosgrove DM, Gill CC, et al: Aortic valve replacement combined with myocardial revascularization. J Thorac Cardiovasc Surg 1988; 95:402.)*

AORTIC REGURGITATION AND CORONARY ARTERY DISEASE

Significant aortic regurgitation occurs less often in older populations, and is also less often encountered with CAD. Most series of patients undergoing aortic valve replacement and CABG include a relatively small number (10 to 25%) of patients with aortic insufficiency.[3,11–14] While the operative management of patients with aortic regurgitation and CABG is similar to that previously described, aortic insufficiency produces different pathophysiology that has implications for perioperative management, and the presence of an incompetent aortic valve introduces subtle nuances to the intraoperative management of these patients.

Clinical Presentation

Patients with aortic regurgitation and coronary artery disease usually present in one of three ways. The aortic regurgitation may be asymptomatic and detected incidentally during evaluation for symptomatic coronary disease. Second, the patient may be asymptomatic, yet a routine physical examination reveals a murmur of aortic insufficiency that leads to cardiac evaluation and detection of coronary disease. Finally, patients may present relatively late in the course of valvular heart disease with congestive heart failure due to decompensation of the volume-overloaded left ventricle or ischemic damage or both. Patients therefore may present with no symptoms and essentially normal physiology, a classic ischemic syndrome, or congestive heart failure. The physical signs also will depend on the nature of the presentation. In general, all patients with aortic insufficiency have an audible early diastolic blowing murmur. In late stages of the disease, signs of congestive heart failure, including rales and peripheral edema, may be present.

The preoperative evaluation of a patient with aortic insufficiency and CAD is no different from that previously described for patients with aortic stenosis and ischemic heart disease. Echocardiography is particularly useful in detecting aortic regurgitation because the murmur is sometimes subtle and difficult to detect. In addition, echocardiography gives important information regarding both ventricular contractile function and ventricular size. Since many patients with aortic regurgitation are asymptomatic, careful evaluation for changes in ventricular size or function is important because the presence of these changes may constitute an indication to proceed with surgical intervention in the absence of symptoms.

Pathophysiology

Aortic regurgitation increases left ventricular preload and causes left ventricular dilatation. Dilatation does not occur acutely, and patients with acute aortic insufficiency are often severely symptomatic due to a sudden increase in left ventricular end-diastolic pressure and decrease in net forward cardiac output. Left ventricular dysfunction due to CAD also can produce left ventricular dilatation. Valve replacement relieves some of the preload but does not immediately result in improved left ventricular contractility. Revascularization may produce improved contractility by recruitment of hibernating myocardium.[7,10] This operation does not increase left ventricular afterload.

The indications for surgery in aortic regurgitation continue to be somewhat controversial, and are reviewed in depth in the section on aortic valve disease. The evaluation of valvular pathology proceeds along similar lines as those described above, with emphasis on echocardiographic results. However, this evaluation is somewhat more difficult when CAD is also present, because there might be an impact on ventricular function that revascularization may or may not improve. Nevertheless, except in advanced stages of diffuse three-vessel coronary artery disease, myocardial abnormalities due to coronary artery obstructions are usually regional and can be distinguished from global dysfunction due to volume overload from the insufficient valve. Making this distinction is of paramount importance in the preoperative assessment and risk stratification of these patients. Again, decisions about timing of aortic valve surgery in the presence of CAD are different than in cases of isolated valvular disease, with emphasis on fixing the valve earlier in the course of the disease.

Operative Management

The operation is conducted in a fashion similar to that described for aortic stenosis and CAD. However, in the presence of aortic insufficiency, antegrade cardioplegia in the aortic root cannot be given because the cardioplegia solution leaks into the left ventricle. In general, retrograde cardioplegia is used under these circumstances, with doses of antegrade cardioplegia given into the coronary ostia with hand-held catheters after the aorta has been opened.

Considerations in weaning from cardiopulmonary bypass are somewhat different from those described for aortic stenosis. Patients with aortic regurgitation are more likely to have dilated ventricles that tolerate increases in afterload poorly. Therefore, successful perioperative management of these patients requires careful attention to adjustments in preload and afterload. In patients with volume-overloaded ventricles due to aortic insufficiency, vasodilators may be an important component of postoperative management. Drugs such as milrinone and dobutamine have a role because they provide both inotropic support and ventricular unloading. The mechanical ventricular unloading device—the intra-aortic balloon pump—also may be used. It is rare that mechanical circulatory assistance with a ventricular assist device is required. Its use should be reserved for younger patients without comorbid conditions in whom prompt improvement in ventricular function is anticipated.

Results

Early results after operation for aortic regurgitation and CAD include an expected hospital mortality rate of less than 10%.[3,11] Incremental risk factors for hospital death are similar to those described previously, with advanced age and poor ventricular function having the greatest impact. Late survival after this operation is similar to that for aortic stenosis and CAD (see Fig. 50-3).[12–17] Despite the impression that patients with aortic insufficiency and CAD do not do as well as those with aortic stenosis, aortic insufficiency has not been an independent risk factor for early or late mortality.[3] Interestingly, recovery of ventricular ejection fraction does have a favorable impact on late mortality. When ventricular dilatation and diminution in ventricular systolic function occur in the setting of aortic regurgitation, these often are irreversible changes. While some improvement of function can occur with elimination of the volume overload and with revascularization in patients with combined valvular and coronary artery diseases, there may be less recovery of ejection fraction in patients with aortic insufficiency compared with aortic stenosis. Failure of recovery of ventricular function in this setting may have an impact on long-term survival, but not one so great as to render aortic insufficiency an independent risk factor for late death.

MITRAL REGURGITATION AND CORONARY ARTERY DISEASE

Successful management of patients with mitral regurgitation and CAD remains one of the greater challenges in adult cardiac surgery. This group of patients tends to be sicker, and their surgical care is accomplished at higher risk.[1,18–21] This is almost certainly because of the complex interaction between the left ventricle and the mitral valve. Normal valve function depends on normal function of the entire mitral apparatus, which includes the ventricular wall and the papillary muscles. Similarly, normal ventricular function depends on competence of the mitral valve. Therefore, there is unique potential for CAD and mitral valve disease to interact, making the patient sicker, the pathophysiology more complicated, and the surgical management more difficult.

In patients with preserved ventricular function, the pathophysiology and management strategies are not significantly different from those for treatment of isolated mitral regurgitation or CAD. Of course, the operation is more complex and longer, and therefore, as has been described previously, a carefully conceived operative plan with special attention to myocardial preservation is important. However, the more interesting problems are in those patients with mitral insufficiency and CAD who do not have normal hearts, and in fact, most patients with this disease combination do not have normal ventricular function.

Clinical Presentation

The spectrum of clinical presentation ranges from patients who are asymptomatic to those who are moribund in cardiogenic shock. The patient may have no signs or symptoms of heart disease, or may have predominant symptoms of failure, ischemia, or both. Finally, patients may present with acute syndromes often related to myocardial infarction and the sudden development of mitral insufficiency. These patients are extremely ill when they present in congestive heart failure and cardiogenic shock. Management of these patients is the most difficult.

Findings on physical examination obviously relate to the nature of the presentation, and can range from signs of mild mitral insufficiency to severe congestive failure or cardiogenic shock. An electrocardiogram may show evidence of ischemic heart disease. All patients should undergo echocardiography. The echocardiogram is particularly useful because it gives information both about the valve and about ventricular geometry and function. Transesophageal echocardiography is especially useful in the evaluation of mitral function. Assessments of mitral valve leaflet structure and function, chordal anatomy, and functioning of the papillary muscles and adjacent ventricular wall via transesophageal echocardiography are invaluable. All these data are important in planning the operative approach to the mitral valve and assessing the risk of surgery. Cardiac catheterization is performed in these patients for the same reasons outlined for patients with aortic valve disease. Any patient with angina pectoris or a positive stress test and any patient with mitral insufficiency over the age of 40 should have coronary angiography before surgery. As noted previously, cardiac catheterization also provides information about hemodynamics that is important in planning the operation.

Pathophysiology

Mitral regurgitation increases left ventricular preload and decreases afterload at the expense of cardiac output. Ischemic damage causes ventricular dilatation with decreased contractility and an increase in left ventricular filling pressures. These lesions combined cause synergistic decompensation and can produce pulmonary hypertension and secondary tricuspid regurgitation. Cardiac output may be very low, especially in patients with acute mitral insufficiency. Mitral insufficiency may occur in association with CAD, but often the CAD is the cause of mitral insufficiency. The pathophysiology of primary mitral insufficiency can be due to involvement of the valve leaflets, the annulus, the subvalvular apparatus, or some combination of all of the above. A detailed understanding of the pathophysiology of primary mitral insufficiency is important for planning the operative approach.

When CAD is the cause of mitral insufficiency by its effect on regional and global ventricular function, the pathophysiology is more complicated. Global ventricular

dysfunction from CAD can produce ventricular dilatation with mitral annular dilatation and subsequent mitral insufficiency. The jet of mitral regurgitation is usually central and often can be managed with annuloplasty. Alternatively, regional wall motion abnormalities involving the papillary muscle and the adjacent ventricular wall can produce dynamic changes that produce insufficiency of the mitral valve. These abnormalities are now becoming better understood and are discussed more completely in Chapter 41.

Correction of mitral insufficiency either by valve repair or valve replacement produces an instantaneous increase in left ventricular afterload. The ventricle no longer has the low-impedance left atrial chamber in which to eject blood and must overcome systemic afterload in systole. Even when myocardial ischemia is reversible, recruitment of hibernating myocardium may take time. These factors in combination with the sudden increase in left ventricular afterload are responsible for the difficulty and increased risk of managing this entity. Secondary right ventricular failure may be present or ensue because pulmonary hypertension does not decrease immediately after mitral valve repair or replacement, and CAD also may affect right ventricular function.

Symptomatic mitral insufficiency and symptomatic CAD are the usual indicators for combined surgery. As noted, patients with acute illnesses may be in extremis. Ventricular dysfunction is not per se a contraindication to surgery, especially if it is due to reversible ischemia. Patients with global irreversible cardiomyopathy and mitral insufficiency should not be operated on because the ventricle tolerates the increase in afterload poorly and results are unsatisfactory. Estimation of the viability of the myocardium and demonstration of reversible ischemia using thallium or PET scanning therefore are important.

Finally, with the left atrial enlargement that is common, patients often present with chronic or recent-onset atrial fibrillation. This further acts to reduce cardiac output and may also benefit from ablation therapy at the time of surgery.

Operative Management

One important preoperative decision in patients with mitral regurgitation and CAD is whether there is, in fact, any need for valve surgery. Since mitral regurgitation in the presence of CAD may be functional and due to reversible myocardial ischemia, revascularization alone may improve mitral regurgitation. It is important, therefore, to distinguish organic from functional mitral insufficiency. Intraoperative transesophageal echocardiography is an essential tool for assessment of mitral valve function in this setting.[22] Patients with no preoperative congestive heart failure, absent or only transient murmurs of mitral insufficiency, normal pulmonary pressures in the operating room, and trace to mild mitral insufficiency by transesophageal echocardiography after induction of anesthesia probably do not need mitral valve surgery at all.[23] Many of these patients will appear to have more mitral regurgitation and higher pulmonary pressures at catheterization or when they are ischemic than when they are under anesthesia. Clearly, however, those with moderate to severe insufficiency will need to have the valve regurgitation addressed.[24] Several recent studies suggest that the quality of modern surgical results justifies a more aggressive approach to valve repair in patients with moderate mitral insufficiency and CAD.[25–28] Some patients with ventricular enlargement and annular dilation secondary to CAD and/or mitral insufficiency may be managed with annuloplasty alone. Patients with organic mitral valve disease such as leaflet prolapse, chordal rupture, or chordal elongation need primary repair. Restricted leaflet motion is frequently a complication of ischemic changes in ventricular shape. Standard leaflet resection techniques for posterior flail segments are indicated. In sicker patients, and those with restricted leaflet motion or more complex lesions (severe myxomatous degeneration), an edge-to-edge leaflet approximation (the "Alfieri stitch") may be appropriate.[29] This is especially true in patients with extensive calcification of the posterior annulus or severely restricted posterior leaflet motion.[30] As noted elsewhere, results of mitral repair and CABG are superior to those of mitral valve replacement, which should be avoided except in the setting of acute, severe mitral insufficiency due to papillary muscle rupture.[31]

Anesthetic considerations are similar to those described previously, although it must be recognized that these patients are in general sicker than patients with aortic valve disease, and in some cases are among the sickest patients treated. Monitoring includes a radial artery line and a pulmonary artery catheter. As suggested earlier, transesophageal echocardiography is particularly important in this group of patients. Setup for cardiopulmonary bypass is similar to that described earlier. However, both venae cavae are cannulated for venous return (Fig. 50-5). This is usually accomplished by introducing the cannulas through purse-strings in the superior vena cava and low in the right atrium. After clamping the aorta, cardioplegia is administered antegrade and then retrograde. Subsequent doses of cardioplegia are given retrograde. As with aortic disease, special attention must be paid to protecting the right ventricle during periods of prolonged retrograde cardioplegia.

The most common incision is in the wall of the left atrium anterior to the right pulmonary veins. Preparative dissection of the interatrial groove usually facilitates exposure using this incision. Another choice for exposure of the mitral valve is the transseptal approach. This allows for direct visual insertion of the retrograde cardioplegia catheter through a purse-string, and affords an excellent view of the mitral valve, especially if the left atrium is not enlarged, without excessive stretching of the right atrium or the cavae. If necessary, the incision can be carried up into the dome of the left atrium for even greater exposure. Other incisions are discussed in the section on mitral valve disease. Choice of coronary artery grafts is similar to that for aortic disease.

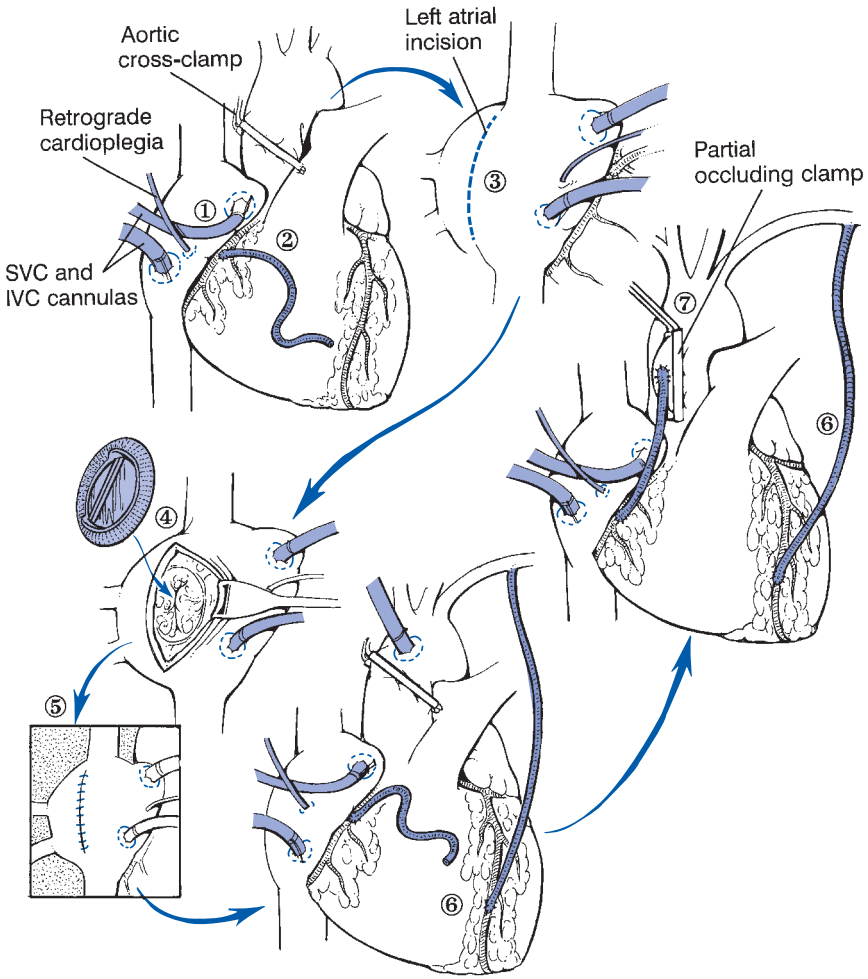

Figure 50-5. Operative sequence for mitral valve replacement and coronary artery bypass grafting. (1) Cannulation and cross-clamping of the aorta with antegrade and retrograde cardioplegia. (2) Distal vein graft anastomoses are performed. (3) Left atriotomy is performed after dissection in the interatrial groove. (4) Mitral valve repair or replacement with the prosthesis of choice. (5) Closure of left atriotomy. (6) Distal anastomosis using the mammary artery is performed. (7) Proximal graft anastomosis is done. In this case, the cross-clamp has been removed and a partially occluding aortic clamp used.

The first choice in surgery for mitral insufficiency is valve repair. When valve repair is impossible, valve replacement follows the same guidelines set forth in Chapter 43. However, in patients with this disease combination and an abbreviated life expectancy, a stronger rationale for use of a tissue prosthesis may exist.[32] Regardless of the type of prosthesis, an effort should be made to retain continuity between the papillary muscles and the mitral annulus. The attachments to the posterior leaflet usually can be retained in their entirety without interfering with prosthesis function. The anterior leaflet must be resected either in whole or in part to avoid left ventricular outflow tract obstruction or interference with mechanical valve function. However, major chordal attachments may still be preserved and incorporated into the annular suture line. Regardless, standard practice is to retain continuity between the mitral annulus and the subvalvular apparatus whenever the mitral valve is replaced. Short- and long-term ventricular function appear to be better when this is done. Obviously, in this clinical setting, in which ventricular function has a significant impact on short- and long-term results, all steps should be taken to ensure optimal myocardial performance postoperatively.

Patients with papillary muscle rupture due to infarction are usually extremely sick. Valve replacement is almost always required. Some surgeons have reported success with reimplantation of the papillary muscle. This strategy is risky in these sick patients because the operation must be both expeditious and effective. Multiple attempts to achieve mitral valve competence are tolerated poorly. A reimplanted, infarcted papillary muscle does not necessarily restore mitral valve competence and also may be subject to late breakdown.

As in combined aortic valve and coronary artery surgery, distal graft anastomoses are performed first (see Fig. 50-5). At this point, after the atrium has been opened, it may be prudent to undertake an arrhythmia ablation procedure in selected patients. Radiofrequency or cryoablation probes can be used to create a lesion set within the left and right atria, as described elsewhere in this text (see Chapter 58). The left atrial appendage may be oversewn. Valve repair or replacement is then carried out, followed by performance of the mammary artery anastomosis. Proximal graft anastomoses can be done either after release of the cross-clamp and application of a partially occluding clamp or with the cross-clamp in place. Weaning from cardiopulmonary bypass is similar to that in patients with aortic insufficiency and CAD. Again, in this group of patients, afterload reduction using drugs or the intra-aortic balloon pump may be required. Inotropic drugs with

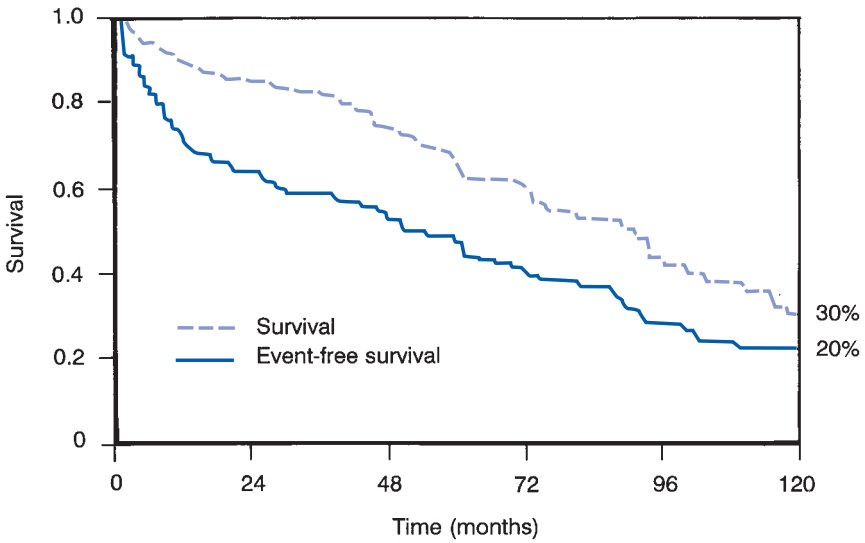

Figure 50-6. Survival and event-free survival after mitral valve replacement combined with coronary artery bypass grafting in 278 patients. (*Adapted with permission from Lytle BW, Cosgrove DM, Gill CC, et al: Mitral valve replacement combined with myocardial revascularization: Early and late results for 300 patients, 1970 to 1983. Circulation 1985; 71:1179.*)

afterload-reducing capabilities such as dobutamine and milrinone may be indicated. The surgeon should have a low threshold for adding a drug such as milrinone to epinephrine because this combination has some theoretical advantages as a result of positive inotropic and unloading effects, as well as a reduction in pulmonary artery pressures. Alternatively dobutamine, which has both central inotropic and peripheral afterload-reducing effects, may be a first-choice drug. Since some of these patients are particularly sick, little time should be wasted in futile attempts to wean from cardiopulmonary bypass on medications and without the intra-aortic balloon. There should be a low threshold for insertion of the intra-aortic balloon in patients whose hemodynamics may be quite tenuous for hours to days after surgery, especially when the operation is an emergency.

Another consideration for a select subset of patients with this disease is the incorporation of ventricular remodeling into the operation. A large body of work is now emerging indicating that patients with anterior infarctions and dilated cardiomyopathy, mitral insufficiency, and CAD will benefit from exclusion of the infarcted area and remodeling of the left ventricle with return to elliptical shape.[33] This can be performed safely, along with mitral repair and coronary revascularization, in carefully selected patients. The result can be a dramatic increase in ejection fraction with greatly improved postoperative function.

Strict attention must be paid to right ventricular function in this group of patients, although right ventricular failure is more common in the setting of mitral stenosis. Right ventricular failure must be anticipated and correctly diagnosed and managed. The presence of a falling systemic blood pressure and cardiac output with falling pulmonary artery pressure and/or pulmonary capillary wedge pressure should prompt a search for right ventricular failure, which is manifested by a rising central venous pressure. Failure to recognize this and inappropriate administration of fluid can lead to irreversible right ventricular failure.

Results

Hospital mortality for this group of patients is higher than for most other forms of acquired heart disease. Early mortality rates range from 3% in good-risk patients to 60% in the sickest patients.[15–21,34] The higher mortality is seen in patients with acute ischemic mitral valve disease and severe ventricular dysfunction who require emergency surgery. Incremental risk factors for early death include age, functional class, ventricular function, pulmonary pressures, and cardiogenic shock. Late survival in patients with this entity is 55 to 85% at 5 years and 30 to 45% at 10 years (Fig. 50-6).[15–21,35]

In general, patients who survive surgery have good relief of symptoms. Significant risk factors for late death include preoperative functional class, left ventricular function, and an ischemic as opposed to a degenerative etiology for mitral insufficiency (Fig. 50-7).

MITRAL STENOSIS AND CORONARY ARTERY DISEASE

Patients with mitral stenosis and CAD usually have good left ventricular function and often are a relatively easy group of patients to take care of because the mitral stenosis protects the left ventricle from hemodynamic loads. CAD may cause left ventricular dysfunction, but this is unusual. A more usual concern is right ventricular dysfunction postoperatively, since in patients with mitral stenosis, pulmonary hypertension, with its potential to produce right ventricular failure and tricuspid insufficiency, is often encountered.

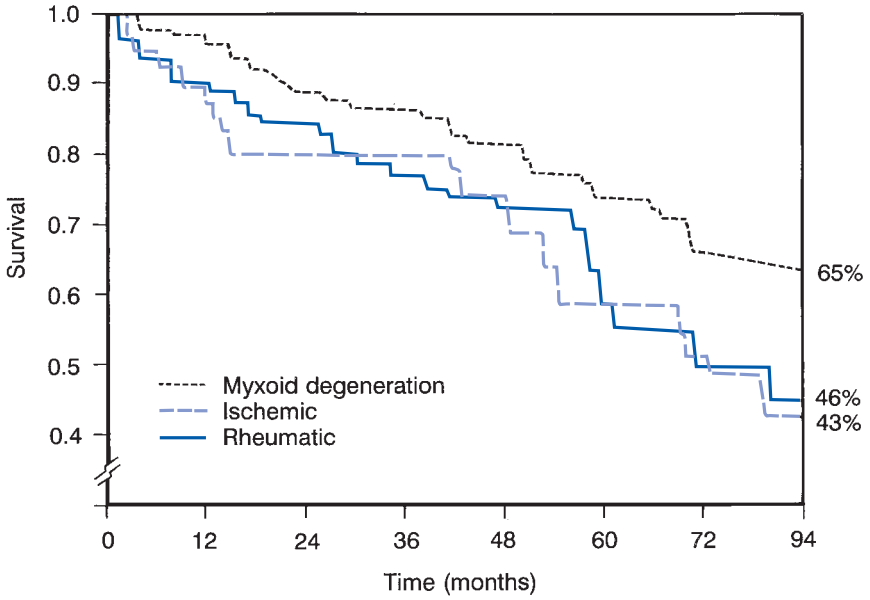

Figure 50-7. Survival after mitral valve replacement and coronary artery bypass grafting based on the etiology of mitral valve disease. A survival advantage for patients with myxoid degeneration of the mitral valve is demonstrated. (*Adapted with permission from Lytle BW, Cosgrove DM, Gill CC, et al: Mitral valve replacement combined with myocardial revascularization: Early and late results for 300 patients, 1970 to 1983. Circulation 1985; 71:1179.*)

Clinical Presentation

As implied earlier, mitral stenosis is usually the dominant lesion in patients with mitral stenosis and CAD. Therefore, symptoms usually are due to the valvular lesion. Patients may have congestive heart failure with shortness of breath, orthopnea, and fatigue. Atrial fibrillation is a common presenting symptom with mitral stenosis. Patients with mitral stenosis and CAD infrequently have angina as a presenting symptom. The electrocardiogram may show evidence of right ventricular strain and hypertrophy. Transesophageal echocardiography confirms the diagnosis of mitral stenosis and usually shows a small left ventricle with preserved contractile function. The right ventricle may be enlarged and hypertrophied. Cardiac catheterization further confirms the diagnosis by showing a gradient across the mitral valve. Other important information gleaned from invasive catheterization includes a measurement of the pulmonary artery pressures and central venous pressure. The degree of pulmonary hypertension is a marker of the severity and duration of mitral stenosis and alerts the surgeon to the potential for right ventricular failure postoperatively. An elevated central venous pressure is a potential sign that right ventricular decompensation has already occurred. Coronary angiography should be done in all patients with angina pectoris, and as noted before, in any patient over age 40 in whom mitral valve surgery is anticipated.

Pathophysiology

Unlike the other entities described, mitral stenosis and CAD do not have significantly synergistic pathologic effects on the heart. CAD usually has more profound effects on the left ventricle, which remains protected in patients with mitral stenosis until late in the disease. The right ventricle is the chamber most vulnerable to the effects of long-standing mitral stenosis, as noted. However, even with right ventricular hypertension, the potential impact of CAD on right ventricular function in adults is usually insignificant. In the rare patient with diffuse CAD and ischemic cardiomyopathy, the risk of surgery is enhanced because of global ventricular dysfunction.

The indications for surgery, not surprisingly, are usually determined by the severity of the mitral stenosis. Patients with significant heart failure and low cardiac output from mitral stenosis whose calculated valve area is less than 1 cm^2 should have a mitral valve operation and associated bypass grafting if significant CAD is present. A rare patient may have significant CAD and mild mitral stenosis detected incidentally. These patients may be managed with CABG and mitral commissurotomy if this is technically feasible.

Operative Management

Monitoring, perfusion setup, and operative sequence are identical to those described for treatment of mitral regurgitation and CAD. Transesophageal echocardiography is useful to assess both the feasibility of mitral commissurotomy (or more extensive mitral repair) and the results of valvuloplasty. In most patients with mitral stenosis, valve replacement is required because irreversible damage to the leaflets and subvalvular apparatus is usually extensive. A mechanical prosthesis is used most often because the majority of patients have chronic atrial fibrillation from left atrial enlargement, and long-term anticoagulation is indicated. However, the potential benefits of an ablation procedure (as discussed above) within the left and right atria also may have an impact on prosthetic choice.

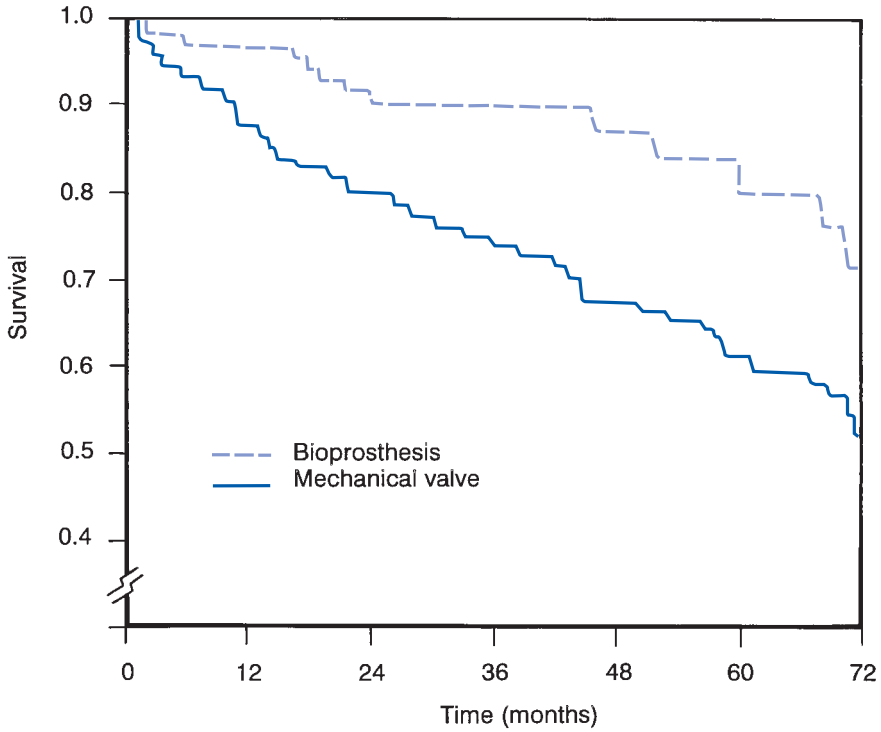

Figure 50-8. Comparative survival after mitral valve replacement and coronary artery bypass grafting for patients having mitral valve replacement with a bioprosthesis (n = 82) or mechanical valve (n = 100). *(Adapted with permission from Lytle BW, Cosgrove DM, Gill CC, et al: Mitral valve replacement combined with myocardial revascularization: Early and late results for 300 patients, 1970 to 1983. Circulation 1985; 71:1179.)*

Transesophageal echocardiography is often important in monitoring both right and left ventricular function postoperatively. The early differentiation between left and right ventricular failure is facilitated by the use of this modality during weaning from cardiopulmonary bypass. If inotropic drugs are required, their selection should be based in part on the consideration that pulmonary hypertension and right ventricular failure might be an important component of the clinical syndrome. Drugs such as isoproterenol, dobutamine, and especially milrinone (the latter often in combination with norepinephrine) may be indicated for their combined beneficial effects on right ventricular contractility and pulmonary vascular resistance. Judicious use of inotropic drugs and careful administration of fluid should result in optimal cardiac output. The intra-aortic balloon is almost never useful in these patients because right ventricular problems predominate, and the intra-aortic balloon has little direct effect on right ventricular function. Temporary support with a right ventricular assist device may be employed because mitral valve replacement can lead to dramatic decreases in pulmonary artery pressures and subsequent recovery of right ventricular function.

Results

Early mortality after combined surgery for mitral stenosis and CAD is approximately 8%.[12–14,15–18,27] This is not significantly different from results of surgery in lower-risk patients with mitral regurgitation and CAD. Long-term probability of survival is approximately 50% at 7 years and in one series was not significantly different from that for patients with ischemic mitral insufficiency.[15–17,19–21,35] Interestingly, long-term survival of patients with myxoid degeneration of the mitral valve and CAD (65%) was significantly better than survival of the patients with rheumatic or ischemic mitral valve disease and CAD in at least one series (see Fig. 50-7).[19] As implied, rheumatic valve pathology is a risk factor for late death, as is poor preoperative left ventricular function and the presence of ventricular arrhythmias. Interestingly, the use of a bioprosthesis without anticoagulants confers both a survival advantage and an event-free survival advantage in these patients (Fig. 50-8). These data lend support to the hypothesis that biologic valves may be appropriate for mitral replacement in older patients and in those with CAD, whose expected life span may be shorter than the expected durability of the replacement device.[32]

AORTIC STENOSIS, MITRAL REGURGITATION, AND CORONARY ARTERY DISEASE

Patients with aortic stenosis, mitral regurgitation, and CAD often present with aortic stenosis as the predominant lesion. It is important to note that functional mitral regurgitation may improve after relief of aortic stenosis with concomitant reduction in left ventricular systolic pressure. If the mitral valve is not intrinsically diseased, it may not require surgery.

Clinical Presentation

Patients with these diseases often present identically to patients with aortic stenosis and CAD, but may do so earlier because of the combined valvular lesions. Angina, congestive heart failure, and syncope may be presenting symptoms alone or together. It is relatively uncommon for symptoms due to mitral insufficiency to be predominant. Echocardiography is an extremely important tool in this disease combination. Careful evaluation of the mitral valve, often using transesophageal echocardiography, is necessary to determine the degree of intrinsic mitral valve disease, since improvement in mitral insufficiency is expected after aortic valve replacement and relief of left ventricular obstruction. It is critical to determine whether or not anatomic abnormalities of the mitral valve are present that might not reverse with aortic surgery alone. Of course, cardiac catheterization is required, as it is for the other disease entities described.

Pathophysiology

Aortic stenosis increases left ventricular afterload and the potential amount of mitral regurgitation. The left ventricle may be better preserved in this setting than in patients with isolated mitral insufficiency and CAD. Also as noted, the mitral valve may not be structurally diseased. Because of earlier presentation, pulmonary hypertension and subsequent right ventricular failure and tricuspid valve incompetence are usually not prominent features. Because relief of outflow obstruction helps left ventricular function immediately, these patients often do quite well.

The indications for surgery are usually the same as for aortic stenosis and CAD. Critical aortic stenosis, when documented, requires valve replacement; if significant CAD is present, coronary artery bypass grafts are also done. Mitral valve repair is almost always necessary and possible when mitral insufficiency is moderate to severe and/or anatomic abnormalities of the valve are detected. If absolutely necessary, valve replacement may be performed. End-stage ventricular dysfunction with ventricular dilatation and myocardial thinning is the primary cardiac contraindication to surgery.

Operative Management

Anesthesia and perfusion setup are identical to those described for mitral valve and coronary artery surgery. In this entity, intraoperative transesophageal echocardiographic monitoring plays an important role because the intraoperative assessment of mitral valve function before and after bypass is critical. The choice of valves for aortic replacement is the same as described previously. In most situations, however, bioprosthetic valves should be considered, especially if the mitral valve is to be repaired.

Under almost all circumstances in which anatomic abnormalities of the mitral valve are detected or in which mitral insufficiency is severe, mitral valve repair should be considered. Annuloplasty may be all that is required if the mitral insufficiency is due to annular dilatation and there is a symmetric central jet of regurgitation. More complex disease may require more extensive repair or even replacement of the mitral valve. When the decision is made not to operate on the mitral valve, transesophageal echocardiography is done to assess residual mitral valve dysfunction following aortic valve replacement and coronary artery bypass surgery. If moderate or severe mitral regurgitation remains, the valve is repaired or replaced. This is technically more difficult after the aortic valve has been replaced, since the prosthesis in the aortic position hinders exposure of the mitral valve. Therefore, every effort must be made to assess mitral valvular morphology and function before starting cardiopulmonary bypass.

As in the other entities described, distal graft anastomoses are performed first (Fig. 50-9). After these grafts are completed, the aorta is opened and the aortic valve is resected. Replacement of the aortic valve, however, is deferred until after the mitral valve operation. However, it is important to resect the aortic valve before replacing the mitral valve to improve exposure of the latter. In addition, sutures used for mitral valve repair or replacement, if placed first, may become disrupted during resection or débridement of the aortic valve and annulus. After resection of the aortic valve, the atrium is opened and the mitral operation is performed. The atrium is closed with a vent across the mitral valve. The aortic valve is then replaced and the aorta is closed. The internal mammary artery graft is done last. Proximal graft anastomoses can be done with the aortic cross-clamp in place or after removal of the cross-clamp and placement of a partially occluding clamp, as described previously.

As noted, this group of patients may have preserved ventricular function, and weaning from cardiopulmonary bypass may be relatively easy. Inotropic drugs and the intra-aortic balloon can be used as indicated.

Results

Early hospital mortality is 12 to 16%.[36,37] Not surprisingly, predictors of early death include severe mitral regurgitation, lower ejection fraction with more severe symptoms of heart failure, and the presence of triple-vessel CAD. Late survival is approximately 60% at 72 months (Fig. 50-10). Multivariate predictors of late mortality include advanced symptoms of heart failure and increased severity of mitral insufficiency.

AORTIC AND MITRAL REGURGITATION AND CORONARY ARTERY DISEASE

Not many patients have regurgitation of both the aortic and mitral valves and CAD. These patients usually have rheumatic heart disease and present early in the course of the disease. Aortic regurgitation may be the primary valve pathology in a patient with significant CAD. Patients may

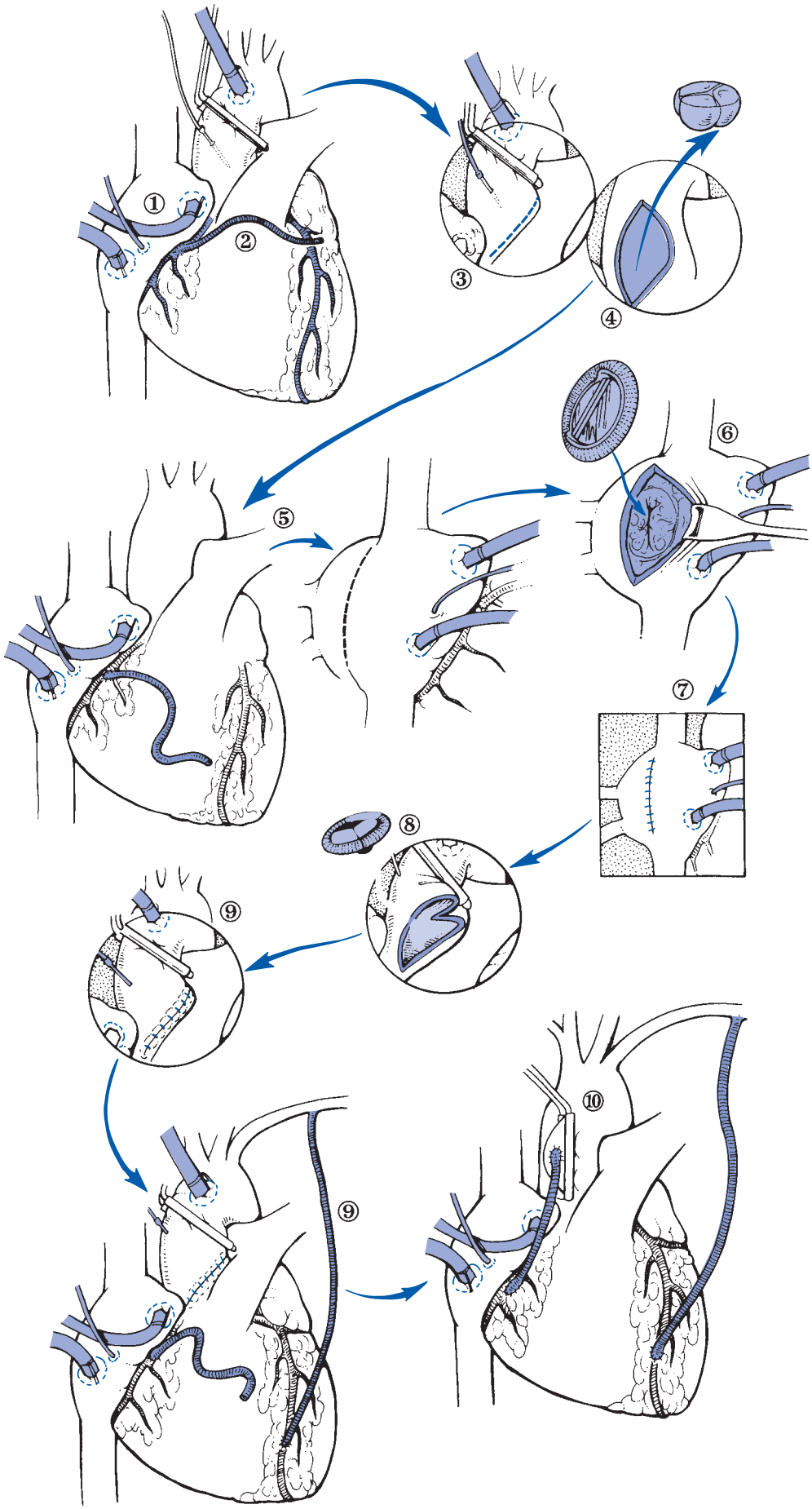

Figure 50-9. Operative sequence for aortic valve replacement, mitral valve replacement, and coronary artery bypass grafting. (1) Cannulation with cross-clamping of the aorta and administration of antegrade and retrograde cardioplegia. (2) Distal graft anastomoses are performed. (3) Aortotomy with standard oblique incision. (4) The aortic valve is resected but not replaced. (5) Standard left atriotomy after dissection in the interatrial groove. (6) Mitral valve repair or replacement with the prosthesis of choice. (7) Closure of the left atriotomy. (8) Aortic valve replacement with prosthesis of choice. (9) Closure of aortotomy and performance of distal anastomosis with the internal mammary artery. (10) Proximal graft anastomoses are performed. In this illustration, a partially occluding clamp has been applied to the aorta.

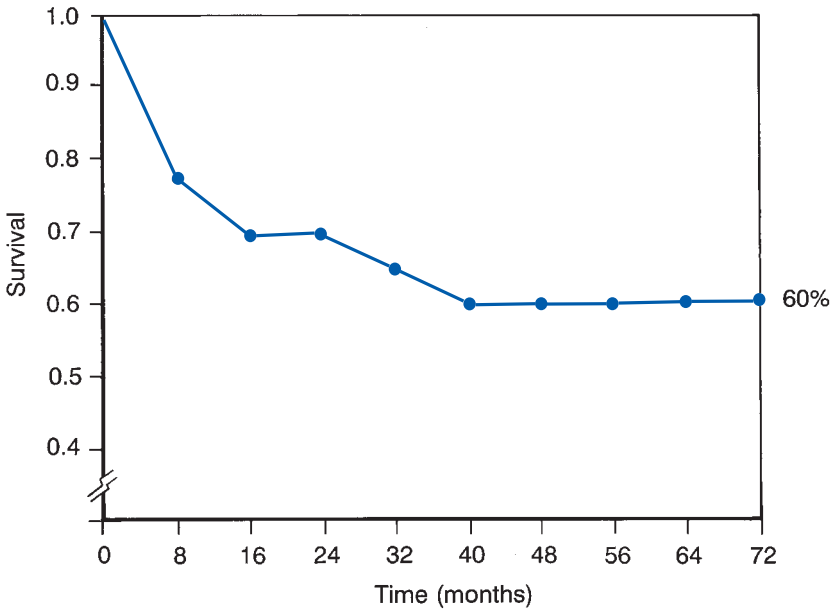

Figure 50-10. Long-term survival after combined aortic and mitral valve replacement and coronary artery bypass grafting. (*Adapted with permission from Akins CW, Buckley MJ, Daggett WM, et al: Myocardial revascularization with combined aortic and mitral valve replacements. J Thorac Cardiovasc Surg 1985; 90:272.*)

have mitral disease secondary to left ventricular dilatation from ischemia as well as from aortic regurgitation. Organic mitral valve disease may not be present. Assessment of left ventricular contractility may be difficult because of the alterations in preload and afterload produced by this combination of lesions. In addition, the presence of reversible ischemia may obscure accurate assessment of ventricular function. Therefore, assessment of myocardial viability is important.

Clinical Presentation

Most patients with this combination of cardiac lesions present with congestive heart failure. It is unusual to see a patient with angina as the primary symptom who also has significant insufficiency of both the aortic and mitral valves. Typical murmurs of aortic and mitral insufficiency are present, and the patient may have other signs of chronic congestive heart failure, including rales and peripheral edema. If myocardial infarction is a significant component of the pathophysiology and presentation of the disease, evidence of it may be seen on electrocardiogram and echocardiogram. On echocardiography, patients may have regional wall motion abnormalities if infarction has occurred, as well as global ventricular dilatation and dysfunction from the combined valvular lesions. Cardiac catheterization defines the coronary anatomy and helps define the severity of the valvular insufficiency and ventricular dysfunction. Accurate assessment of true left ventricular function is difficult in this entity. Mitral insufficiency may abnormally inflate visual measurements of ejection fraction because the ventricle can eject into the low-pressure pulmonary venous circuit. The misleading ejection fraction combined with the multiple volume overloads of leaking aortic and mitral valves and the potential contribution of dysfunctional myocardium from ischemia make it very difficult to get an accurate perception of preoperative left ventricular function. Thallium or PET scans may be useful to assess which areas of dysfunctional myocardium may be viable and potentially recruitable after revascularization.

Pathophysiology

Symptoms and signs of left ventricular failure develop as the left ventricle dilates. In patients with rheumatic disease with both valves intrinsically damaged, ischemic disease may be minimal. In the more common setting of patients with aortic regurgitation and severe ischemia, mitral regurgitation is likely to be secondary to both of these processes, and valve repair should be possible. Correction of aortic regurgitation reduces preload, whereas correction of mitral insufficiency increases afterload. The dilated myopathic ventricle may not have sufficient reserves to maintain adequate output under these circumstances. Higher postoperative preload may need to be maintained while afterload is reduced. Any additional contractility as a result of revascularization, given a smaller left ventricle, should further improve output. Hence, forward flow should improve if ventricular contractility is maintained or increased. However, because of the multiple, uncontrollable variables that inhibit preoperative assessment of ventricular function, prediction of expected improvement from this operation is difficult.

This consideration is extremely important. Patients with severe and irreversible ischemic myocardial disease and poor ventricular function will not do well with operative treatment of this entity. Therefore, preoperative assessments of myocardial viability and reversible ischemia are important. It is also important to assess whether organic mitral valve disease is present. The best results in these patients are in those in whom no mitral operation, or at most annuloplasty, is required.

Operative Management

Details of the operative technique are similar to those described previously. Because of the presence of aortic insufficiency, retrograde cardioplegia must be used in conjunction with hand-held antegrade ostial cannulas as necessary. Transesophageal echocardiography is required in the operating room for the assessment of mitral valve function. Residual 1+ to 2+ mitral regurgitation may be acceptable in certain patients because relief of aortic regurgitation can be expected to reduce ventricular size, which may lead to improvement of mitral regurgitation with time. Similarly, myocardial revascularization also may lead to ultimate improvement in ventricular and mitral valve function.

In weaning from cardiopulmonary bypass, afterload reduction is extremely important because of the large preoperative volume overload of the heart. Drugs that reduce ventricular afterload, including vasodilators and inotropic drugs such as milrinone, may be particularly appropriate. The intra-aortic balloon pump may be needed.

Results

Early hospital mortality in this group of patients may be high, and if myocardial failure is severe, overall mortality rates exceed the range already noted for double-valve and coronary artery surgery.[36,37] Important determinants of risk in these patients are the familiar ones. In several series, predictors of hospital death and late events included severe mitral regurgitation, lower ejection fraction, more severe symptoms of congestive heart failure, and severe triple-vessel CAD.

SUMMARY

This chapter has reviewed the management of patients with valvular and ischemic heart disease. The discussion has focused on management of disease of the aortic and mitral valves, since these are the valves most frequently affected in adults who present with these combined diseases.

Rather than concentrate on the details of the technical aspects of valve implantation or coronary artery grafting, the discussion has focused on the particular problems for surgical management that the combined pathophysiology of valvular and ischemic heart disease produces. As has been noted often during the discussion, there is usually an interaction between valve function, myocardial perfusion, and ventricular performance. Dysfunction of the aortic and mitral valves has secondary effects on ventricular function, and the addition of CAD can make this interaction more complex. Therefore, the pathophysiology of these disease states can be complicated. In order to manage these entities successfully, this pathophysiology must be understood so that accurate estimates of risk and reasonable expectations for results can be achieved.

In almost every case, ventricular function and severity of mitral incompetence are important short- and long-term risk factors. Also, functional mitral insufficiency in the absence of anatomic abnormalities of the mitral valve may resolve after aortic and/or coronary artery surgery, and therefore an operation on the mitral valve may not be required. Finally, data from several sources suggest that patients with both coronary artery and valvular heart disease should be considered for a tissue prosthesis because of reduced life expectancy and the benefits of avoiding long-term anticoagulation.

In addition, the complex interaction between ventricular function, valvular function, and coronary ischemia requires that the operation be well planned with attention paid to expeditious surgery with short myocardial ischemia times and good myocardial preservation. Much of the discussion in this chapter, therefore, has focused on the operative plan and the development of a rational approach to intraoperative and postoperative management of these patients.

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PART

V

Diseases of the Great Vessels

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CHAPTER 51

Aortic Dissection

T. Brett Reece • G. Randall Green • Irving L. Kron

Thoracic aortic dissection occurs as blood flow is redirected from the aorta (true lumen) through an intimal tear into the media of the aortic wall (false lumen). A dissection plane that separates the intima from the overlying adventitia along a variable length of the aorta is created within the media. The acute form of aortic dissection is often rapidly lethal, while those surviving the initial event go on to develop a chronic dissection with more protean manifestations. The purpose of this chapter is to review the etiology and pathogenesis of aortic dissection, examine current diagnostic algorithms, and provide detailed descriptions of contemporary surgical techniques for treatment. Additional information regarding follow-up and the subsequent management of these patients is presented to provide a comprehensive understanding of a clinical entity that has challenged physicians and surgeons for centuries.

HISTORY

Sennertus is credited with the first description of the dissection process, but the earliest detailed descriptions of the clinical entity appeared in the 17th and 18th centuries, during which time Maunoir named the process aortic "dissection."[1,2] Laennec defined the propensity of the chronically dissected aorta to become aneurysmal.[3] Aortic dissection was exclusively a postmortem diagnosis until the first part of the 20th century, but in 1935 Gurin attempted surgical intervention with the first aortic fenestration procedure to treat malperfusion syndrome.[4] In 1949, Abbott and Paulin advanced surgical treatment by theoretically preventing aortic rupture by wrapping the aorta with cellophane.[5] Other attempts at surgical treatment over the years met with limited clinical success, though certain concepts regarding surgical management are still in use today. With the advent of cardiopulmonary bypass, De Bakey and Cooley forever altered the natural history of aortic dissection by successfully performing primary surgical repair using techniques not remarkably different from contemporary procedures.[6–8] Investigators such as Wheat made substantial contributions by defining physiologically based medical management algorithms to complement surgical correction.[9] There is still considerable controversy regarding surgical versus medical treatment of certain forms of acute thoracic aortic dissection.

CLASSIFICATION

The classification systems used for aortic dissection are based on the location and extent of dissection. The particular type is then subclassified based on the timing of dissection. Acute dissection has traditionally been used to describe presentation within the first 2 weeks, while the term chronic is reserved for those patients presenting at greater than 2 months following the initial event. The more recently added subacute designation is sometimes used to describe the period between 2 weeks and 2 months.

Two classification systems are most frequently used in clinical practice: the De Bakey and the Stanford systems (Fig. 51-1). The De Bakey system differentiates patients based on the location and extent of aortic dissection.[10] The advantage of this system is that four different groups of patients with different forms of aortic dissection emerge and provide the greatest opportunity for subsequent comparative research. In contrast, the Stanford system proposed by Daily and associates is a functional classification system.[11] All dissections that involve the ascending aorta are grouped together as type A, regardless of where the primary tear occurs. Proponents of the simpler Stanford system contend that the clinical behavior of patients with aortic dissection is essentially determined by involvement of the ascending aorta. Critics, however, suggest that individual patients in the type A classification may be quite different from one another depending on the distal extent of dissection. Drawing clinical conclusions from such a potentially heterogeneous patient

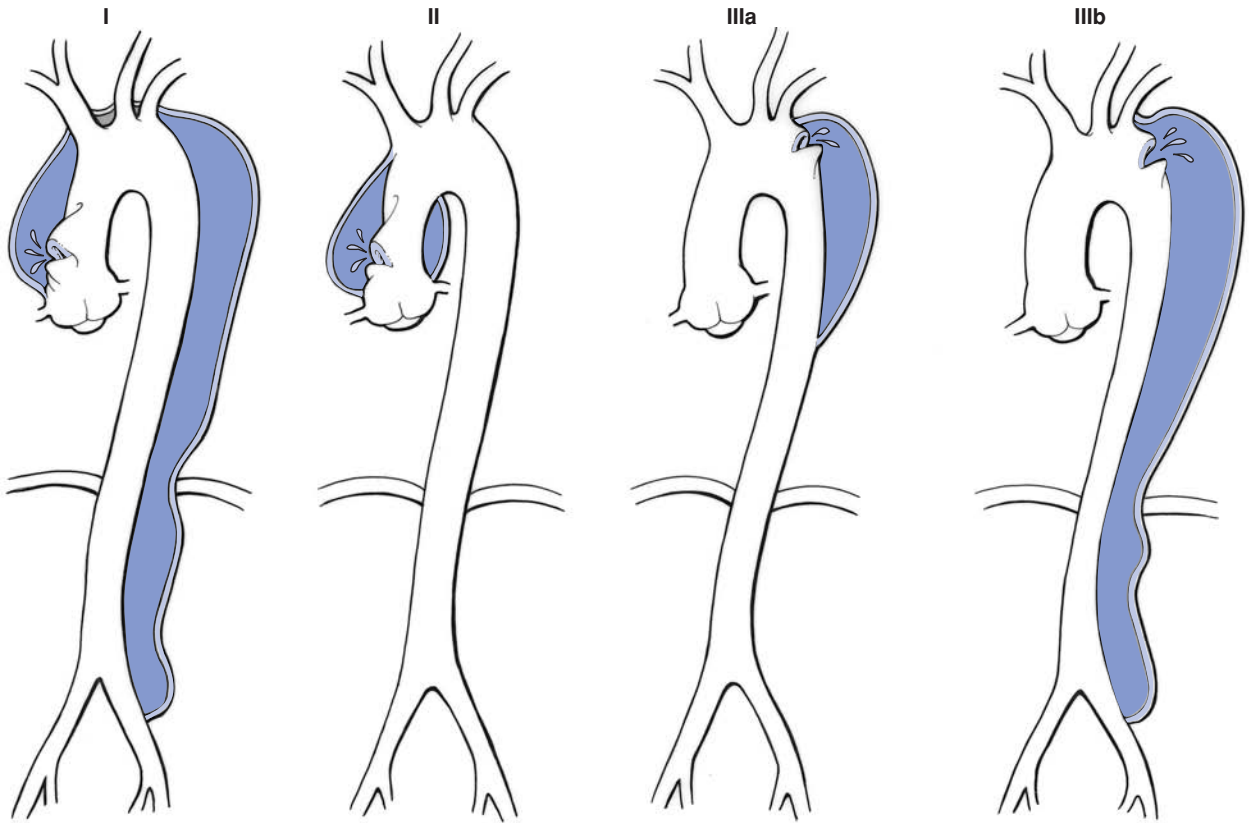

Figure 51-1. Classification of aortic dissection. De Bakey type I and Stanford type A include dissections that involve the proximal aorta, arch, and descending thoracic aorta. De Bakey type II only involves the ascending aorta; this dissection is included in the Stanford type A. De Bakey type II and Stanford type B include dissections that originate in the descending thoracic and thoracoabdominal aorta regardless of any retrograde involvement of the arch. These are subdivided into subtypes a and b, depending on abdominal aortic involvement.

population has inherent limitations. The Stanford system will be used throughout this chapter.

INCIDENCE

Aortic dissection is the most frequently diagnosed lethal condition of the aorta. Dissection occurs nearly three times as frequently as rupture of an abdominal aortic aneurysm in the United States.[12] There is an estimated worldwide prevalence of 0.5 to 2.95 per 100,000 per year; the prevalence ranges from 0.2 to 0.8 per 100,000 per year in the U.S., resulting in roughly 2000 new cases per year. These figures are, however, only an estimate. In one autopsy series, the antemortem diagnosis was made in only 15% of patients, revealing that many immediately fatal events go undiagnosed.[13] Clinically, type A dissections occur with an overall greater frequency (Table 51-1).

ETIOLOGY AND PATHOGENESIS

There are several hypotheses regarding the etiology of the intimal disruption (primary tear) that permits aortic blood flow to create a cleavage plane within the media of the aortic wall. This was originally viewed as a consequence of a biochemical abnormality within the media upon which normal mechanical forces in the aorta acted to create an intimal tear. The link between the abnormal media, termed cystic medial necrosis or degeneration, and the primary tear has not been scientifically established. In fact, medial degeneration is found in only a minority of patients with acute aortic dissection and most are children.[14] This theory has lost support over the years.

Alternatively, there are data supporting a relationship between aortic dissections and intramural hematoma. Advocates of this theory suggest that bleeding from vasa vasorum into the media creates a mass, which results in localized areas of increased stress in the intima during diastole. These areas then permit intimal disruption. In fact, between 10% and 20% of patients thought to have acute aortic dissection are found to have intramural hematoma, suggesting that it may be a precursor to dissection.[15] Penetrating atherosclerotic ulcers have been implicated as the source of intimal disruption in certain cases, yet support for the concept has waned over the years. The pattern of atherosclerotic involvement of the thoracic aorta resulting in penetrating ulcer and the frequency of dissection throughout the aorta do not support this theory.

Table 51–1.

Clinical Characteristics of Patients Presenting with Acute Type A and B Thoracic Aortic Dissections

	Type A	Type B
Frequency	60–75%	25–40%
Sex (M:F)	1.7–2.6:1	2.3–3:1
Age (y)	50–56	60–70
Hypertension	++	+++
Connective tissue disorder	++	+
Pain		
Retrosternal	+++	+,–
Interscapular	+,–	+++
Syncope	++	+–
Cerebrovascular accident	+	–
Congestive heart failure	+	–
Aortic valve regurgitation	++	+,–
Myocardial infarction	+	–
Pericardial effusion	+,–	+++
Pleural effusion	+,–	+,–
Abdominal pain	+,–	+,–
Peripheral pulse deficit	Upper and lower extremities	Lower extremities

While no single disorder is responsible for aortic dissection, several risk factors have been identified that can damage the aortic wall and lead to dissection (Table 51-2). These include direct mechanical forces on the aortic wall (i.e., hypertension, hypervolemia, and derangements of aortic flow) and forces that affect the composition of the aortic wall (i.e., connective tissue disorders or direct chemical destruction). Hypertension is the mechanical force most often associated with dissection and is found in greater than 75% of cases. Although the role of increased strain on the aortic wall is intuitive, the mechanism by which hypertension actually leads to dissection is unclear. Similarly, hypervolemia, high cardiac output, and an abnormal hormonal milieu certainly contribute to the increased incidence of dissection in pregnancy, but the mechanism is unclear. Atherosclerosis is not a risk factor for aortic dissection except in preexisting aneurysms or in the case of atherosclerotic ulceration, which may lead to dissection in the descending thoracic aorta. Iatrogenic trauma to the aortic intima may result in dissection. Catheterization procedures, aortic root and femoral artery cannulation for cardiopulmonary bypass, aortic cross-clamping, surgical procedures performed on the aorta (aortic valve replacement and aorto-coronary bypass grafting), and placement of intra-aortic balloon pumps have all been reported to result in dissection. Aortic transection as a result of trauma rarely results in excessive dissection and deserves differentiation from the process of aortic dissection. This process is usually limited to the aortic isthmus, and in addition to the risk of rupture may present as a circular prolapse of the intima and media, producing aortic obstruction referred to as "pseudo-coarctation" (Fig. 51-2).

Table 51–2.

Risk Factors for Type A and B Thoracic Aortic Dissection

Hypertension
Connective tissue disorders
Ehlers-Danlos syndrome
Marfan disease
Turner syndrome
Cystic medial disease of aorta
Aortitis
Iatrogenic
Atherosclerosis
Thoracic aortic aneurysm
Bicuspid aortic valve
Trauma
Pharmacologic
Coarctation of the aorta
Hypervolemia (pregnancy)
Congenital aortic stenosis
Polycystic kidney disease
Pheochromocytoma
Sheehan syndrome
Cushing syndrome

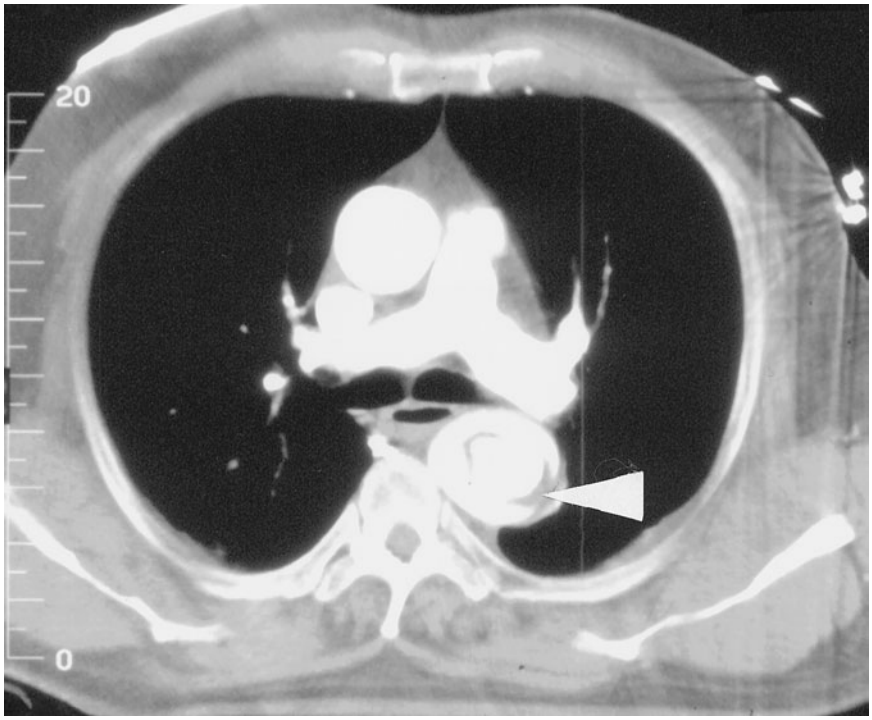

Figure 51-2. Axial image of CT arteriogram showing a nearly circumferential dissection flap (arrowhead) as a result of acute traumatic aortic dissection.

Once a cleavage plane exists in the media, the aortic wall floating within the lumen is termed the dissection flap and is composed of the aortic intima and partial-thickness media. The primary tear is usually greater than 50% of the circumference of the aorta, but the full circumference is rarely involved. The primary tear in type A dissection is usually located on the right anterior aspect of the ascending aorta and follows a somewhat predictable course, spiraling around the arch and into the descending thoracic and abdominal aorta on the left and posteriorly. The dissection may propagate in a retrograde fashion for a variable distance as well to involve the coronary ostia; this occurs in roughly 11% of all dissections.[15] Myocardial ischemia and rupture into the pericardium are the cause of death in as many as 80% of deaths from acute dissection. Often the distal false lumen communicates with the true lumen through one or more fenestrations within the dissection flap. The false lumen may also end blindly in as many as 4 to 12% of patients, in which case blood in the false lumen frequently becomes thrombotic. The false lumen may also penetrate the adventitia causing rupture and death. Regardless of whether the true and false lumens communicate, perfusion of aortic side branches may be compromised by the dissection, resulting in end-organ ischemia (Fig. 51-3). If these acute complications are avoided, the weakened outer aortic wall, composed of partial media and the adventitia, may dilate over time resulting in aneurysm formation. This evolving dilatation is the reason for operation in the majority of chronic dissections regardless of type.

The adventitia provides most of the tensile strength of the aortic wall with little contribution from the media. The media is composed of concentrically arranged smooth muscle interposed with connective tissue proteins such as collagen, elastin, and fibrillin within the ground substance. Abnormal constituents of the media, as in certain connective tissue disorders such as Marfan disease and Ehlers-Danlos syndrome, are associated with aortic dissection. Marfan syndrome is an autosomal dominant inherited disorder in which a point mutation in the fibrillin-1 gene located on the long arm of chromosome 15 results in an abnormal media. The incidence of Marfan syndrome is approximately 1 per 5000 live births. There are, however, many incomplete forms of the disease and as many as 25% may be sporadic, in which no known fibrillin abnormalities are observed. Type IV Ehlers-Danlos syndrome is a connective tissue disorder of the pro(1(III) chain of type III collagen with an incidence of 1 in 5000. The structurally abnormal media is susceptible to dissection. Of note, there are also familial aggregations of dissection without discernible biochemical or genetic abnormalities.

ACUTE AORTIC DISSECTION

Clinical Presentation

Signs and symptoms

As many as 40% of patients suffering acute aortic dissection die immediately. Those surviving the initial event may be stabilized with medical management, and it is these patients in whom subsequent therapeutic intervention for aortic dissection has altered the natural history of the disease. The

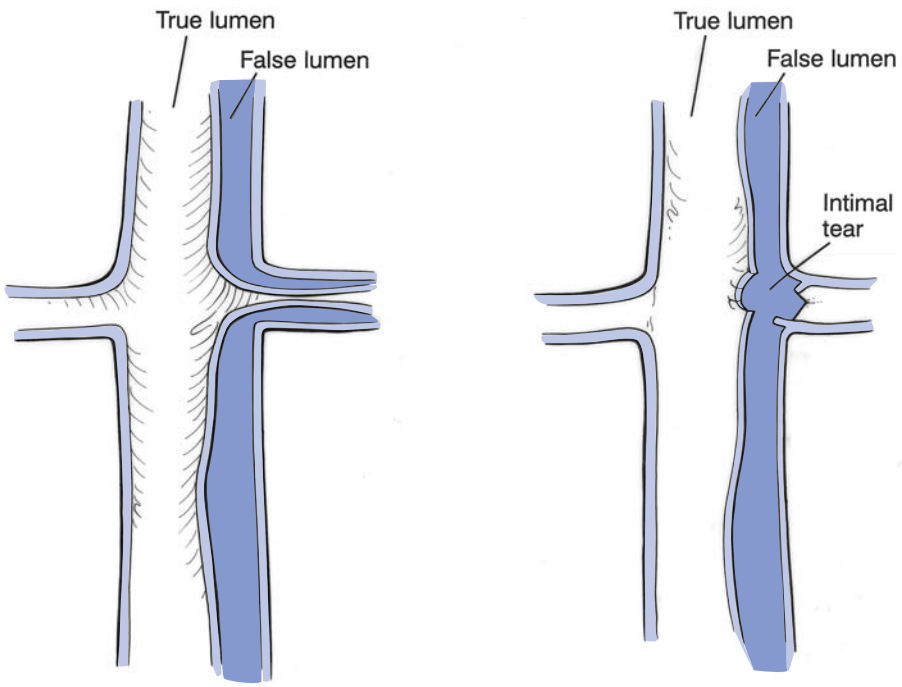

Figure 51-3. Diagram of aortic dissection. (A) An intact dissection membrane compresses the true lumen and causes malperfusion of a branch artery. (B) Rupture of the dissection membrane that may or may not restore blood flow to the branch.

clinical outcome is eventually determined by dissection type and timing of presentation, patient-related factors, and the quality and experience of the individuals and institution providing care.

The initial evaluation of a stable patient with suspected aortic dissection includes a detailed history and physical examination focusing on those elements likely to rule in the diagnosis. Most importantly, the diagnosis of aortic dissection requires a high level of suspicion. Up to 30% of patients ultimately diagnosed with acute dissection are first thought to have another diagnosis. Aortic dissection should always be considered in the setting of severe, unrelenting chest pain, which is present in most patients. Patients usually have no previous episodes of similar pain, which often causes anxiety. Pain is usually located in the mid-sternum for ascending aortic dissection, and in the interscapular region for descending thoracic aortic dissection (see Table 51-1). The location of maximum pain tends to change as the dissection extends in an antegrade or retrograde direction. Such "migratory pain" should arouse clinical suspicion. The character of the pain is often described as "ripping" or "tearing." The pain is constant with greatest intensity at the onset. Although painless dissection has been described, it usually occurs in the setting of an existing aneurysm in patients in whom the pain of a new dissection may not be differentiated from chronic aneurysm pain. Patients may also present with signs or symptoms related to malperfusion of the brain, limbs, or visceral organs. These findings confuse the true diagnosis, as the obvious signs of ischemia distract the historian from a less apparent initial episode of pain.

Elements of the past medical history such as primary hypertension, presence of aneurysmal disease of the aorta, or familial connective tissue disorders are useful as risk factors to help establish the diagnosis. Illicit drug use is an increasingly important predisposition to ascertain during the initial evaluation. The differential diagnosis of chest pain as a result of aortic dissection includes diagnoses such as myocardial ischemia, aortic aneurysm, acute aortic regurgitation, pericarditis, musculoskeletal pain, and pulmonary embolus. It is essential to consider aortic dissection in each case, as specific therapy (e.g., thrombolytic therapy for acute myocardial infarction) may impact the survivability of acute dissection.

Patients suffering acute dissection appear ill. Tachycardia is usually accompanied by hypertension in the setting of baseline essential hypertension and increased catecholamine levels from pain and anxiety. Hypotension and tachycardia may result from aortic rupture, pericardial tamponade, acute aortic valve regurgitation, or even acute myocardial ischemia with involvement of the coronary ostia. An abnormal peripheral vascular examination is present in a minority of patients with acute aortic dissection, but when present an abnormal pulse exam may indicate the type of dissection. Absence of pulses in the upper extremity suggests ascending aortic involvement, whereas pulse deficits in the lower extremities speak to involvement of the distal aorta. These findings are subject to change as the dissection progresses or reentry into the true lumen occurs. Auscultation of the heart may reveal a diastolic murmur consistent with acute aortic regurgitation or an S_3 indicating left heart volume overload. Physical exam findings such as jugular venous distension and a pulsus paradoxus are signs of pericardial tamponade that should be identified in any unstable patient to initiate the correct diagnostic and treatment algorithms. Unilateral loss of breath sounds, usually the left, may indicate hemothorax as a result of aortic leak or rupture with hemothorax. Alternatively, a pleural effusion may exist secondary to pleural

inflammation related to the dissection. This finding requires additional evaluation prior to treatment.

A complete central and peripheral neurologic exam is critical in that abnormalities are present in up to 40% of acute type A dissections. Involvement of the brachiocephalic vessels with loss of brain perfusion may result in transient syncope or stroke. Syncope may also result from rupture into the pericardium and is an ominous sign. Stroke rarely improves with restoration of blood flow and may even cause hemorrhage and brain death, yet surgery is indicated in such patients. Fortunately, stroke is a presenting feature in fewer than 5% of patients with acute type A dissection. Loss of perfusion to intercostals or lumbar arteries may result in spinal cord ischemia and paraplegia. Peripheral nerve ischemia as a result of malperfusion may yield findings similar to spinal cord malperfusion and should be discerned, as these patients often improve with restoration of blood flow. Acute aortic dissection may also cause superior vena cava syndrome, vocal cord paralysis, hematemesis, Horner syndrome, hemoptysis, and airway compression as a result of local compression and mass effect.

Diagnostic studies

Routine diagnostic studies including blood tests, chest x-ray, and electrocardiogram (ECG) should be obtained, but are often not sufficient to establish the diagnosis of acute aortic dissection. ECG often reveals no ischemic changes. Obvious ischemic changes are present in up to 20% of acute type A dissections, while only nonspecific repolarization abnormalities are present in nearly one-third of patients with coronary ostial involvement. The ECG may also reveal left ventricular hypertrophy in those patients with long-standing hypertension. The chest x-ray is abnormal in 60 to 90% of patients with acute dissection (Fig. 51-4). Although most patients have at least one, if not several abnormal findings, a normal chest x-ray does not rule out the diagnosis. Blood should be drawn and sent for complete blood count, serum and electrolytes, creatine kinase with myocardial isoenzymes, and troponin, and a blood type and screen are obtained. These tests obtained at the time of initial observation are usually unremarkable. There is frequently a mild to moderate leukocytosis. Anemia may result from sequestration of blood or hemolysis. Liver function tests, serum creatinine, myoglobin, and lactic acid may all be abnormal in the setting of certain malperfusion syndromes.

Diagnostic imaging

Diagnostic imaging is essential to clarify the anatomy of an acute aortic dissection, regardless of clinical certainty of diagnosis or the acuity of the patient. The diagnosis should be made rapidly with minimal distress for the patient. Two imaging modalities currently meet these criteria and are used to diagnose acute aortic dissection: computed tomography (CT) and echocardiography. Magnetic resonance imaging (MRI) and aortography, with or without intravascular ultrasound, are used to diagnose acute aortic dissection but are second-line modalities for various reasons. The benefits, disadvantages, and diagnostic accuracy of each are useful when choosing the most appropriate study for a particular clinical situation (Table 51-3). Each test provides disruption, reentry points, whether there is flow or thrombus in the false lumen, status of the aortic valve, presence and nature of myocardial ischemia, and brachiocephalic and aortic branch vessel involvement. Specific data may be necessary for operative planning and subsequent management to define the imaging study most appropriate for a particular patient.

Helical CT scanning is widely available and is now the most frequently utilized test to diagnose acute aortic dissection. It requires intravenous contrast medium that may limit its use in certain clinical situations, but generates images familiar to most practitioners and has a high sensitivity and specificity. This technique can be performed quickly, fulfilling

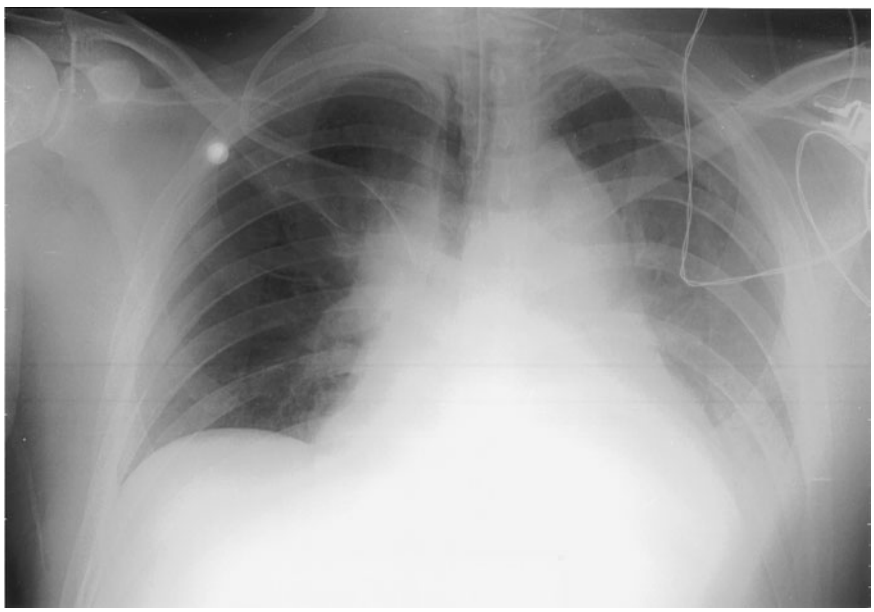

Figure 51-4. Plain chest x-ray exhibiting many features of acute type A dissection, such as a widened mediastinum, rightward tracheal displacement, irregular aortic contour with loss of the aortic knob, an indistinct aortopulmonary window, and a left pleural effusion.

Table 51–3.

Sensitivity and Specificity of Various Imaging Modalities Useful for the Diagnosis of Thoracic Aortic Dissection

Imaging study	Sensitivity	Specificity
Aortography	80–90%	88–93%
Computed tomography	90–100%	90–100%
Intravascular ultrasound	94–100%	97–100%
Echocardiography		
Transthoracic	60–80%	80–96%
Transesophageal	90–99%	85–98%
Magnetic resonance imaging	98–100%	98–100%

the requirements for use in the early management of acute dissection. Additional structures such as the pleural and pericardial spaces are imaged. When performed and formatted as an arteriogram, aortic branch vessels may also be evaluated; involvement of the brachiocephalic vessels is identified with nearly 96% accuracy. The diagnosis of dissection requires two or more channels separated by a dissection flap (Fig. 51-5). Transaxial two-dimensional images can be reconstructed to display three-dimensional images of the aorta that not only aid in diagnosis, but also are useful for operative planning.

Transesophageal echocardiography (TEE) is currently the second most frequently utilized study for making the diagnosis of acute aortic dissection. It is widely available, requires no intravenous contrast or radiation, and generates dynamic images of the aorta from which the diagnosis can be made (Fig. 51-6). It requires operator expertise both to acquire the necessary images and to conduct the examination safely. Although the safest setting in which to perform TEE is the operating room under general anesthesia, it can be performed in a monitored setting using topical anesthesia and light sedation. Patient comfort is paramount in this situation, as rupture has been reported during difficult studies and a complete examination of the entire aorta is necessary to exclude the diagnosis of acute dissection. Absolute contraindications to TEE include esophageal abnormalities such as varices, stricture, or tumor. A full stomach or recent meal are relative contraindications, but

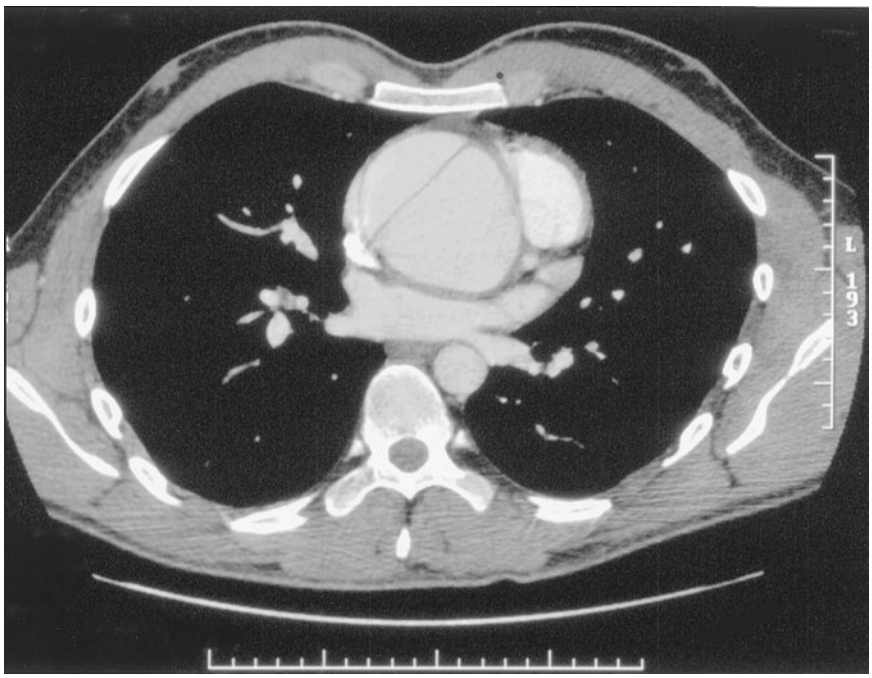

Figure 51-5. Axial image of CT arteriogram of acute type A dissection showing a dissection flap in the mid-ascending aorta.

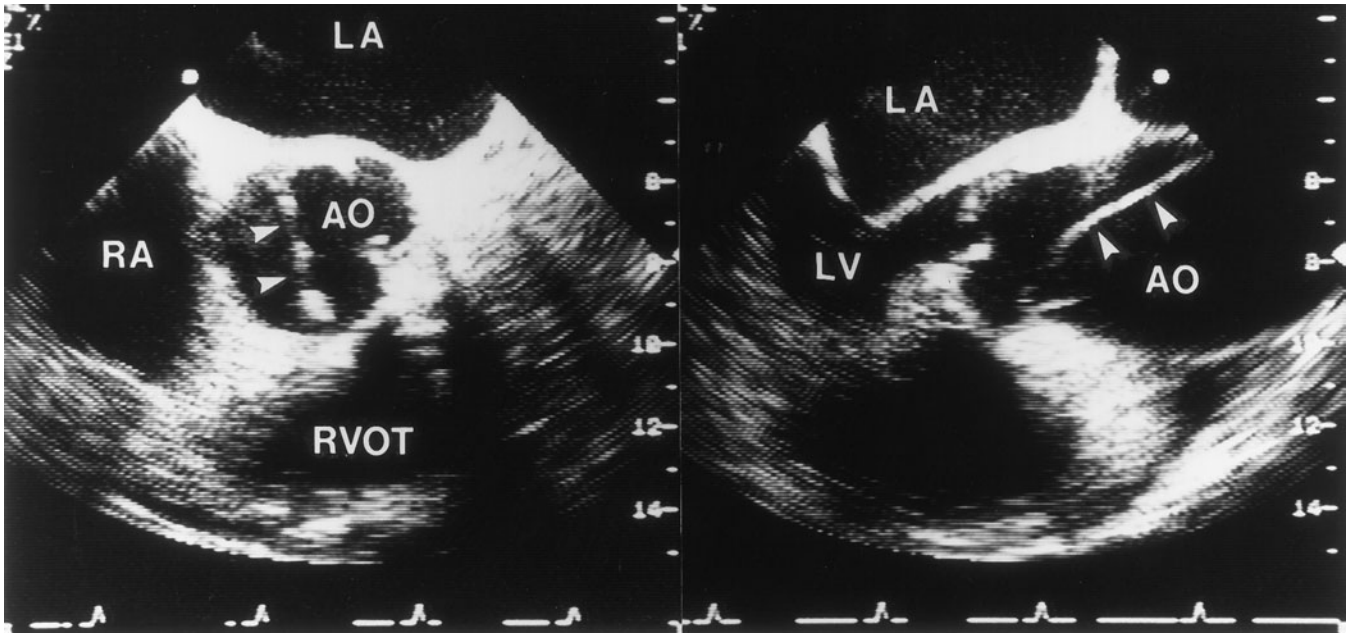

Figure 51-6. Transesophageal echocardiogram showing the dissection membrane (arrows) in the short (left panel) and long (right panel) views of a type A dissection.

recognition of these conditions permits safe examination with few complications in the vast majority of patients. Criteria for making the diagnosis of acute aortic dissection include visualization of an echogenic surface separating two distinct lumens, repeatedly, in more than one view, and that can be differentiated from normal surrounding cardiac structures. The true lumen is identified by expansion during systole and collapse in diastole. Communication of the false lumen is found by identifying distal tears in the flap and flow in the false lumen with the addition of color Doppler; the absence of flow indicates false lumen thrombosis. TEE additionally may provide high-quality images of the aortic valve and pericardial space. The coronary ostia are directly evaluated and regional left ventricular function may be assessed to identify myocardial ischemia indirectly. Color flow Doppler reliably quantifies aortic regurgitation and may be used to assess for additional valvular abnormalities. The pericardium and pleural space are also visualized and therefore effusions may be identified.

Transthoracic echocardiography provides images of the ascending aorta and sections of the aortic arch that may yield the diagnosis, but with much less sensitivity than transesophageal imaging. As such, transthoracic imaging may prove useful, but is generally insufficient to reliably establish the diagnosis. Transthoracic evaluation is additionally limited by patient-related factors including body habitus, emphysema, and mechanical ventilation. A negative transthoracic study should be complemented by a transesophageal study, which provides greater detail of the entire aorta.

Aortography was the first study used to diagnose acute dissection in 1939 and until recently was considered the gold standard for diagnosis. It is an invasive test requiring nephrotoxic contrast media in which the aorta is visualized in multiple two-dimensional projections. The diagnosis of dissection depends on visualization of the intimal flap, two distinct lumens, or compression of the true lumen by flow through an adjacent false lumen (Fig. 51-7). Indirect signs of dissection include the presence of branch vessel abnormalities

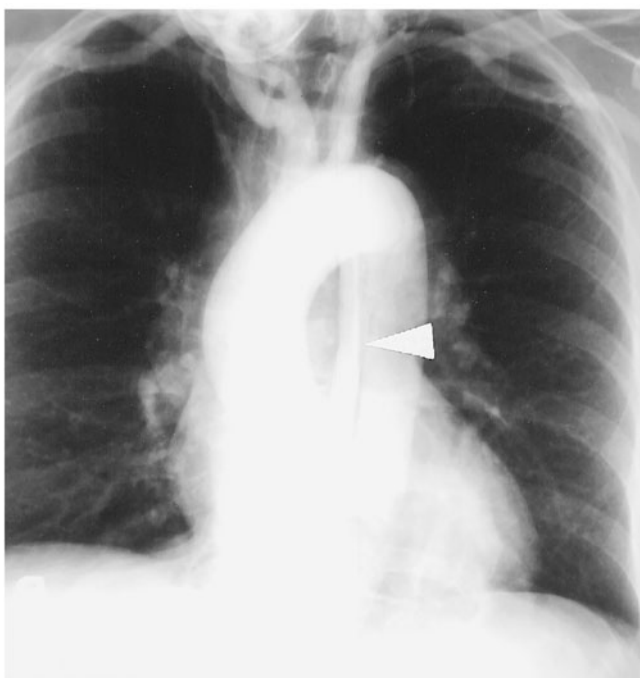

Figure 51-7. Aortogram of acute type B dissection illustrating differential contrast enhancement of the true and false lumens in the descending thoracic aorta. The intimal flap (arrowhead) can be seen separating the two lumens.

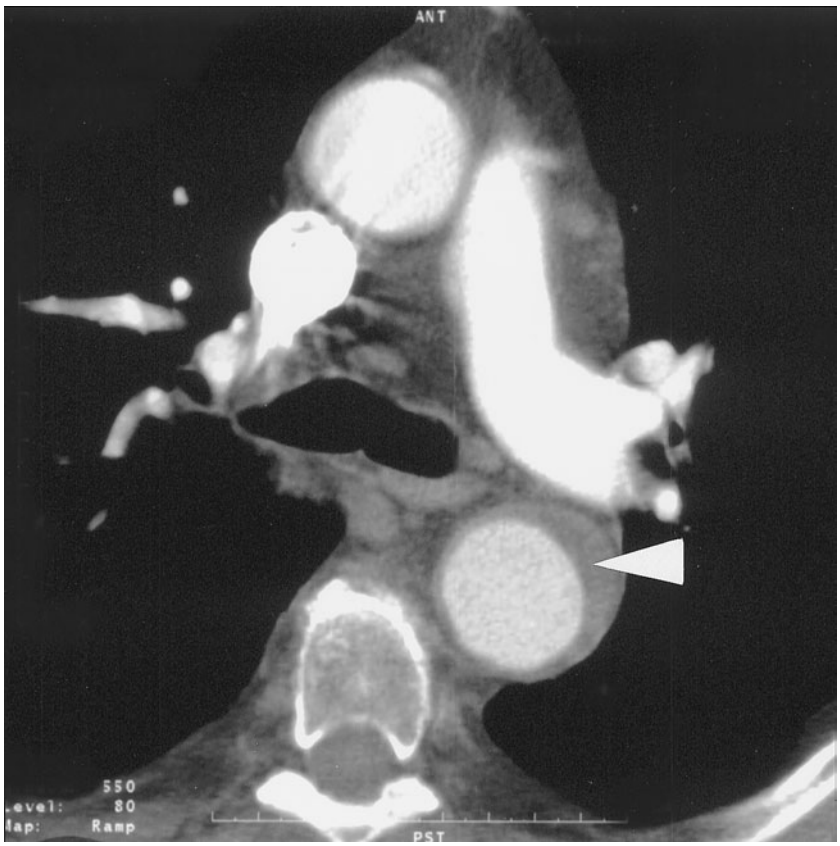

Figure 51-8. Axial image from a CT arte-riogram showing an intramural hematoma of the descending thoracic aorta (arrowhead).

and abnormal intimal contour on injection of the false lumen. The status of the aortic valve may be evaluated and coronary angiography in the setting of type A dissections is possible only with this diagnostic test. However, coronary angiography is not recommended given that the coronary ostia are involved in 10 to 20% of acute type A dissections and are easily evaluated at the time of surgery. Coronary atherosclerosis is present in 25% of all patients with acute aortic dissection, but even in those patients repair of the dissection should take precedence. Aortography is sometimes useful in acute type B dissections with evidence of mesenteric ischemia or oliguria, and in type A dissection with signs of malperfusion because catheter-based intervention may be possible. Aortography can have a high false-negative rate secondary to thrombosis of one lumen or when contrast equally opacifies each lumen, impairing distinction of a separate true and false lumen.[13,16] The diagnosis of intramural hematoma may also be difficult given the absence of intimal disruption, while penetrating atherosclerotic ulcer is usually easily visualized. Visualization of the dissection variants is best with either CT scanning or MRI (Figs. 51-8 and 51-9). One major limitation to the use of aortography in the acute setting is the need for skilled personnel. The time required to assemble this team varies with each institution, rendering aortography less useful when compared to other immediately available diagnostic tests. Aortography also requires arterial access, which can be painful and precipitate rupture or dissection extension.

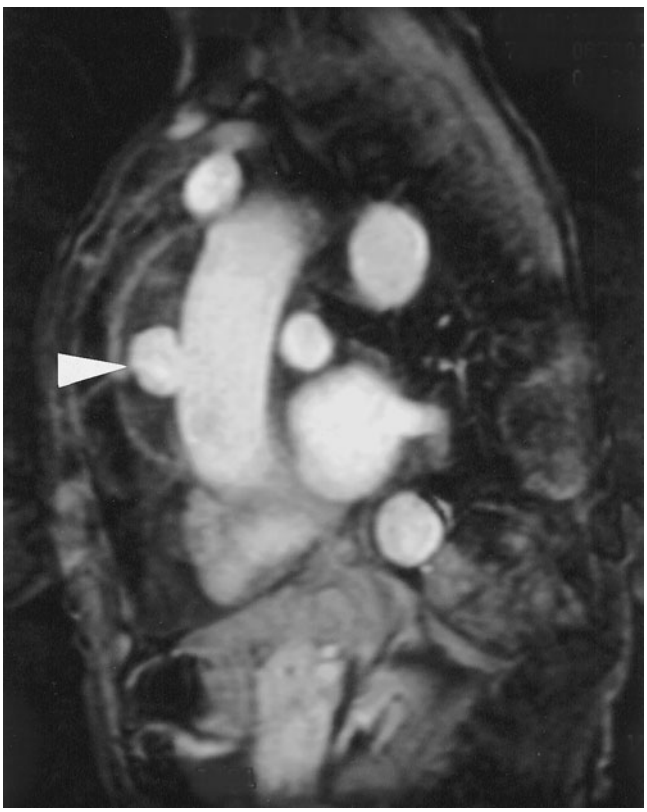

Figure 51-9. Sagittal contrast-enhanced MRI of penetrating atherosclerotic ulcer of the ascending aorta (arrowhead).

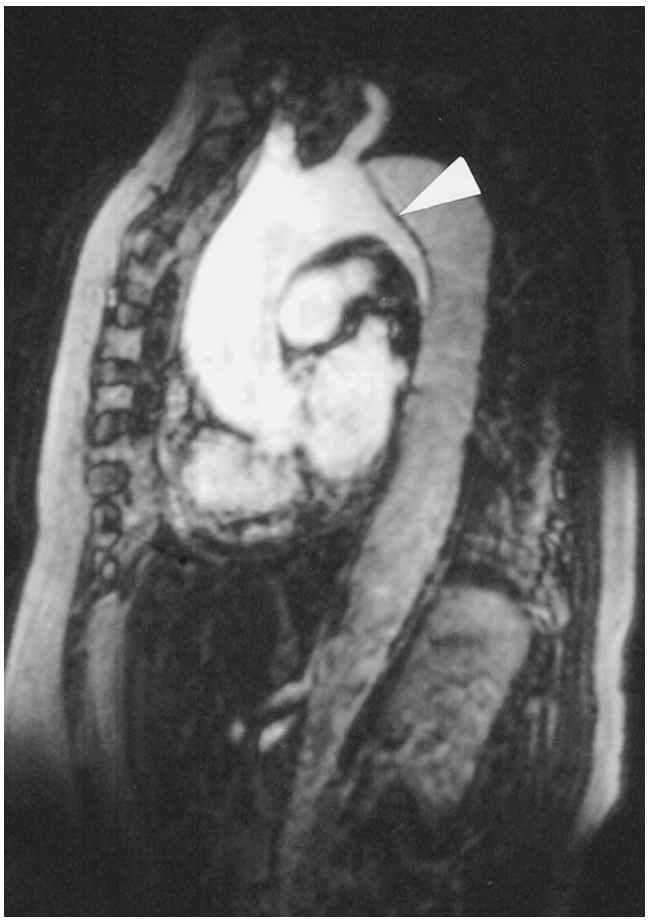

Figure 51-10. Sagittal contrast-enhanced magnetic resonance image of a chronic type B dissection. The dissection flap (arrowhead) is clearly identified and the false lumen appears to extend the entire length of the thoracic and abdominal aorta (darker posterior lumen).

Intravascular ultrasound is a catheter-based imaging tool that provides dynamic imaging of the aortic wall and an intimal flap in patients with aortic dissection. It is particularly useful in delineating the proximal and distal extent of dissection and for identifying the true and false lumens in questionable cases during aortography. High-resolution images of the normal three-layered aortic wall are differentiated to identify the abnormally thin wall adjacent to the false lumen. Because the aortic wall itself is imaged, intramural hematoma and penetrating atherosclerotic ulcers may also be identified. Currently, as an isolated imaging study, it is time consuming and requires skilled personnel, as with aortography, and generally is not useful as an initial study in the acute setting. It may be most useful in combination with aortography when the initial imaging studies are negative, yet there remains a high clinical suspicion of dissection.

MRI and the newer contrast-enhanced magnetic resonance angiography generate superior images, reliably demonstrating aortic dissection (Fig. 51-10). In fact, some consider this the gold standard imaging study given the published diagnostic accuracy. Dissection is identified as an intraluminal membrane separating two or more channels (Fig. 51-11). MRI provides detailed images of the entire aorta, the pericardium, and pleural spaces similarly to those obtained with CT. Cine imaging may also be used to evaluate left ventricular function, the status of the aortic valve, and flow in aortic branch vessels, as well as flow in the false lumen. It is, however, not widely available and the presence of ferromagnetic metal contraindicates its use. Another disadvantage of MRI is that artifact is identified in up to 64% of studies, which underscores the need for expert radiologic interpretation of the images. These factors account for its infrequent use in the acute setting.

Diagnostic strategy

The evaluation of suspected acute aortic dissection begins with a determination of the clinical likelihood that the diagnosis is correct and an evaluation of the hemodynamic stability of the patient. The unstable patient should undergo ECG to rule out acute coronary syndrome and be transferred immediately to the operating room. Medical management may be initiated as soon as the diagnosis is suspected. It is our practice to intubate and mechanically ventilate such patients while essential monitoring lines are placed. A transesophageal echocardiogram is then performed. If TEE fails to reveal acute aortic dissection, a hemodynamically unstable patient will then have a protected airway and invasive monitoring lines for subsequent evaluation of alternative diagnoses and continued resuscitation. If, however, acute dissection is suspected despite a negative TEE, CT arteriogram or aortography (potentially with intravascular ultrasound) is the next study of choice.

Clinically and hemodynamically stable patients permit a more detailed history and physical examination with imaging decisions tailored to specific aspects of the presentation. At the University of Virginia, such patients are first evaluated with a CT arteriogram. A CT scanner is located in the emergency department and these data may be obtained in less than 15 minutes. If that study is negative yet the diagnosis is still entertained, TEE is performed. In a recent review, an average of 1.8 imaging studies was used to correctly diagnose acute aortic dissection.[13] Although TTE is a relatively insensitive study (especially in the descending thoracic aorta), patients with suspected acute type A dissection may first undergo that study. If positive, subsequent confirmation using TEE may be performed in the operating room to expedite surgical management; if negative, either CT scanning or TEE performed in the intensive care unit is appropriate.

Natural History

Fifty percent of patients suffering acute type A aortic dissection are dead within 48 hours.[17] A conventional wisdom has evolved that acute type A dissection carries a "1% per hour" mortality. Newer data, however, reveal a different prognosis such that medical management may be considered in certain

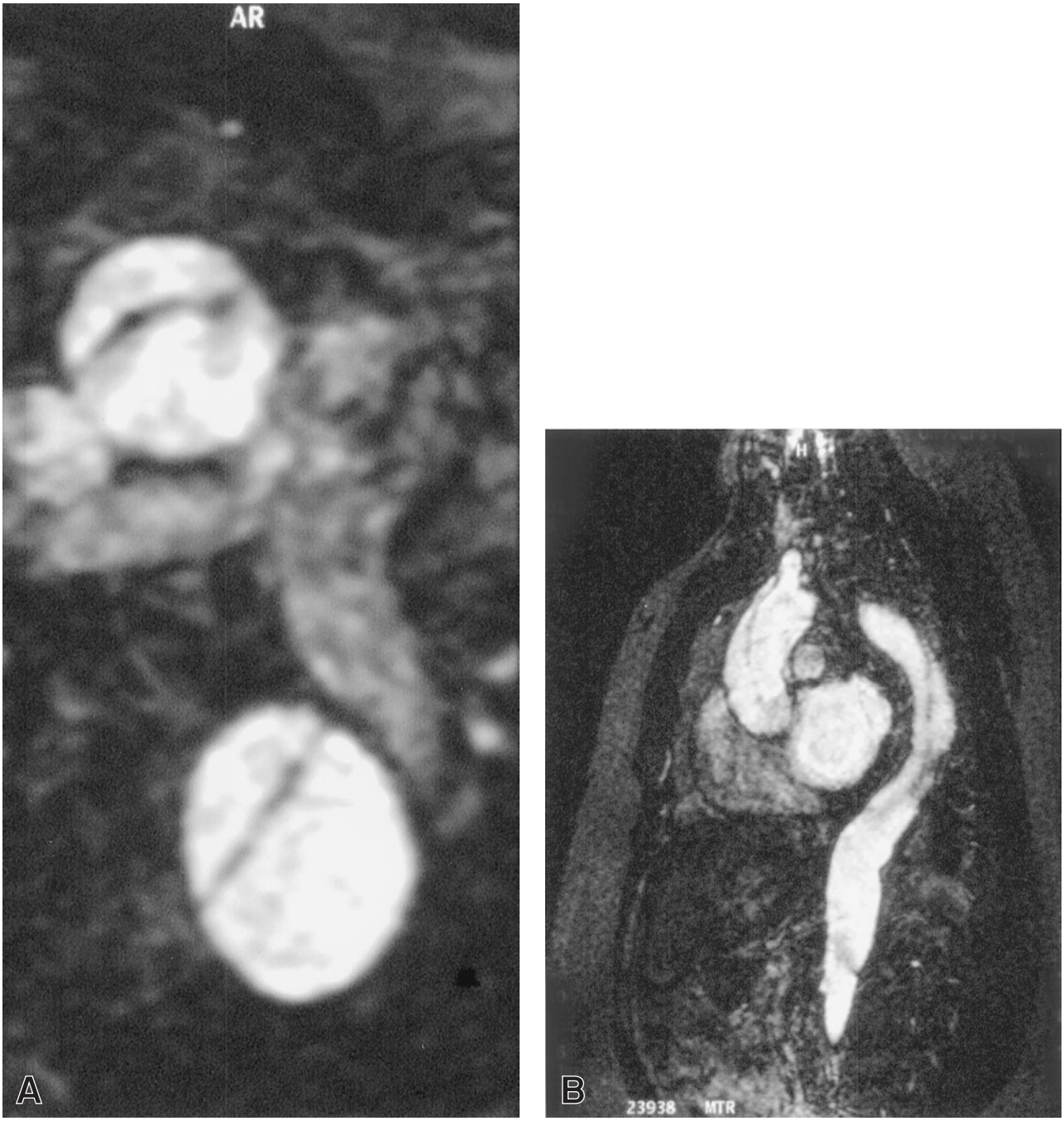

Figure 51-11. Axial (A) and sagittal (B) contrast-enhanced magnetic resonance images of a chronic type A dissection.

high-risk groups. In one such study, type A dissection was managed medically in 28% of patients for various reasons with a 58% in-hospital mortality.[18] Regardless, this relatively high mortality demonstrates that patients surviving acute type A dissection must be quickly and aggressively diagnosed and managed.

The natural history of acute type B dissection is difficult to determine, primarily because early autopsy series failed to analyze these patients as a distinct group. As a result, most of the studies estimate a 50% mortality for untreated acute type B dissection. More contemporary data from Elefteriades and associates, however, reveal a 9% initial hospital mortality for acute type B dissection, with 66% of the remaining patients having no specific aortic complications requiring surgery.[19] These data are obviously influenced by modern medical treatment but speak to a more benign clinical course when compared to type A dissection.

Initial Medical Management

Recognizing the natural history of patients with aortic dissection dictates that management occurs as part of the initial diagnostic evaluation. The initial patient encounter therefore focuses as much on making the diagnosis as in identifying factors that require immediate treatment. The site of this initial evaluation and resuscitation is determined primarily by the hemodynamic stability of the patient. The unstable patient belongs in the operating room, whereas a more detailed diagnostic approach from which management follows on an urgent basis can be undertaken in stable patients. Therefore, the hypotensive patient who may be hypovolemic as a result of blood loss into the thorax or pericardium undergoes the aforementioned evaluation and resuscitation on transfer to the operating room. It is preferable to avoid procedures such as TEE or central line placement on an awake patient outside the operating room because hypertension resulting from patient discomfort may precipitate aortic rupture or propagation of dissection.

In the stable patient, blood pressure is measured in both arms and immediately treated to achieve a target systolic blood pressure between 90 and 110 mm Hg. Blood pressure control in hypertensive patients with pain should first be treated with narcotic analgesics. In general, the goals of hypertension management in acute aortic dissection are twofold.[9] First, aortic wall stress is lowered by decreasing the systolic blood pressure, which reduces the possibility of rupture. Second, shear stress on the aorta is decreased by minimizing the rate of rise of aortic pressure to decrease the likelihood of dissection propagation, so-called anti-impulse therapy. The drugs most commonly used for these purposes are sodium nitroprusside and esmolol. Sodium nitroprusside is a direct arterial vasodilator with a short onset and duration of action, which make it ideal to rapidly achieve the target systolic blood pressure. The rate of rise of aortic pressure, however, is increased when sodium nitroprusside is used alone. Esmolol is added to decrease the inotropic state of the myocardium and to decrease the heart rate. This drug is a $beta_1$-selective blocking agent with a short half-life that can easily be titrated to achieve the target blood pressure. Loading doses for esmolol and sodium nitroprusside should be avoided to prevent hypotension. Alternative $beta_1$-blocking drugs such as propranolol or metoprolol, and the combined alpha and beta-blocker labetalol are appropriate in the subacute phase. Alternatively, calcium channel blockers may be necessary to reduce systolic blood pressure in those patients with a contraindication to beta-blocker use. There are, however, no compelling data supporting their efficacy in acute dissection.

Operative Indications

The goals of surgery in acute type A dissection are to prevent aortic rupture into the pericardium or pleural space and to avoid involvement of the coronary ostia or aortic valve

Table 51–4.

Operative Indications for Acute and Chronic Type A and B Thoracic Aortic Dissection

Dissection type	Operative indication
Acute	
Type A	Presence
Type B	Rupture
	Malperfusion
	Progressive dissection
	Failure of medical management
Chronic	
Type A	Symptoms related to dissection (congestive heart failure, angina, aortic regurgitation, stroke, pain)
	Malperfusion
	Aneurysm
Type B	Symptoms related to dissection
	Malperfusion
	Aneurysm

(Table 51-4). The presence of ascending aortic involvement is, therefore, an indication for operative management in all but the highest-risk patients. The difficulty arises in determining which patients are high risk and which additional factors should affect the management algorithm. Patient age, for example, is not regarded as an absolute contraindication to surgery. This fact should perhaps be considered, however, given the few reported survivors of operative treatment for acute type A dissection who are greater than 80 years of age. Neurologic status at the time of presentation can also affect the decision to operate. While most agree that obtunded or comatose patients are unlikely to improve with surgical repair, complications such as stroke or paraplegia at the time of presentation are not contraindications to surgical correction. The status of the dissection should not be a factor; thrombosis of either lumen occurs, but these patients remain at risk for lethal complications and surgery is indicated. Similarly, patients with subacute type A dissection who present or are referred longer than 2 weeks following the event require operation. Scholl and colleagues demonstrated that these patients have avoided the early complications of dissection and may safely undergo elective operation rather than emergency repair.[20]

The goals of surgical management of complicated acute type B dissection are the prevention of free rupture and continued perfusion of end organs in the absence of symptoms. The advent of endovascular intervention has provided another option for the type B dissection; however, indications for these procedures are identical to the indications

for open intervention. The most frequent causes of death in acute type B dissection are aortic rupture and visceral malperfusion. These, however, occur much less frequently with medical management than do complications of acute type A dissection treated nonoperatively. Between 70 and 80% of patients with acute type B dissection survive the acute and subacute phases with medical management alone. Such success with medical management has traditionally relegated surgical treatment for acute type B dissections to the complications of medical management of progression of disease (see Table 51-4). The indications for repair include contained or free aortic rupture, acute aortic expansion, malperfusion syndrome, pain or progression of dissection despite maximal medical management, and failure of medical management to control hypertension. Although medical management of acute type B dissection is the rule in most centers, some centers advocate immediate surgical intervention in selected patients with uncomplicated acute type B dissection. Factors that may favor early operation in acute type B dissection are the presence of Marfan syndrome, a large false aneurysm, arch involvement, and presumed medical compliance issues.[21] As in acute type A dissection, acute paralysis does not contraindicate surgery because patients can have remarkable improvement following revascularization.

There is some debate regarding the treatment of patients diagnosed with intramural hematoma and penetrating atherosclerotic ulcer. Recent data regarding the natural history of these dissection variants have made the issue less confusing. Intramural hematoma may lead to acute rupture in up to 35% of patients, whereas regression or no change in the hematoma is seen in the majority of medically managed patients surviving the initial period. Similarly, patients with penetrating atherosclerotic ulcer were found to have a 42% rate of acute rupture.[22] As a result of these relatively high acute rupture rates, the Yale group currently recommends early operative intervention for intramural hematoma and penetrating ulcer involving the ascending aorta. In the descending aorta, medical management with anti-impulse therapy and a low threshold for operative intervention result in the lowest mortality. These patients require continuous observation and repeat diagnostic imaging after 3 to 5 days in the hospital to monitor the lesion.

Operative Technique

Anesthesia and monitoring

Anesthesia used during the repair of aortic dissections is often narcotic-based with inhalational agents for maintenance. Single-lumen endotracheal tubes are used for procedures performed through a median sternotomy, while double-lumen endotracheal tubes are useful but not mandatory for procedures performed through a left thoracotomy. Monitoring lines often include central venous access with a pulmonary artery catheter and one or more arterial pressure monitoring lines specific to the operation performed. One or two radial arterial lines and at least one femoral line are required to ensure adequate perfusion of the upper and lower body. All patients require a TEE probe for various reasons. Core body temperature is monitored in the bladder using a Foley catheter and in the esophagus using a nasopharyngeal probe. A wide skin preparation to include the axillary and femoral arteries is essential to provide all possible cannulation options.

Neurologic monitoring is available, but its utility remains controversial. Advocates of both cerebral and spinal cord monitoring argue that these monitors are able to detect injury to neurons prior to irreversible cellular injury.[23] Thus, this warning allows for detection of imminent injury and subsequent evasion of injury. Opponents argue that there is a significant learning curve and that the injury has already occurred once these monitors can identify ischemic neurologic changes. Depending on the location of the dissection and the resultant location of the vascular control can dictate the type of monitoring desired. Manipulation of the ascending aorta and arch can affect cerebral perfusion. In these cases, transcranial Doppler or near-infrared spectroscopy have been utilized. Intraoperative transcranial Doppler monitoring is utilized to identify malpositioned cannulas or to document need for adjustment of retrograde perfusion.[24] Opponents of transcranial Doppler argue difficulty with low baseline flow in patients and poor signal with thick temporal bones, which confounds interpretation of the results and the response to them. Continuous noninvasive near-infrared spectroscopy can be utilized to monitor cerebral oxygenation, a marker of cerebral blood flow. Although the role of noninvasive near-infrared spectroscopy in aortic dissection has not been elucidated, advocates extrapolate use from studies on carotid endarterectomy and coronary bypass.[25,26] Noninvasive near-infrared spectroscopy can be utilized for identification of regional oxygenation changes during the case, which may be particularly useful during normothermic periods of these cases.[23] Somatosensory evoked potentials are argued to be useful in identifying neurologic injury ranging anywhere from the peripheral nerve to the brain. These studies may even identify ischemic cerebral injury during hypothermic circulatory arrest earlier than electroencephalography.[27] Somatosensory evoked potentials can also be useful in the detection of spinal cord ischemia and guide the identification of crucial spinal cord vasculature requiring reimplantation. The use of somatosensory evoked potentials at some centers has led to reduced intraoperative and postoperative paraplegia.[28] Neurologic monitoring remains a relatively new technology that is operator-dependent, but probably is useful in experienced hands.

Hemostasis

Surgical procedures for aortic dissection can be associated with significant blood loss. Strict blood conservation is an

important aspect of the operation and at least one cell-saver device should be available. Packed red blood cells, platelets, and fresh frozen plasma should be in the operating room at the start of the operation. Coagulopathy as a result of the preoperative status of the patient, cardiopulmonary bypass, and deep hypothermic circulatory arrest contribute to excessive blood loss. Improvements in vascular graft material have all but eliminated this as a reason for intra- and postoperative blood loss. Antifibrinolytic drugs such as ε-aminocaproic acid and aprotinin are useful hemostatic adjuncts. Aprotinin is particularly useful when used in either the full or one-half Hammersmith regimen, and is most effective when administered prior to the operation. In patients in whom deep hypothermic circulatory arrest is used, aprotinin is administered in our practice only after the period of circulatory arrest. Until recent reports on the magnitude of renal and thrombotic complications with its use, aprotinin was a mainstay of hemostasis for these cases. Although its use is now considered controversial, some surgeons would still consider its use in dissection repair due to the relative coagulopathy in these cases compared to more straightforward cases on cardiopulmonary bypass.[29] Currently, the role of aprotinin is unclear even within our practice. Patients will often require transfusion of fresh frozen plasma, platelets, and possibly cryoprecipitate. Fibrin glues and hemostatic materials such as Surgicel and Gelfoam are useful as systemic coagulopathy is corrected.

Cardiopulmonary bypass

There are various options for arterial and venous cannulation sites based on the type of dissection. Arterial cannulation of the uninvolved distal aortic arch is preferable in acute type A dissection. Cannulation of the true lumen of the dissected ascending aorta is possible. The true lumen can be safely accessed using the Seldinger technique over a long wire introduced and guided by TEE.[30] Alternative sites include the right subclavian and the innominate artery for antegrade perfusion, or either femoral artery with retrograde aortic perfusion. Access of the axillary is described both using direct cannulation of the vessel or by cannulation of a silo graft sewn to the artery, with a low risk of complications including stroke.[31–33] However, direct axillary cannulation appears to cause more morbidity than side arm cannulation, including further dissection, brachial plexus injury, and limb ischemia.[34] The aortic dissection often involves the innominate artery, making access to the true lumen of this vessel more hazardous. In any case of retrograde aortic perfusion, it is essential to monitor proximal perfusion with a functioning radial arterial catheter.

There is debate over which femoral artery to cannulate in the setting of lower extremity malperfusion with a pulse deficit. Dissection of the abdominal aorta often leaves the left femoral artery originating from the false lumen, and therefore cannulation of the right femoral artery will most often perfuse the true lumen. Perfusion of the false lumen can cause retrograde dissection and malperfusion of aortic branch vessels arising from the true lumen. In that event, cardiopulmonary bypass should be stopped for aortic cannulation through an alternative site to achieve whole body perfusion. If the chest has been opened, direct cannulation of the ascending aorta is often successful when guided by TEE. An alternative cannulation technique is through the left ventricular apex and aortic valve. The cannula is then held in position with an ascending aortic tourniquet. Fortunately, there are usually multiple reentry tears throughout the dissection flap which permit perfusion of both lumens regardless of the lumen cannulated.

Venous cannulation is most often accomplished through the right atrium using a two-stage venous cannula, while bicaval cannulation is reserved for certain cases in which retrograde cerebral perfusion is preferred during circulatory arrest. A left ventricular vent is necessary in the setting of aortic valve incompetence and is easily placed through the right superior pulmonary vein or rarely through the left ventricular apex wall. Cardioplegia is administered retrograde through a coronary sinus catheter with additional protection via direct cannulation of the undissected coronary ostia.

The formerly popular "clamp and sew" technique used for repair of acute type B dissection has largely been replaced by the use of partial left heart bypass. Arterial cannulation sites for this technique include the distal thoracic aorta for limited dissections of the proximal descending thoracic aorta or the femoral artery for those extending into the abdomen. Venous drainage of oxygenated blood is through the left inferior pulmonary vein or the left atrium via the appendage when accessible. This technique does not require an oxygenator or pump suction and therefore the dose of heparin (100 U/kg) is less than with full cardiopulmonary bypass.

Cerebral protection

Surgical repair of aortic dissection involving the arch requires disruption of adequate blood flow to the brain during a period of circulatory arrest. Cerebral protection during that period is paramount and may be achieved through either deep hypothermia with cessation of electrical activity or some form of continued cerebral perfusion. Deep hypothermia during circulatory arrest was the first method used to perform operations on the aortic arch and remains an effective method for shorter procedures. Generally, periods of circulatory arrest up to 14 minutes are acceptable at 25°C, and periods up to 31 minutes appear to result in only transient neurologic sequelae at 15°C in a small number of patients.[35] Specifically, the risk of transient neurologic dysfunction on cognitive testing following a period of circulatory arrest is roughly 10% at less than 30 minutes, but increases to 15% at 40 minutes, 30% at 50 minutes, and 60% at 60 minutes.[36]

It is critical to correctly estimate brain temperature to ensure expected outcome. Nasopharyngeal and tympanic temperatures are measured to estimate brain temperature but are imperfect. For that reason, some groups use electroencephalographic silence to determine the appropriate point at which to discontinue cooling and perfusion. Slow systemic

cooling on cardiopulmonary bypass (20 to 25 minutes) while maintaining a maximal temperature gradient between perfusate and patient of less than 10°C is ideal. The head is then packed in ice to maintain a low brain temperature. While cooler temperatures increase the safe interval of circulatory arrest, cooling to lower than 15°C may result in a form of nonischemic brain injury and is therefore not recommended. Methylprednisolone and thiopental administration during cooling are adjunctive measures thought by some to decrease cerebral metabolic requirements during the period of circulatory arrest, but we currently do not use either. Reinstitution of cardiopulmonary bypass with systemic rewarming following repair proceeds without exceeding a 10°C temperature gradient to at least 37°C, as core body temperature often falls briefly after cessation of active warming and separation from cardiopulmonary bypass. Furosemide and mannitol are administered to initiate diuresis and to promote free radical scavenging following circulatory arrest.

Continued cerebral perfusion during the period of circulatory arrest is an alternative technique for cerebral protection, especially for circulatory arrest times >20 minutes. Cerebral blood flow may be delivered in either a retrograde or antegrade fashion. The technique for retrograde cerebral perfusion depends on the venous cannulation strategy. If bicaval cannulation is required, reversing flow through the superior vena caval cannula with a proximally placed tourniquet is simple and effective. Dual-stage venous cannulation requires placement of a retrograde coronary sinus catheter into the superior vena cava through a purse-string suture. Retrograde cerebral perfusion has the added benefit of flushing atherosclerotic material and air from the brachiocephalic vessels. A flow rate necessary to produce a superior vena caval pressure of 15 to 25 mm Hg is considered optimal. Selective antegrade cerebral perfusion has recently gained popularity. Once the aortic arch is open, the innominate artery and the left common carotid artery are encircled with vessel occluders and each lumen is cannulated with a retrograde coronary sinus cannula. With the left subclavian artery occluded, flow rates are slowly increased to achieve perfusion pressures of 50 to 70 mm Hg at the desired circulatory arrest temperature. These cannulas are then removed just prior to completing the anastomosis of the brachiocephalic vessels to the vascular graft, at which time cardiopulmonary bypass may be reinstituted.

Techniques for type A dissection

The exposure for procedures performed on the ascending aorta and the proximal arch is through a median sternotomy. This can be modified with supraclavicular, cervical, or trapdoor incisions to gain exposure to brachiocephalic vessels or the descending thoracic aorta. When dissecting the distal arch, it is important to identify and protect both the left vagus nerve with its recurrent branch and the left phrenic nerve. Replacement of the ascending aorta in type A dissections is best performed by an open distal anastomosis technique if the arch is involved (30%) or if arch involvement is unknown. The open distal anastomotic technique requires clamping the mid-ascending aorta and cardiac arrest via administration of antegrade and/or retrograde cardioplegic solution. The dissected ascending aorta proximal to the clamp is then opened. Evaluation and surgical correction of the aortic valve is ideally performed at this time while systemic cooling continues. If dissection does not involve the aortic root, the aorta is transected 5 to 10 mm distal to the sinotubular ridge. If dissection involves the sinotubular ridge, the proximal aorta is reconstructed by reuniting the dissected aortic layers between one or two strips of Teflon felt using either 3-0 or 4-0 polypropylene suture. Safi and associates use a technique of interrupted pledgeted horizontal mattress sutures as compared to the felt sandwich technique. In their experience, this provides superior stabilization and decreases the potential for subsequent aortic stenosis. There has also been a great deal of enthusiasm for reuniting the dissected layers using gelatin-resorcinol-formalin glue or the newer BioGlue (CryoLife International, Kennesaw, Ga). There are, however, concerns regarding each of the commercially available types of glue. Excessive application of these adhesives has been reported to lead to redissection of the vessel, anastomotic pseudoaneurysm formation, and potential infectious complications.[37–40] Most reviews focus on the tissue toxicity of the formalin component in these adhesives as the source of the reported complications.[41]

Once the temperature reaches 18 to 20°C, perfusion is discontinued during a brief period of circulatory arrest. The aortic clamp is released and the intima of the aortic arch is inspected and repaired accordingly (Fig. 51-12). If the intima is intact, the distal anastomosis is performed and the graft is

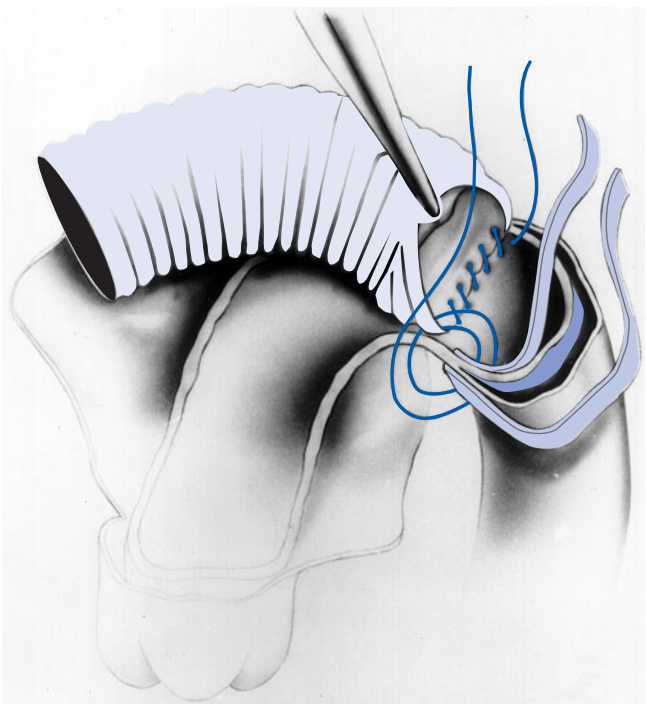

Figure 51-12. The false lumen of the distal aorta is closed and the aortic wall is reconstructed with inside and outside felt strips.

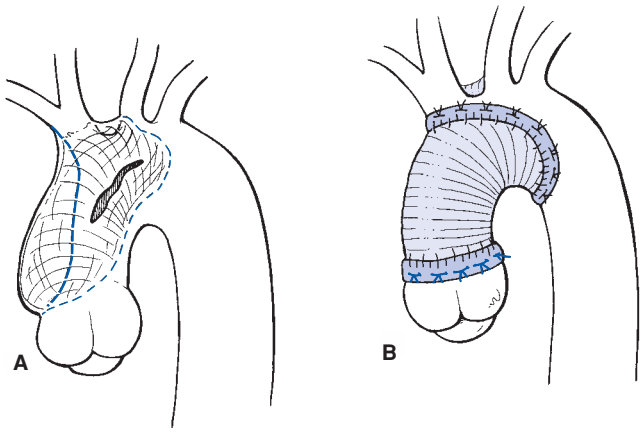

Figure 51-13. (A) The type A dissection extends into the proximal aortic arch. (B) The distal dissected aortic wall is reconstructed with inside and outside felt strips to replace part of the arch and ascending aorta.

cannulated, de-aired, and clamped for resumption of cardiopulmonary bypass with systemic warming. If the intima of the arch is violated, then a hemiarch reconstruction is performed (Fig. 51-13). We have only rarely found it necessary to perform a complete arch resection for an acute dissection. If a complex aortic root procedure is required, it is often useful to repair the aortic root with one vascular graft and use a separate graft to create the distal aortic anastomosis. The two grafts are then measured, cut, and anastomosed to provide the correct length and orientation for aortic replacement.

If the ascending aorta cannot be cross-clamped, the patient is cooled to 20°C with subsequent circulatory arrest. The distal aortic reconstruction is performed first in this circumstance, at which time the graft is cannulated and proximally clamped with resumption of cardiopulmonary bypass and systemic rewarming. Cannulation of the graft for antegrade systemic perfusion and rewarming is associated with improved neurologic outcome compared to retrograde perfusion and should be performed whenever possible. Newly available vascular grafts include 7- to 8-mm Dacron sidearm grafts for easy cannulation to facilitate this technique. Because a cross-clamp is not applied, the left ventricle must be decompressed once fibrillation starts during systemic cooling (approximately 20°C) to prevent distension and irreversible myocardial injury. Proximal ascending aortic repair is completed during the period of rewarming.

An alternative to the open distal technique is possible when dissection is limited to the ascending aorta or the proximal arch away from the origin of the brachiocephalic vessels. Antegrade arterial perfusion is achieved through distal arch or right subclavian artery cannulation; retrograde perfusion via cannulation of a femoral artery has traditionally provided acceptable results. An aortic cross-clamp is applied tangentially just proximal to the innominate artery. The ascending aorta is resected to include the inferior aspect of the arch. The layers of the dissected aorta proximal to the clamp are then reunited if necessary and the ascending aorta replaced with an appropriately sized, beveled vascular graft. The proximal reconstruction and anastomosis may then be performed and the entire procedure performed without requiring deep hypothermia and circulatory arrest.

Isolated dissection of the aortic arch is rare. Classified as a type A dissection, it requires resection of the arch at the site of intimal disruption and aortic replacement. Surgical management of the brachiocephalic vessels is determined by the integrity of the adjacent intima. If intact, the brachiocephalic vessels are reimplanted as a Carrel patch into a vascular graft after repair (Fig. 51-14). If the dissection involves individual vessels, each may require repair and reimplantation individually into the graft used for arch replacement (Fig. 51-15).

Aortic root dissection often fails to violate the intima of the coronary ostia. Repair of the ascending aorta at the sinotubular junction is therefore sufficient to reunite the aortic root layers and provide uninterrupted coronary blood flow. Minimal disruption of the coronary ostial intima should be repaired primarily with 5-0 or 6-0 polypropylene suture. If, however, the ostium is circumferentially dissected and an aortic root replacement is necessary, an aortic button should be excised and the layers reunited with running 5-0 polypropylene suture, glue, or both. Coronary buttons are then reimplanted into the vascular graft or to a separate 8-mm vascular graft as part of a Cabrol repair (Fig. 51-16). Aortocoronary bypass grafting is performed only when the coronary ostium is not reconstructible and as a last resort.

Acute type A dissection is complicated by aortic valve insufficiency in up to 75% of patients. Fortunately, preservation of the native valve is successful nearly 85% of the time. The mechanism of aortic insufficiency in most cases is the loss of commissural support of the valve leaflets. This is repaired using pledgeted 4-0 polypropylene sutures to reposition each of the commissures at the sinotubular ridge (Fig. 51-17). The dissected aortic root layers are then reunited using 3-0 polypropylene suture and either one or two strips of Teflon felt. Bioglue is placed between the layers prior to suture repair of the sinotubular ridge to buttress the repair and reform the sinuses of Valsalva. Aortic valve preservation must always be performed using intraoperative TEE to assess the valve postoperatively. No more than mild aortic insufficiency should be present. In addition to commissural resuspension, techniques exist to spare the aortic valve and replace the aortic root in acute type A dissection, but the experience is early and the number of patients few. This topic is covered in greater detail in the section on surgical techniques for chronic type A dissection.

If the aortic valve cannot be spared, replacement of the ascending aorta and valve should be performed using a composite valve graft or homograft. The composite valve graft is implanted using horizontal mattress 2-0 Tycron sutures to encircle the annulus and to seat the valved conduit (Fig. 51-18). The previously excised and reconstituted coronary buttons are reimplanted into the vascular graft with running 5-0 polypropylene suture (Fig. 51-19). The left

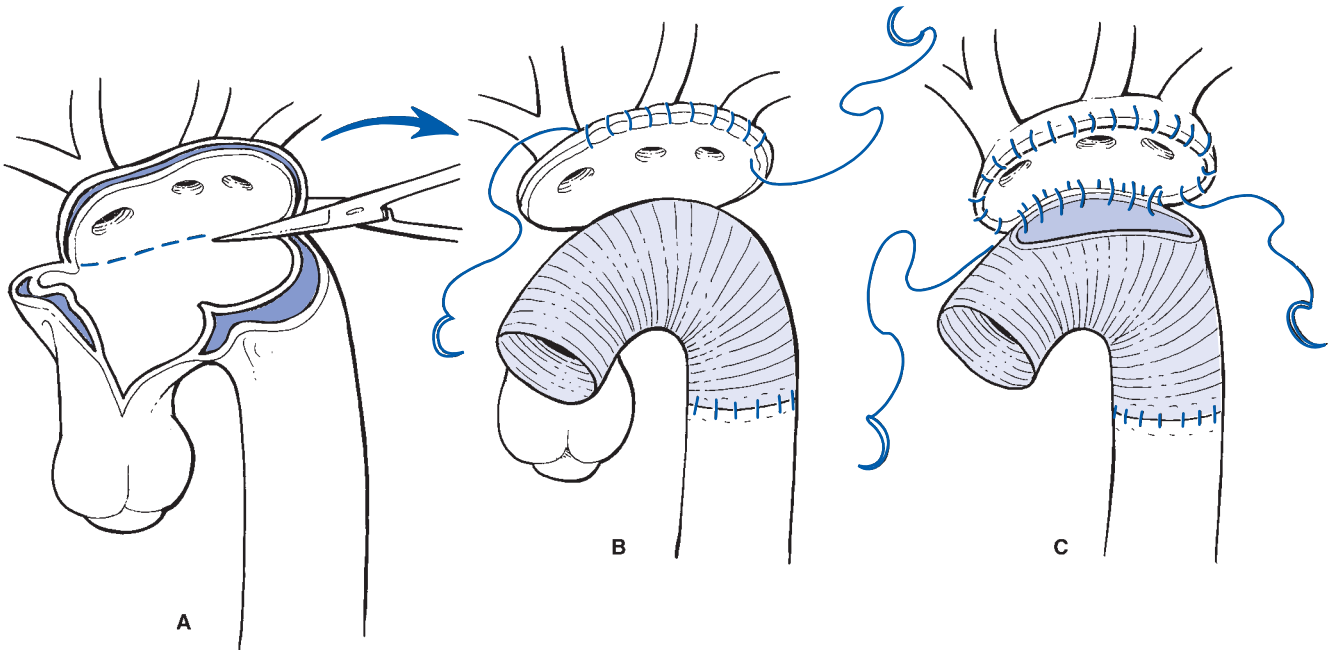

Figure 51-14. Brachiocephalic vessels can be reattached to an arch graft as a unit if the inner cylinder of origin of each vessel remains intact. (A) The arch vessels are excised as a unit from the superior surface of the dissected aortic arch. (B) The separated layers of the brachiocephalic patch are reunited using inner and outer felt strips and continuous suture. (C) A corresponding hole is cut in the aortic graft and the continuous brachiocephalic unit is sutured into place.

coronary button is implanted first, at which time the graft is clamped and placed under pressure to define the proper orientation and position of the right coronary button. The aortic homograft is similarly implanted using horizontal mattress 2-0 Tycron sutures, except that a generous margin of aortic root below the coronary buttons is retained for a second hemostatic suture line of running 4-0 polypropylene. This is an ideal solution for individuals who have a contraindication to anticoagulation or for young females. The Ross procedure (pulmonary autograft) is not applicable in those patients with connective tissue disorders and is not recommended in acute dissection.

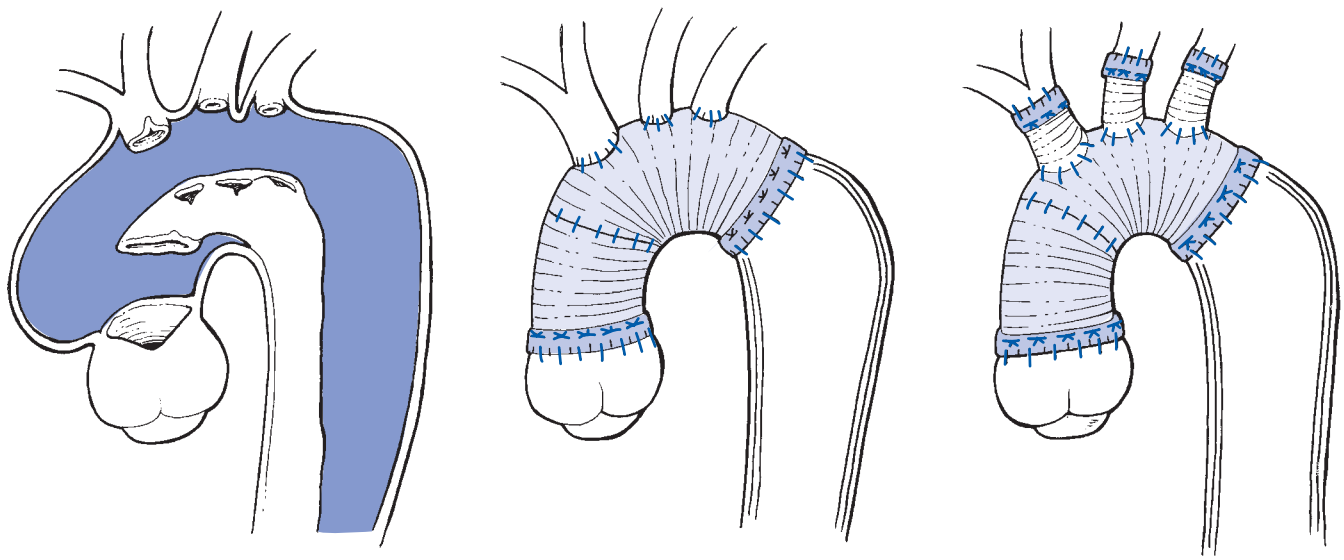

Figure 51-15. The brachiocephalic vessels are separated from the true lumen by the dissected false lumen (left panel). If individual brachiocephalic vessels are also damaged beyond repair, short interposition grafts are added to reconnect each artery to the aortic graft (right panel).

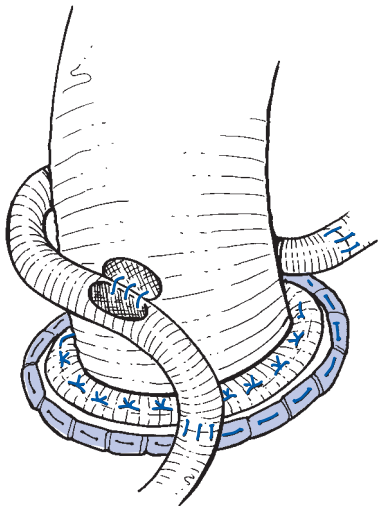

Figure 51-16. Illustration showing the attachment of the coronary ostia to the graft using the Cabrol technique. The ends of a 60-mm Dacron graft are sewn end to end to each coronary ostium. A side-to-side anastomosis is made between the intercoronary tube graft and the aortic graft.

Endovascular stent grafting is currently under investigation as a definitive form of management in acute type B dissection and in conjunction with surgery for acute type A dissection. Long-term data and prospective comparisons to surgery will be necessary before percutaneous management can be recommended as an alternative to surgery.

Techniques for type B dissection

The right lateral decubitus position is optimal for surgical treatment of acute type B dissections requiring operation. The pelvis is canted posteriorly to allow access to both sets of femoral vessels. A posterolateral thoracotomy in the fourth intercostal space provides sufficient access to the aorta; notching the fifth and sixth ribs posteriorly permits visualization of the entire thoracic aorta distally. A thoracoabdominal incision may be required to access the abdominal aorta in the case of visceral malperfusion. This may be performed either through the abdomen or the retroperitoneum. The left hemidiaphragm must be carefully divided in a radial fashion while marking adjacent sites on each side of the division with metal clips. This provides all necessary exposure and facilitates subsequent diaphragm approximation at the end of the case.

The ideal operation for acute type B dissection is replacement of as little of the descending thoracic aorta as is necessary. The extent of replacement rarely exceeds the proximal third and includes the primary tear in most cases. Such a strategy optimizes preservation of intercostal arteries perfusing the spinal cord to combat an incidence of paraplegia that may be as high as 19% following surgery for acute type B dissections.[42] This point is controversial, however, and some groups advocate replacement of the entire thoracic aorta. Any less extensive aortic replacement leaves dissected aorta with the potential for late aneurysmal dilation when there is perfusion of the false lumen. The ideal strategy to minimize spinal cord malperfusion yet resect all involved aorta has not been proven.

Once the thoracic aorta has been exposed, the operation continues with division of the mediastinum between the left subclavian and the left common carotid arteries. The left subclavian artery is encircled with an umbilical tape and Rommell tourniquet. It is essential that the left vagus and recurrent laryngeal nerves are identified and preserved during the course of the dissection. Ultimately, the entire distal arch must be free enough to place an aortic clamp between the left common carotid and left subclavian arteries. Next, the proximal descending thoracic aorta is circumferentially mobilized, dividing intercostal arteries in the segment to be excised. The left inferior pulmonary vein is then dissected and a 4-0 polypropylene purse-string suture placed posteriorly to cannulate for partial left heart bypass. Following the administration of 100 U/kg of intravenous heparin, 14F cannulas are inserted into the left inferior pulmonary vein and either a normal-appearing area of descending thoracic aorta or percutaneously into either femoral artery. Bypass is then initiated with flow rates between 1 and 2 L/min. The left subclavian artery is controlled and vascular clamps are placed on the aorta proximally and distally on the mid-thoracic aorta. Right radial artery pressure is measured to maintain proximal aortic systolic pressure between 100 and 140 mm Hg and mean femoral artery pressure greater than 60 mm Hg.[43] The aorta is then opened longitudinally and bleeding from intercostal arteries is controlled by suture ligation. Transection of the aorta distal to the origin of the left subclavian artery provides a site for the proximal anastomosis. This is performed using 3-0 polypropylene suture and may require external reinforcement with Teflon felt strips.

The graft inclusion technique is another technique in which the posterior aspect of the proximal aorta is not fully transected. The proximal anastomosis is then made to the intact posterior aspect of the aorta. We do not recommend this technique since one cannot be certain of anastomosing all layers of the aorta. The size of the vascular graft is based on the diameter of the distal aorta and beveled to match the aorta proximally. This anastomosis may include the origin of the left subclavian to treat dissection in this vessel. A separate 6- to 8-mm Dacron graft can be used if there is intimal disruption involving the proximal segment of the left subclavian artery. Once the proximal anastomosis is complete, the proximal clamp is released and repositioned on the vascular graft to inspect the anastomosis. Attention is then turned to repairing the distal aorta with Teflon felt or glue. The distal anastomosis is completed, the clamps are released, and partial left heart bypass is terminated. Decannulation is routine except that percutaneously placed femoral artery cannulas 14F or smaller may be removed without direct repair. When cannulas larger than 15F are required, open surgical repair of the femoral arteriotomy is indicated.

Endovascular stent graft placement is another option for type B aortic dissections. These devices are generally

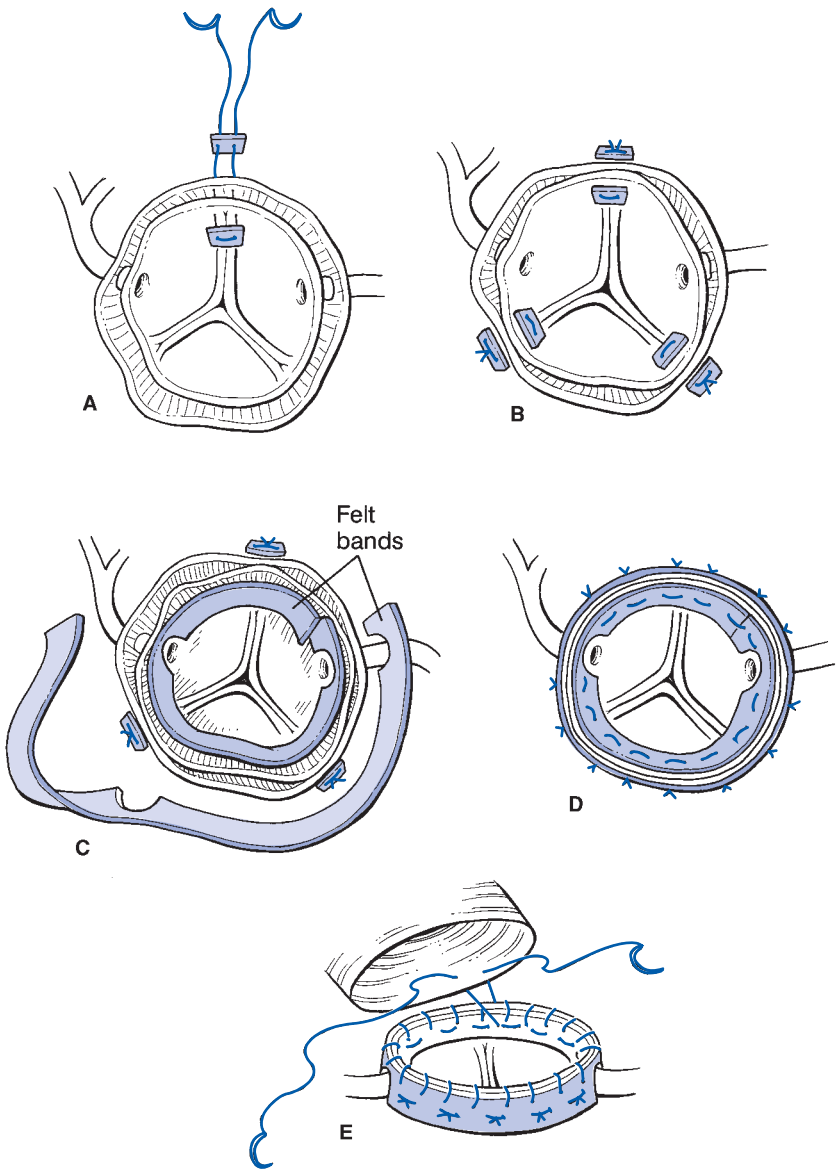

Figure 51-17. Resuspension and preservation of the native aortic valve in a type A dissection. (A) The dissected layers are approximated at each commissure with double pledgeted mattress sutures. (B) The aortic valve commissures are completely resuspended. (C) Thin felt strips (8- to 10-mm wide) are placed inside and outside from the circumference of the aorta. The coronary ostia are not compromised. (D) The aortic walls are sandwiched between the felt strips with a horizontal mattress. (E) A vascular graft is sutured to the reconstructed proximal aorta.

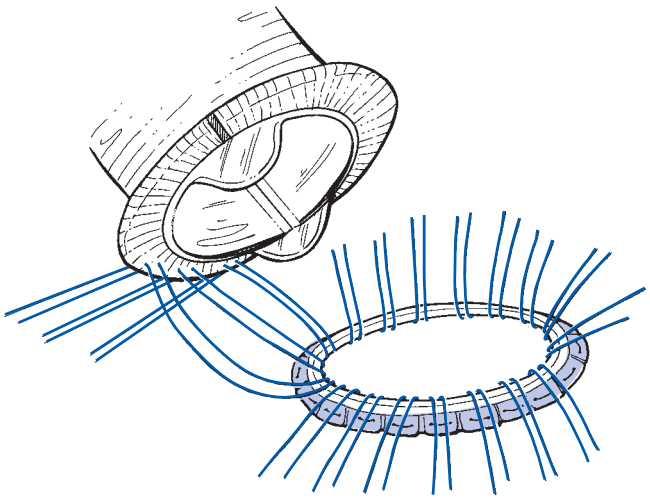

Figure 51-18. Everting 2-0 pledgeted mattress sutures are placed shoulder to shoulder around the aortic annulus to anchor a composite graft containing a St. Jude prosthesis.

introduced through the femoral arteries as access to the thoracic aorta. However, alternative access via the iliac arteries or infrarenal aorta has been described. Fluoroscopy is of course mandatory, but adjuncts like intravascular ultrasound and TEE can be useful in clarifying the true and false lumens as well as the proximal and distal fixation sites of the graft. Important considerations with deployment include graft de-airing, possible aortic blood flow restriction with pharmacologic manipulation, and various deployment strategies, such as partial or rapid deployment. Stent grafts should be oversized 10 to 20% relative to the native aortic diameter to adequately address the dissection. Care must be taken to avoid injury to the proximal aorta during stent graft placement to reduce the risk of retrograde dissection and its inherent morbidity.[44] Due to the curvature of the aorta and the proximal pressure wave, make the landing zone critical for thoracic stent graft placement. In some cases, coverage of the left subclavian artery proximally and retrograde revascularization of the celiac

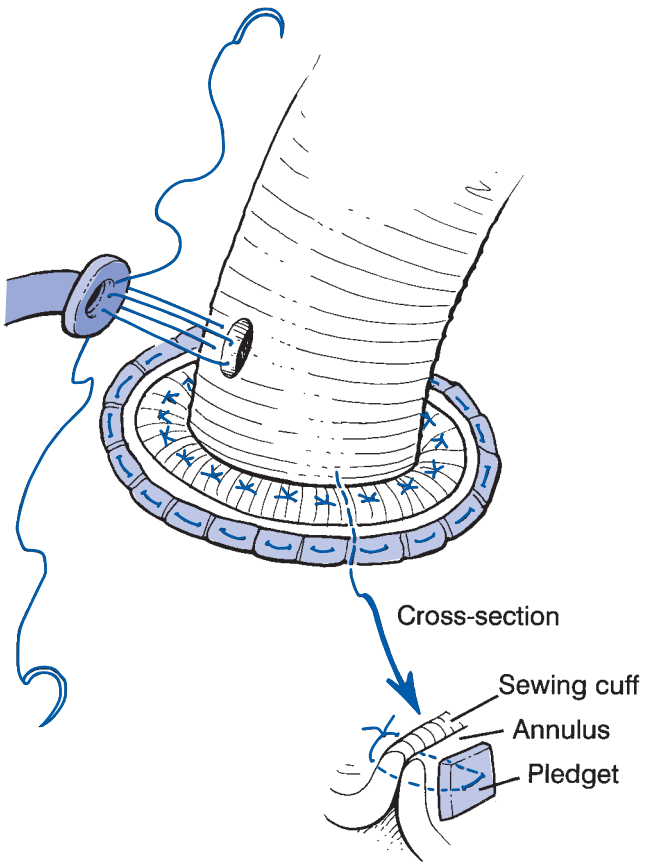

Figure 51-19. The coronary ostia are attached to the graft by the button technique using continuous 5-0 polypropylene suture.

distally may be required to improve the landing zone for the stent graft, thus reducing significant endoleaks.

Rupture of the thoracic aorta prior to or during repair is a catastrophic event often leading to operative death. Successful management requires immediate cannulation of the femoral artery and vein for cardiopulmonary bypass and eventual deep hypothermic circulatory arrest, but only if the ruptured area can be locally controlled. Assisted venous drainage through the femoral vein is often adequate, but direct cannulation of the right ventricle through the pulmonary artery may also be performed. A left atrial vent is placed through the left inferior pulmonary vein once the heart begins to fibrillate; the left ventricle may be vented as well directly through the apex. Once the nasopharyngeal temperature reaches 15°C, the vent is occluded and cardiopulmonary bypass is stopped. The head is placed down and the aorta opened for repair under circulatory arrest. The distal aorta should be clamped to minimize blood loss. Once the proximal anastomosis is performed, the proximal clamp is moved onto the graft and the graft cannulated to resume cardiopulmonary bypass.

Spinal cord ischemia resulting in paraplegia or paraparesis is a recognized complication of acute dissection repair that may be partially preventable and even reversible. The incidence of spinal cord ischemia is between 19 and 36% following repair of acute type B dissection.[42,43] Whereas various strategies exist to prevent spinal cord ischemia during repair of chronic dissection, very few are feasible in the acute setting. Pharmacologic agents such as steroids, free radical scavengers, vasodilators, and adenosine are promising adjuncts to prevent spinal cord ischemia but presently have little to no proven clinical utility. We presently use left atrial to femoral artery bypass and reimplant key intercostal arteries and selectively use cerebrospinal fluid drainage as outlined by Safi and colleagues.[45]

Malperfusion syndrome

Malperfusion of aortic branch vessels may occur from the coronary ostia to the aortic bifurcation and may dominate the presentation of certain patients. Although autopsy series yield a greater percentage of patients with evidence of malperfusion, clinical series reveal that dissection is not infrequently complicated by malperfusion of at least one organ system (Table 51-5).[46,47] Compression of the true lumen by the false lumen is the mechanism by which aortic branch vessel occlusion occurs in the majority of cases. Branch vessels may also be completely sheared off the true lumen and perfused to various degrees by the false lumen. Malperfusion is most often treated with primary surgical repair of the dissection, but catheter-based or open fenestration is reappearing as a potentially more effective treatment.

Percutaneous fenestration, angioplasty, and stenting are relatively new adjuncts to the surgical management of malperfusion syndromes. Renewed interest in these procedures grew from the recognition that hospital mortality of patients presenting with malperfusion was as high as 60%.[48] Surgical fenestration to treat malperfusion, however, reduced the mortality to under 20%.[49,50] Indications for percutaneous fenestration and endovascular stent placement were developed to treat malperfusion syndrome with the goal of improving outcome even further. Direct stenting of

Table 51–5.

Frequency and Location of Malperfusion in Acute Type A and B Thoracic Aortic Dissection

Vascular system	Frequency
Renal	23–75%
Extremities (upper and lower)	25–60%
Mesenteric	10–20%
Coronary	5–11%
Cerebral	3–13%
Spinal	2–9%

obstructed branch vessels and percutaneous fenestration with or without placement of a stent in the true lumen are the procedures most commonly performed. In certain situations, stents may be placed across an existing distal reentry tear to maintain patency and perfusion of the true lumen and the branch vessels. Balloon fenestration may be required to create such a communication between the lumens or to prevent thrombosis of the false lumen from which branch vessels may originate. Early results indicate that this procedure is both safe and effective, with restoration of flow in up to 90% of patients and an average 30-day mortality of 10 to 25%.[51,52] Given that the majority of postoperative mortality in patients with acute dissection and malperfusion is related to the duration of concomitant malperfusion, one strategy is percutaneous reperfusion followed by surgical repair.[53] Percutaneous treatment of malperfusion may also be performed following surgical repair of dissection but with less success in most reports.

The techniques used for surgical treatment of malperfusion depend on the location of the affected branch vessel but are generally quite similar. Malperfusion of the brachiocephalic vessels as a result of acute type A dissection is treated by repairing the dissection proximally if the intima is intact. If the intima is violated or if dissection extends into any brachiocephalic vessel, the artery should be resected from the arch, the layers reunited, and the vessel reimplanted into the arch, perhaps with an interposition vascular graft if necessary. Extra-anatomic bypass to the carotid arteries is an option in unreconstructible cases.

Malperfusion of the intra-abdominal viscera may be apparent at presentation but may also complicate surgical repair of acute type A or B dissections. Again, proximal repair of the dissection is standard treatment, but if this fails or if malperfusion persists despite repair, an additional procedure is necessary. Either open surgical or percutaneous fenestration of the dissection flap is necessary. Percutaneous fenestration is performed by pulling an inflated balloon or a fenestration knife through the dissection flap to create a communication between the two lumens. A surgical fenestration procedure is performed through a midline laparotomy or left flank incision to provide exposure of the infrarenal aorta (Fig. 51-20). Occasionally, fenestration of intra-abdominal aortic branch vessels may be required if the intima is violated beyond the ostia. If the dissection flap cannot be completely excised, the distal vessel layers must be reunited. Consideration should be given to patch angioplasty to prevent narrowing when closing smaller vessels. In the event that perfusion is not reestablished, extra-anatomic bypass may be required.

Obstruction of the terminal aorta or malperfusion of the lower extremities following operative repair is best treated with percutaneous fenestration. Surgical fenestration remains an option if percutaneous techniques fail to reestablish blood flow. In the event that surgical fenestration fails, the best solution is femorofemoral bypass grafting in the setting of unilateral malperfusion, or axillofemoral and femorofemoral bypass grafting if bilateral lower extremity malperfusion exists.

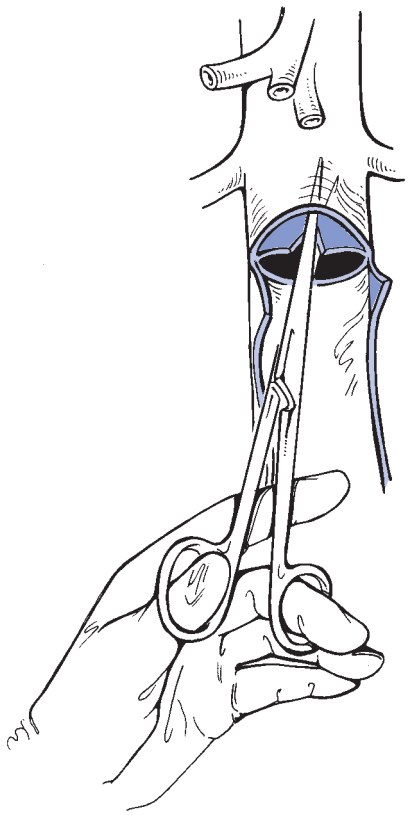

Figure 51-20. Fenestration of the abdominal aorta for visceral malperfusion. A transverse incision is made into the aorta, preferably into nondissected aorta. The proximal dissection membrane is incised and then excised to decompress the false lumen as far proximally as possible. The dissected layers are reconstructed with Teflon felt or glue and the aortotomy is closed directly.

Postoperative Management

Invasive hemodynamic monitoring is used to ensure adequate end-organ perfusion with a target systolic blood pressure between 90 and 110 mm Hg. Early postoperative blood pressure control begins with adequate analgesia and sedation using narcotics and sedative-hypnotic agents. The patient should, however, be allowed to emerge from general anesthesia briefly for a gross neurologic examination. The patient is then sedated for a period to ensure continued hemodynamic stability and to facilitate hemostasis. Coagulopathy is aggressively treated with blood products and antifibrinolytic agents as necessary and by warming the patient. Hematocrit, platelet count, coagulation studies, and serum electrolytes are obtained and corrected as necessary. An ECG and chest radiograph are used to assess for abnormalities and to serve as baseline studies. A full physical exam including complete peripheral vascular exam is performed upon arrival. Despite adequate repair of the dissection, perfusion of the false lumen may persist and therefore malperfusion syndrome remains possible. If an abdominal malperfusion syndrome is suspected postoperatively, this should be aggressively evaluated with ultrasound and subsequent angiography if positive. A strong clinical suspicion is enough to warrant this

evaluation given the consequences of failed recognition. In the morning, if the patient has been hemodynamically stable without excessive bleeding and the results of a neurologic exam are normal, the patient may be weaned from the ventilator and extubated. Management is routine from that point forward.

Long-Term Management

Surviving the operation for acute dissection represents the beginning of a lifelong requirement for meticulous medical management and continued close observation. It has been estimated that replacement of the ascending aorta for type A dissection obliterates flow in the distal false lumen in fewer than 10% of patients. As a result, the natural history of repaired dissection may involve dilatation and potential rupture of the chronically dissected distal aorta. This was the reason for the late death in nearly 30% of DeBakey's original series in 1982 and is currently the leading cause of late death following surgical repair.[54] Often a multidrug antihypertensive regimen including beta-blocking agents is required to maintain systolic blood pressure below 120 mm Hg. There are some data indicating that blood pressure control within a narrow range may alter the natural history of chronic dissection by diminishing the rate of aneurysmal dilatation. The long-term durability of the aortic valve following supracoronary reconstruction is quite good, with freedom from aortic valve replacement of 80 to 90% at 10 years. Progressive aortic insufficiency of the native valve is, however, possible and should be followed with transthoracic echocardiography in some patients.

Follow-up diagnostic imaging is required to monitor aortic diameter in patients with chronic dissection. Spiral CT arteriogram and MRI are the imaging studies of choice. MRI and ultrasound are useful in patients with renal insufficiency and in those requiring only imaging of the abdominal aorta. Echocardiography is useful for imaging the ascending aorta and provides additional information regarding the aortic valve. It is important to recognize the resolution limitations of each imaging modality and inherent imprecision of comparing different imaging modalities to evaluate changes. In general, measurements should be made at the same anatomic level with respect to reproducible anatomic structures (i.e., the sinotubular ridge, proximal to the innominate or left subclavian arteries, or at the diaphragmatic hiatus). It is important to recognize that the false lumen should be included in measurements of aortic diameter whether it is perfused or not. Three-dimensional reconstruction of spiral CT and MRI scans minimizes the error introduced by aortic eccentricity when comparing imaging studies and has simplified following this patient population. The current recommendations are to obtain a baseline study prior to hospital discharge and at 6-month intervals during the first year. If the aortic diameter remains unchanged at 1 year, studies are obtained yearly. Aortic enlargement of more than 0.5 cm within a 6-month period and greater eccentricity on comparison of three-dimensional reconstruction images are high-risk changes for which the interval is decreased to 3 months if surgery is not indicated.

Results

The operative mortality for repair of acute aortic dissection has fallen since DeBakey's original 40% mortality was reported in 1965. Improved intensive care unit and floor care of these patients, earlier recognition of dissection through improved imaging modalities, development of hemostatic vascular graft material, more effective hemostatic agents, and improvements in the safety of cardiopulmonary bypass are likely responsible. In the last two decades, most centers consistently report an operative mortality for acute type A dissection of between 10 and 20%. The high early mortality in acute dissection parallels the number of patients who present profoundly hypotensive and in shock. The mode of death is stroke, myocardial ischemia/heart failure, or malperfusion in most cases. The operative mortality of patients suffering acute type B dissection is higher than for type A dissection because the indications for surgery have traditions of dissection as previously discussed.[19] Early death following acute dissection occurs as a result of aortic rupture or as a consequence of malperfusion.[8]

The published results for long-term survival following acute type A dissection surgically treated over the last decade are roughly 71 to 89% at 5 years and between 54 and 66% at 10 years.[55–57] Operative repair of acute type B dissection yields 5-year survival of 48% with a 10-year survival of 29%.[58]

CHRONIC AORTIC DISSECTION

Clinical Presentation

Signs and symptoms

Chronic aortic dissection is usually asymptomatic. It may be incidentally discovered following an asymptomatic acute dissection; this most often occurs in patients with a preexisting aortic aneurysm. Some patients eventually require surgical treatment for chronic dissection and most do so as a result of aneurysmal dilatation of a chronically dissected aortic segment. Presenting complaints often include intermittent, dull chest pain or even severe skeletal pain from erosion into the bony thorax with large or rapidly expanding aneurysms. Aortic insufficiency may develop with chronic type A dissection and present with typical features of congestive failure including fatigue, dyspnea, and mild, dull chest pain. Infrequently, chronic dissection may result in paralysis/paraplegia from loss of vital intercostal arteries or even distal embolization of thrombus or atheroma from the false lumen. Malperfusion syndrome is an uncommon presentation for patients with chronic dissection given the likelihood that the true and false lumens communicate.

Diagnostic imaging

Diagnostic imaging of chronic aortic dissection is usually performed for surveillance but may also be necessary in patients with symptoms attributable to dissection and for operative planning. As previously discussed, routine follow-up for acute dissection occurs on a scheduled basis and is usually done with either CT or MRI. We prefer CT scanning for patients with normal renal function and no contrast allergy because CT is usually the original imaging study obtained during the acute dissection. The improved accuracy that comes with comparing similar studies combined with the availability, cost, and patient satisfaction make CT favorable for this purpose. MRI is utilized mostly as a follow-up study for patients with renal insufficiency, but is the study of choice to provide precise anatomic detail for operative planning. TEE is useful to follow chronic type A dissection when there is aortic insufficiency. It can provide cross-sectional images of the ascending aorta, but generating images useful for comparison to previous studies is highly dependent on the skill of the operator. For that reason, we use echocardiography to follow patients with aortic insufficiency, but also obtain a CT scan to assess ascending aortic diameter. Aortography is used primarily for operative planning. Patients older than 50 years and those with risk factors for coronary artery disease routinely undergo coronary arteriography prior to operation and images of the aorta are obtained at that time. Aortography is especially useful to determine the origin of aortic branch vessels for operative planning when noninvasive imaging is inadequate (Fig. 51-21).

Natural History

Chronic type A dissection develops in patients who fail to undergo immediate surgical treatment of the acute dissection. In contrast, chronic type B dissection may occur in patients successfully treated medically for the acute process and in those with repaired type A dissection who have a retained dissected descending thoracic aorta. The natural history of acute dissection rarely involves spontaneous healing. This phenomenon is observed in 4 to 31% of medically treated patients. Many patients with distal communication of the false lumen go on to develop aneurysmal dilatation of the aorta. The natural history of this process has been examined and reveals that there is an annual rate of expansion of 2 to 3 mm per year in communicating dissections, and the rate is 1 mm per year in those not communicating. Despite appropriate medical management and close follow-up, 30 to 40% progress to aneurysmal dilatation at 10 years.[59–62] This number is probably even higher in those patients with connective tissue disorders. In one study of 50 patients over a period of 40 months, 18% had fatal rupture and another 20% underwent surgical repair because of symptoms or aneurysm enlargement, emphasizing the need for diligent follow-up care. Risk factors for rupture of chronic type B dissection in that study included older age, chronic obstructive pulmonary disease, hypertension, and marginally pain. Chronic beta-blocker treatment reduces the rate of aortic dilatation as well as the incidence of dissection-related hospital admissions and procedures.[63]

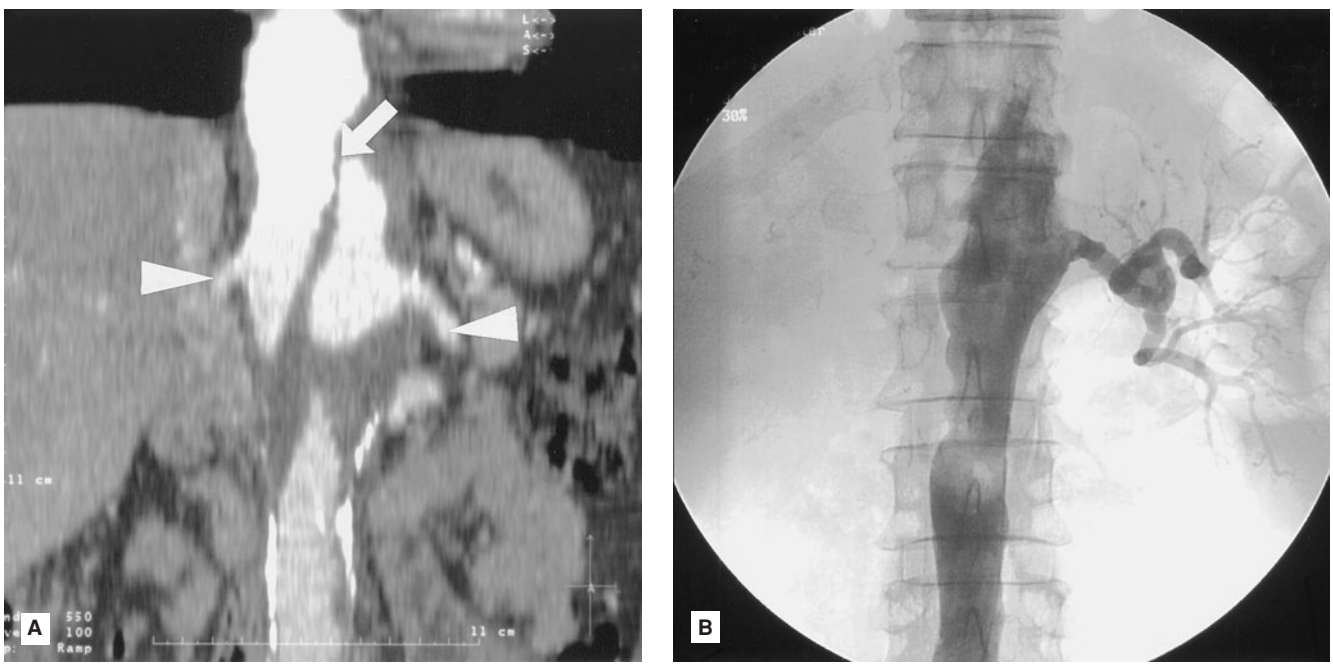

Figure 51-21. Coronal view of contrast-enhanced MRI (A) demonstrating chronic type B dissection with renal arteries (arrowheads) separated by the dissection flap (arrow). Aortogram (B) of the same patient revealing that each renal artery is perfused exclusively by either the true or false lumen. Such tests are often complementary and may influence surgical strategy.

Operative Indications

The operative indications for chronic type A and B dissections are shown in Table 51-4. Chronic type A dissection is rarely symptomatic, yet a minority will present with chest pain as a result of aneurysm expansion or heart failure related to aortic regurgitation. Chronic type B dissection may also present with back pain or infrequently with a malperfusion syndrome. While each of these findings is an indication for intervention, the most common indication for surgical management is aneurysmal dilatation. The Yale group recently reviewed the size criteria indicating operative intervention for thoracic aortic aneurysms.[64] These criteria dictate that replacement should be performed for ascending aortic size greater than 5.5 cm, or 5 cm if a connective tissue disorder is present. Similarly, the two most frequent indications for operative repair of chronic type B dissection are aneurysmal dilatation and malperfusion. In the descending thoracic aorta, replacement is indicated at 6.5 cm, or 6 cm if there is a family history or physical stigmata of a connective tissue disorder. Eccentricity of the aorta was also predictive of rupture, as was rapid expansion (more than 1 cm per year) and continued smoking. Such factors should therefore be considered when deciding to operate based on aneurysm size alone.[65]

Operative Technique

General considerations

The purpose of operation in chronic aortic dissection is to replace all segments of dissected aorta at risk for rupture and to prevent the possibility of subsequent malperfusion syndrome. The conduct of the operation including surgical approach, monitoring lines required, anesthetic technique, and cardiopulmonary bypass is similar to that described for acute dissection. Greater emphasis is placed on methods of cerebral and spinal cord protection and various technical differences exist for aortic valve preservation and to avoid postoperative malperfusion.

Cerebral and spinal cord protection

The incidence of paraplegia following repair of thoracoabdominal aneurysms resulting from aortic dissection is reportedly as high as 10%. Both mechanical and pharmacologic interventions have been advocated over the last decade to reduce this risk. It appears that partial left heart bypass alone as previously described is sufficient for patients with aneurysmal dilatation of the thoracic aorta above the level of T9 and results in a paraplegia rate between 5 and 8%.[66] Aneurysms involving the distal aortic arch require full cardiopulmonary bypass and deep hypothermic circulatory arrest for spinal cord protection. In such cases and in the case of the more extensive thoracoabdominal aneurysms, additional measures have variably reduced paraplegia rates lower than those observed with cord hypothermia alone. Drainage of cerebrospinal fluid as described by Safi and associates is routinely used in our practice for aneurysms extending lower than T9. Reimplanting intercostals and lumbar arteries between T9 and L1 is also important.[67] The aortic cross-clamp is moved progressively distal to perfuse branches as they are implanted. Preoperative identification of the anterior spinal artery origin has been suggested, but the combination of distal perfusion, cerebrospinal fluid drainage, and reimplanting large intercostal and lumbar arteries has provided adequate success at our institution. Additional techniques used for spinal cord protection include measurement of sensory and motor evoked potentials, regional epidural cooling, and the use of a variety of pharmacologic agents for cellular protection.

Techniques for type A dissection

Chronic type A dissection, with or without aneurysmal enlargement, is treated using similar operative techniques described for acute dissection. The particular operation performed depends on the specific pathology involving the aortic root, status of the aortic valve, distal extent of dissection, and brachiocephalic vessel involvement. The pathology of each of these components can be very different in a chronic dissection as compared to the acute process. These differences underlie the need for surgical techniques appropriate to each unique abnormality. In general, the ascending aorta is replaced using a vascular graft to include the entire diseased segment as in acute dissection, but surgical treatment of the aortic valve and creation of the distal anastomosis differ.

Whereas the aortic valve can be repaired in most cases of acute type A dissection by simple commissural resuspension, the rate of aortic valve replacement is much higher in patients with chronic dissection. Preservation of the aortic valve is complicated by morphologic changes in the valvular apparatus such as leaflet elongation and annuloaortic ectasia, which render the valve irreparable in as many as 50%. More severe grades of preoperative aortic regurgitation portend a lower probability of valve preservation. In patients in whom the aortic valve cannot be preserved with simple commissural reattachment, three options exist to treat aortic insufficiency: composite valve-graft replacement, aortic valve replacement with separate ascending aortic replacement, and finally valve-sparing aortic root repair. The technical aspects of composite valve-graft repair were covered under acute type A dissection. Separate aortic valve and ascending aortic replacement are appropriate when there is an operative indication to repair the ascending aorta in the setting of a normal aortic root and structural aortic valve disease. Note that this operation is not appropriate for patients with connective tissue disease. In this situation aortic root replacement is required.

There are several methods for aortic valve preservation when aortic root replacement is indicated. One such technique is performed by reimplanting the valve commissures into an appropriately sized vascular graft, which is secured to the left ventricular outflow tract using multiple horizontal mattress sutures.[68] A more elegant yet time-consuming

technique requires resection of the sinuses of Valsalva leaving a 5-mm rim of aorta circumferentially around the leaflets. Scallops are then created in the vascular graft to resuspend the commissures and remodel the aortic root. David and colleagues advocate Teflon felt reinforcement of the aortic annulus to prevent late annular dilatation and recurrent aortic insufficiency. The midterm outcome of such operations revealed a freedom from reoperation of 97 to 99% at 5 years and a 5-year survival for the aortic dissection subgroup of 84%.[69] Cochran and associates devised a similar technique to recreate the sinuses of Valsalva, which may be more important than previously recognized and contribute to improved long-term valve durability.[70] Such data in patients with chronic dissection are lacking. These techniques appear appropriate for patients with Marfan syndrome and in those with congenitally bicuspid aortic valves.

Treatment of the distal aorta in chronic type A dissection is somewhat controversial. Some advocate obliteration of flow in the false lumen with distal aortic repair, whereas others purposely maintain flow into both the true and false lumen using distal resection of the intimal flap. Those who reunite the chronically dissected aortic layers to perfuse only the true lumen maintain that false lumen perfusion continues through distal reentry tears in over 50%. There is a theoretical concern that important side branches arise exclusively from the false lumen and perfusion may be interrupted with this technique. Our practice at the University of Virginia is to resect the distal chronic dissection flap to obviate such concerns. The distal anastomosis is therefore made to the outer wall of the aorta, which has a great deal of structural integrity. Malperfusion of the brachiocephalic vessels as a result of chronic type A dissection is treated with resection of the dissection flap from the arch. Infrequently, the chronic dissection flap extends into more distal branch vessels and may present as transient ischemic attacks or stroke. In such cases it is often necessary to resect the dissection flap into the branch vessel or reunite the layers distally prior to reimplantation.

Infrequently, chronic type A dissection results in extensive aneurysmal dilatation of the aorta extending from the ascending aorta through the arch and into the descending thoracic aorta. Surgical treatment of such extensive disease has traditionally been performed as a staged procedure in which the ascending aorta and arch are replaced first through a sternotomy. The second stage of the so-called elephant trunk procedure is performed 6 weeks later through a left thoracotomy for replacement of the descending aorta using a second vascular graft. Originally described by Borst and associates, this technique has been used extensively with good results.[71] In some cases, the aorta distal to the left subclavian artery may be so large as to preclude the use of a two-stage repair. Kouchoukos and coworkers recently described a single-stage repair performed through a bilateral anterior thoracotomy in which the arch is repaired first during a brief period of circulatory arrest. Right subclavian and femoral artery cannulation for cardiopulmonary bypass provide proximal and distal perfusion during the subsequent ascending and descending aortic replacement. The hospital mortality was 6.2% and there were no adverse neurologic outcomes in the small series.[72]

Techniques for type B dissection

The techniques used for replacement of the descending thoracic aorta are identical to those described for treatment of acute type B dissection. The extent of resection, however, for chronic type B dissection is usually greater, with the goal of removing all dissected aorta at risk for rupture or symptoms. Usually these operations can be performed through the left chest, but more extensive aneurysms or cases of visceral malperfusion require a thoracoabdominal incision or a staged repair similar to the elephant trunk. The proximal anastomosis is ideally made to undissected normal aorta, but infrequently the distal arch is involved, which requires alteration in surgical strategy. Most of the technical controversy regarding repair of chronic type B dissection centers on methods of spinal cord protection during these operations.

As mentioned we prefer the combination of partial left heart bypass and cerebrospinal fluid drainage. Sites for cannulation are the left inferior pulmonary vein and the left femoral artery or descending thoracic aorta. Depending on the location and extent of the aneurysm, the distal arch is mobilized first. The area between the left common carotid and left subclavian artery is circumferentially dissected, and the left subclavian artery is independently controlled. Partial left heart bypass is then initiated. Ideally clamps are placed between the left subclavian and left common carotid arteries and on the aorta distal to the involved segment. If the entire descending thoracic aorta is diseased, the clamp is placed on the mid-thoracic aorta to perform the proximal anastomosis first. The aorta is opened and small intercostal arteries are oversewn. The proximal anastomosis is made to normal aorta whenever possible with running 3-0 polypropylene; 4-0 polypropylene is used if the tissue is fragile. The clamp is moved distally onto the graft to inspect the proximal anastomosis and achieve hemostasis. Several centimeters of the dissection flap is then resected from the lumen of the distal aorta and the distal anastomosis created to the adventitia of the chronic dissection. In more extensive thoracoabdominal disease, the clamp is progressively moved distal as intercostal arteries below T7 to L2 and visceral vessels are reimplanted (Fig. 51-22). Bypass is terminated and the operation completed.

Full cardiopulmonary bypass with deep hypothermic circulatory arrest may be necessary in patients in whom the proximal anastomosis cannot be safely or adequately performed with a clamp in the usual position. Kouchoukas and associates have a large experience in this area and cite a 6.2% 30-day mortality, 1.9% stroke rate, and no paraplegia in the subgroup of patients with aortic dissection.[73] These data strongly support this simple and elegant technique as one of the most efficacious for spinal cord and visceral organ protection in these complicated procedures.

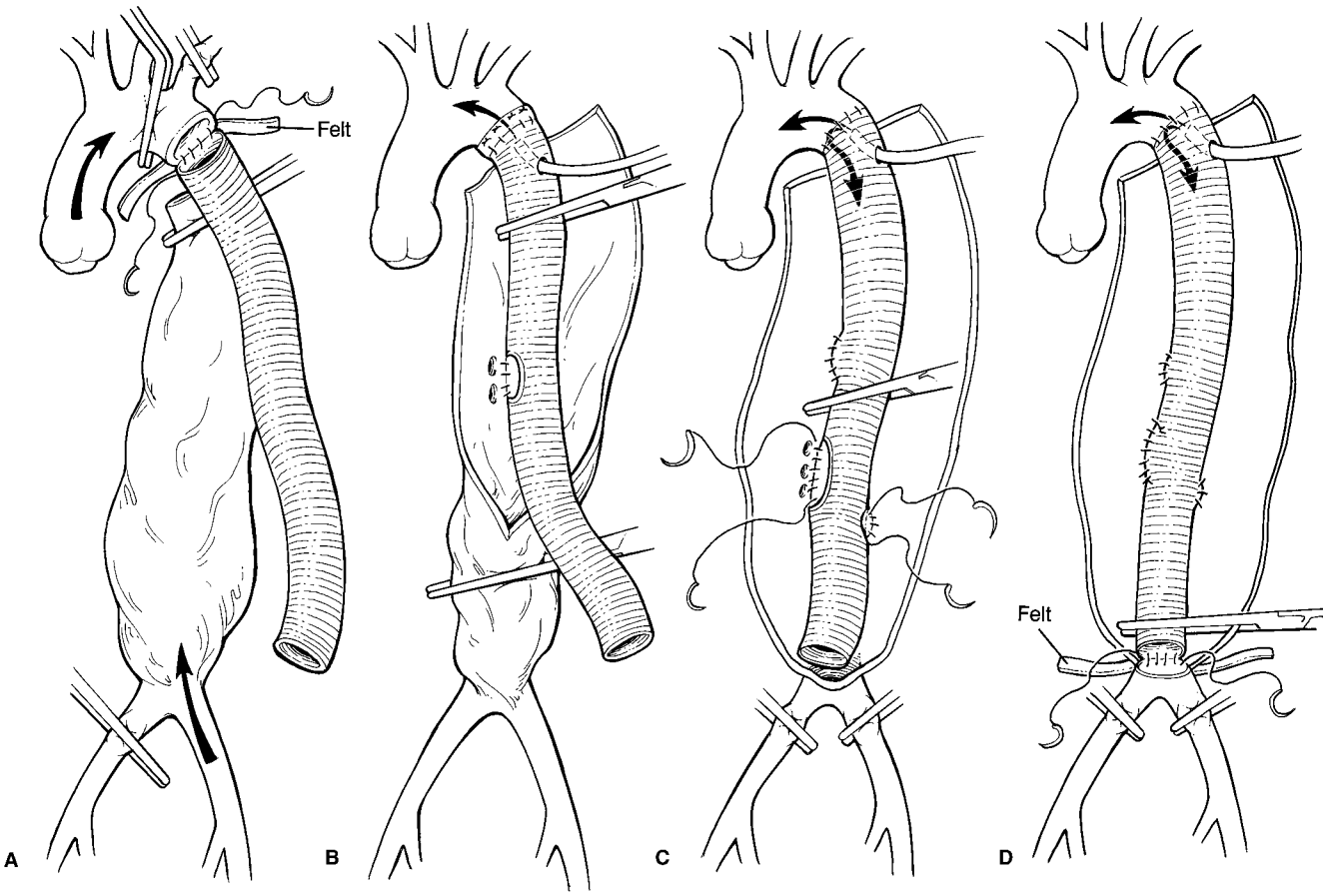

Figure 51-22. Replacement of the thoracoabdominal aorta. (A) A left femoral cannula perfuses the lower body and viscera while the heart continues to eject. The arch is transected near or at the left subclavian and any dissection involving the proximal cuff is repaired. (B) The clamp is moved down and a second arterial cannula is inserted into the proximal graft to perfuse the upper body and heart. The anterior wall of the dissection is incised longitudinally and bleeding intercostals of the upper six pairs are oversewn. A group of lower intercostal arteries above the celiac axis is sutured to the graft. (C) The clamp is moved down and the distal aortic clamp is moved to the left common iliac artery. A patch of aorta containing the celiac, superior mesenteric, and right renal artery is sewn into the graft. The left renal artery is sutured separately to the graft. (D) The proximal clamp is moved below the visceral anastomoses and the distal aortic anastomosis is made to the aortic bifurcation.

Results

The operative mortality for chronic type A dissection is between 4 and 17% and on average is very similar to that reported for chronic type B repair at 11 to 15%.[74,75] The actuarial survival following operation for chronic type A and B dissections is no different at 5 years (59 to 75%) or at 10 years (45%).[58] The stroke rate following repair of chronic type A dissections is 4%. Early neurologic complications occurred in 9%.[75] Regular follow-up of the aortic valve is necessary when the native valve is preserved at the initial operation. This is best performed using transthoracic echocardiography on a yearly basis. Early reports indicated that nearly 20% of patients require reoperation secondary to progressive aortic regurgitation. The most recent data from David and colleagues, however, reveal a 90 ± 4% 5-year freedom from severe or moderate aortic insufficiency in patients with aortic root aneurysm, and 98 ± 2% in patients with ascending aortic aneurysm following valve-sparing surgery.[69]

CONCLUSION

Considerable improvement in the treatment of patients with acute and chronic aortic dissection has occurred over the last 50 years. Continued progress is inevitable and technologies such as endovascular repair may eventually achieve results comparable to surgery. Complex forms of dissection that include aortic root and valvular pathology, however, will require surgical treatment for the foreseeable future. These patients will undoubtedly benefit from the novel basic and clinical research taking place in the areas of spinal cord and cerebral protection, strategies for cardiopulmonary bypass, improved vascular graft technology, and procedures for

preservation of the aortic valve. Such progress may even permit advancement in our greatest remaining clinical challenge, those patients who are hemodynamically unstable following aortic dissection.

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CHAPTER 52

Ascending Aortic Aneurysms

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EARLY DESCRIPTIONS AND SURGICAL INTERVENTIONS

Arterial dilations were first described in the ancient *Ebers Papyrus*, a medical scroll written in Egypt in 2000 B.C. The first accurate description of arterial aneurysms is credited to the Greek physician Galen (A.D. 126–c216). This was based on his observation of false aneurysms in gladiators injured during battle in the 2nd century.[1] Antyllus, during the same time period, made the distinction between traumatic aneurysms and those of a degenerative etiology. Antyllus believed that these lesions were due to clot formation and he was the first to attempt surgical treatment of aneurysms with proximal and distal ligation, opening of the aneurysmal sac, and removal of its contents.[2]

In the late 1500s, the great French surgeon Ambroise Paré (1510–1590) described a death by a ruptured thoracic aortic aneurysm and concluded that internal aneurysms were incurable. Paré also proposed that syphilis played a causative role in some aortic aneurysms, but this was not generally accepted until 1895 when Dohle described the microscopic findings of syphilitic aortitis.[1]

The earliest surgical treatment of aneurysms consisted of interruption of arterial flow via either ligation or the stimulation of thrombosis. These procedures met with variable success depending on the position of the aneurysm and the extent of collateral circulation.[2] Arterial ligation was popularized in the 1800s by John Hunter, who demonstrated safe and reproducible means of ligating certain peripheral arteries.[3] Innovative measures used to cause thrombosis of aneurysms included the insertion of long segments of wire[4] with the application of an electric current,[5] and wrapping of aneurysms with cellophane or other irritating materials.[6,7]

In 1888, Rudolph Matas introduced a very different approach. In an operation he referred to as obliterative endoaneurysmorraphy,[8,9] stitches placed from within the aneurysm sac obliterated the arterial openings. This provided more secure closure of large aneurysms that would have been difficult to ligate externally. Recognizing the importance of maintaining arterial continuity for certain aneurysms, he subsequently devised techniques of restorative or reconstructive endoaneurysmorraphy,[10] in which diseased segments of the aneurysm wall were resected and the remaining vessel wall was reconstructed to reestablish flow. The number of aneurysms to which these techniques could be applied, however, was very limited. The broad application of surgical treatment for major arterial aneurysms would have to await the development of satisfactory conduits and the techniques to insert them.

In the early twentieth century, Alexis Carrell and Charles Guthrie made several advances in the treatment of arterial aneurysms by using advanced anastomotic techniques and the use of aortic homografts as replacement conduits. This work later won Carrell the Nobel Prize and provided the basis for modern anastomotic techniques and use of graft replacements.[11]

Evolution of Modern Surgical Techniques

Replacement of the ascending aorta was first attempted without the use of cardiopulmonary bypass by Cooley and DeBakey in 1952 when they reported removal of a sacciform ascending aortic aneurysm by lateral resection and aortorrhaphy.[12] The first modern replacement of the ascending aorta with the use of cardiopulmonary bypass was subsequently reported by Cooley and DeBakey using an aortic allograft in 1956.[13] Mueller and associates combined allograft insertion with aortic valve repair in 1960 in a patient with Marfan syndrome.[14] As the need for conduits grew, attention was shifted to the development of a suitable artificial conduit. The first fabric to be utilized was Vinyon N cloth by Blakemore and Voorhees in New York City in 1954.[15] Dacron was subsequently introduced by DeBakey,[2] who

discovered it in a Houston department store, and it soon became the artificial conduit of choice for aortic replacement. Technical improvements in graft replacements included the impregnation of these polyester grafts with albumin, collagen, or gelatin, which has greatly reduced the blood loss through the grafts.

Replacement of the supracoronary ascending aorta with a synthetic graft and separate mechanical aortic valve replacement was performed by Starr and colleagues in 1963.[16] Wheat and coworkers[17] in 1964 resected the ascending aorta and entire aortic root except for small tongues of aortic tissue surrounding the coronary arteries. They then performed a mechanical valve insertion and fashioned the proximal tube graft to accommodate the coronary arteries, which were left in situ. The first use of a composite valve-graft conduit to replace the aortic root and ascending aorta was done by Bentall and De Bono in 1968.[18] The coronaries were left intact in the aortic wall and the surrounding aortic tissue was sewn to orifices that were created in the tube graft. The remaining aorta was wrapped tightly around the tube graft, creating an inclusion cylinder arrangement. In 1981 Cabrol and colleagues used an 8- to 10-mm Dacron graft to facilitate the restoration of coronary blood flow following aortic root replacement.[19] Variations of these pioneering procedures using modern low-profile mechanical valves and hemostatic collagen- or gelatin-impregnated woven Dacron grafts are commonly performed today.

INCIDENCE AND RISK FACTORS

Aortic aneurysms are the 13th leading cause of mortality in the United States.[20] The incidence of thoracic aortic aneurysms is estimated to be 5.9 cases per 100,000 person-years,[21] and the incidence appears to be increasing as a result of routine screening studies, improved imaging modalities, and increased clinical awareness. Aneurysm disease is the most common indication for surgical therapy on the thoracic aorta and replacement of the ascending aorta accounts for the majority of thoracic aortic procedures.[22] The mean age at the time of diagnosis ranges from 59 to 69 years.[23] Men are typically diagnosed at a younger age and there is a 2:1 to 4:1 male predominance.[23]

Traditional risk factors have included smoking, hypertension, atherosclerosis, and well-defined genetic disorders such as Marfan syndrome and Ehlers-Danlos syndrome.[21,24–27] Subtler forms of inherited metabolic disorders are being elucidated,[28] and perhaps play a role in more instances than was previously suspected. Syphilis, at one time the predominant etiology of ascending aortic aneurysms, has become very uncommon with the development of effective antibiotics. Bicuspid and unicuspid aortic valves are associated with ascending aortic aneurysms and dissections beyond that which can be attributed to simple hemodynamic disturbance, suggesting an underlying abnormality of the aortic wall.[29]

ETIOLOGY AND PATHOPHYSIOLOGY

General

Most of the elasticity and tensile strength of the aorta is derived from its medial layer, which consists of approximately 45 to 55 lamellar units of elastin, collagen, smooth muscle cells, and ground substance. In the ascending aorta, the elastin content is high, consistent with its compliant nature, and diminishes as one proceeds distally into the descending thoracic and abdominal aorta. The media also becomes thinner distally, and in the abdominal aorta the total number of lamellae is reduced by approximately one-half.[30]

The aortic wall is a biologically active environment. Smooth muscle cells synthesize and degrade elastin, collagen, and proteoglycans.[31] In the media of a typical ascending aortic aneurysm there is fragmentation of elastic fibers, and loss of smooth muscle cells[32] or alteration in smooth muscle cell function.[31] The resulting pathologic entity is referred to as cystic medial degeneration or cystic medial necrosis. In advanced forms there is a dramatic loss of elastic fibers and smooth muscle cells with the accumulation of a basophilic amorphous material giving the media a true cystic appearance.[32] Subtler degrees of elastic fiber fragmentation are normal, and the diameter of the ascending aorta typically increases with age.[33] Smoking has been associated with increased concentrations of elastolytic enzymes within the aortic wall, possibly hastening this process.[33,34] The role of atherosclerosis is controversial.

During systole, the ascending aorta expands, converting a portion of the kinetic energy of left ventricular contraction into potential energy in the aortic wall. During diastole the aorta recoils, converting this potential energy once again into the kinetic energy of forward flow.[35] This coupling of the left ventricle and aorta ensures efficient forward flow during both phases of the cardiac cycle. With weakening of the aortic wall and loss of elasticity, dilation ensues. Dilation results in increased wall tension relative to intra-aortic pressure according to the law of Laplace. This amplifies the injurious forces on the aortic wall produced by hypertension and results in progressive dilation. These pathologic changes in the aortic wall can result in inefficient ventricular-aortic coupling, aortic valve incompetence, and the potential for rupture or dissection.

Idiopathic Cystic Medial Degeneration

Cystic medial degeneration is the most common etiology of ascending thoracic aortic aneurysm disease.[36] Elastic fiber fragmentation is a normal process of aging,[33] but is accelerated in some individuals for poorly understood reasons. This results in premature weakening of the aortic wall, aneurysmal dilation, and the potential for rupture or dissection. Many cases that are now considered idiopathic may in the future be described as subtle disorders of metabolism that accelerate aortic wall degeneration in response to common risk factors.

Genetic Disorders

Marfan syndrome

Marfan syndrome is an autosomal dominant connective tissue disorder, with potentially life-threatening cardiovascular manifestations.[37] The estimated frequency is 1 per 10,000 births.[38] This disorder has been traced to the fibrillin gene of chromosome 15,[39–43] with more than 70 different defects identified thus far.[44] It is believed that one-third of cases are secondary to spontaneous mutations.[45] Fibrillin is one of the major structural components of the elastic fiber.[46] The resulting abnormal elastic fibers are prone to disruption and result in histologic findings consistent with cystic medial degeneration of the smooth muscle layer at an early age.[32] Seventy-five to eighty-five percent of patients with Marfan syndrome have dilation of the aortic sinuses and annulus in addition to the ascending aorta. This morphology, referred to as annuloaortic ectasia, is the classic presentation of Marfan syndrome, but can occur in the absence of a known connective tissue disorder. Because of the frequent aortic root involvement, aortic insufficiency is common.[47] In addition, one half of patients with Marfan syndrome also have mitral regurgitation.[21]

Ehlers-danlos syndrome

Ehlers-Danlos syndrome is an inherited disorder of connective tissue with multiple subtypes characterized by various defects in the synthesis of type III collagen.[48] Type IV Ehlers-Danlos may be associated with life-threatening cardiovascular manifestations including ascending aortic rupture without dissection. Type IV Ehlers-Danlos is most commonly a sporadic genetic disorder, but may be inherited as an autosomal dominant trait.[48,49] Spontaneous arterial rupture is the most common cause of death and usually involves the mesenteric vessels.[49] Less commonly, patients develop abdominal or thoracic aortic aneurysms or dissections.[50,51] Surgical treatment is challenging because of the friable nature of the vascular tissue.

Familial aneurysms

Certain families, without phenotypic expression of Marfan syndrome, exhibit strong histories of ascending aortic aneurysm formation and dissection transmitted in an autosomal dominant fashion. In a recent study of 15 such families, 9 demonstrated evidence of linkage to the 5q locus, although the specific gene and product have not been identified.[28] None of the 15 families demonstrated linkage to the fibrillin gene. Further investigation will likely reveal other examples of more subtle inherited or spontaneously occurring disorders of metabolism that result in accelerated deterioration of the aortic wall.

Bicuspid aortic valve disease

Bicuspid aortic valve disease is the most common congenital anomaly and occurs in 0.9 to 2.0% of the population or approximately 4 million people in the United States. There is evidence to suggest an intrinsic smooth muscle abnormality which leads to a higher rate of cystic medial degeneration in those patients with congenital bicuspid valve disease.[52,53] Those patients with bicuspid aortic valve disease and aneurysmal dilation of the ascending aorta should be considered for earlier surgery due to the intrinsic weakness of the aorta.[54]

Atherosclerosis

Atherosclerosis is reported to be the second most common cause of aneurysmal degeneration in the ascending aorta.[21] Atherosclerosis is less commonly seen in ascending aortic aneurysms than in descending thoracic or abdominal aortic aneurysms and it has long been theorized that the development of invasive atheromas results in destruction of elastic fibers and smooth muscle cells in the media, resulting in weakening and dilation.[21] This process was proposed as the primary etiology of descending thoracic and abdominal aortic aneurysms, and the second most common cause of ascending aortic aneurysms.[21,55] These theories are now challenged by the concept that atherosclerosis is a concomitant process that infiltrates a diseased media with altered barriers.[56] This would explain the divergent course of the atherosclerotic abdominal aorta towards obstructive versus aneurysmal disease.

Aneurysms Associated with Aortic Dissection

Patients who survive acute dissection of the ascending aorta often have or will develop an associated aneurysm. This aneurysmal dilation most commonly originates from the false lumen of the aortic dissection. This outer wall of the false lumen consists of only the weak outer media and adventitia. The rate of expansion is higher than in other types of ascending aortic aneurysms, as the barrier to dilation and rupture is only this outer one-third of the media and the adventitia.[21,57] Aortic dissection is discussed in Chapter 51.

Aneurysms Associated with Aortic Valve Disease

Aneurysms of the ascending aorta are frequently associated with bicuspid and unicuspid aortic valves. Although initially thought to be secondary to poststenotic dilation, a primary structural abnormality of the aortic wall appears contributory. Aortic enlargement occurs at an accelerated pace in congenitally stenosed valves compared to trileaflet valves with equivalent degrees of stenosis.[29,58] Aortic dissection occurs in patients with bicuspid aortic valves at a rate 10-fold that of the normal population, a trend that is not found in other forms of aortic stenosis.[24] This strongly implies an inherent weakness in the aortic wall.

Infection

Bacterial (mycotic) aneurysms

Primary bacterial infection of the ascending aortic wall resulting in aneurysm formation is rare. These aneurysms are termed mycotic aneurysms regardless of the infectious

pathogen. This is believed to occur either after an episode of bacterial endocarditis or from an aortic jet lesion causing endothelial trauma.[59] Organisms most commonly isolated from patients with mycotic aneurysms are, in order of decreasing frequency, *Staphylococcus aureus, S. epidermidis, Salmonella*, and *Streptococcus*.[60] Mycotic ascending aortic aneurysms are usually the result of infective valvular endocarditis.[59] Infection of laminar clot within a previously formed aneurysm may also occur after transient bacteremia.[60]

Syphilitic aneurysms

Before the advent of antibiotics, syphilitic aortitis, caused by the spirochete *Treponema pallidum*, was the most common cause of ascending aortic aneurysms. Syphilitic aortitis causes an obliterative endarteritis of the vasa vasorum which results in ischemic injury to the aortic media with subsequent destruction of elastic and muscular elements.[32] The media is replaced by a thickened fibrous tissue, which begins to dilate. This process most commonly involves the ascending aorta and arch,[61] but may involve the root as well. If the regions of the coronary ostia are involved, significant coronary obstruction may occur.[1] Antibiotic therapy does not reverse the vascular pathology and aneurysm formation.

Arteritis

Ascending aortic aneurysms may develop as the result of inflammatory conditions such as Takayasu arteritis, Kawasaki disease, Behçet disease, and giant cell arteritis. Takayasu arteritis most commonly involves the aortic arch and its major branches, but may involve any or all segments of the aorta. Takayasu arteritis usually produces obstructive lesions, but may have a dilative component in 15% of cases.[62] Giant cell arteritis (temporal arteritis) may lead to weakening of the aortic wall and eventual aneurysm formation or dissection.[63,64] In one population-based study temporal arteritis was associated with a greater than 17-fold increase in the risk of developing a thoracic aneurysm.[65] Medial destruction of the aortic wall by these inflammatory pathologies is the etiology of aneurysm formation.

Trauma

Chronic traumatic aneurysms of the aorta are rare and usually involve the descending aorta rather than the ascending aorta. Although the ascending aorta is the site of rupture in 20% of blunt aortic injuries, survival beyond the initial injury is unusual, with the patient usually succumbing to acute cardiac tamponade and other concomitant injuries.[66] This subject is covered in Chapter 57.

Pseudoaneurysms

Pseudoaneurysms are defined as aneurysmal dilations that do not contain all layers of the arterial wall. The wall of a pseudoaneurysm is composed primarily of variable layers of the media, adventitia, thrombus, and surrounding structures.[33] Postoperative pseudoaneurysms may occur at an aortic suture line or at the site of aortic cannulation. Causes include technical error, acute dissection, native tissue degeneration, or deterioration of the graft or suture material.[67,68] The use of modern monofilament suture and low-porosity collagen- or gelatin-impregnated Dacron grafts,[69] as well as the abandonment of the inclusion cylinder technique,[70,71] have lessened the incidence of this complication. Less commonly, pseudoaneurysms of the ascending aorta occur after trauma or infection.

NATURAL HISTORY

General

The aorta functions not only as a conduit delivering blood to the tissues, but also as an important modulator of the entire cardiovascular system.[72] The appropriate application of surgical treatment depends on an understanding of the relative risks of surgery versus the natural history of the disease. The natural history of untreated aneurysms of the thoracic aorta often concludes with patient death because of rupture or dissection. Figure 52-1 shows the estimated actuarial survival curve for 72 patients who were diagnosed with thoracic aneurysms from 1951 to 1980 and were followed nonoperatively. Seventy-four percent of the patients experienced

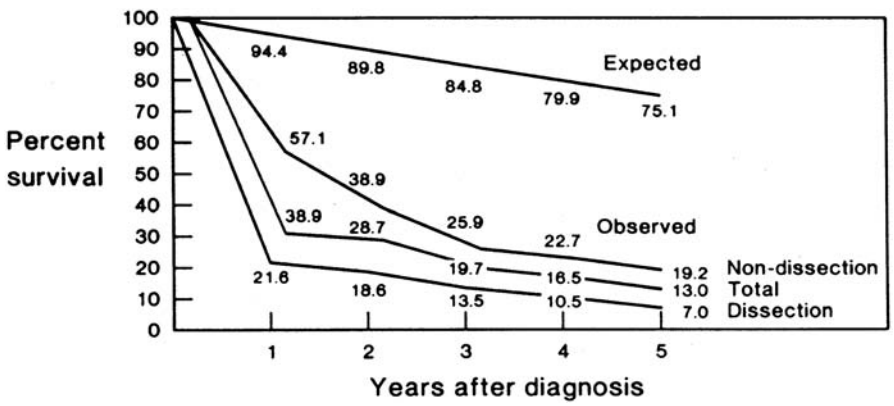


Figure 52-1. Actuarial survival estimates of 72 patients followed nonoperatively with thoracic aneurysms and dissections. *(Reproduced with permission from Bickerstaff et al.[21])*

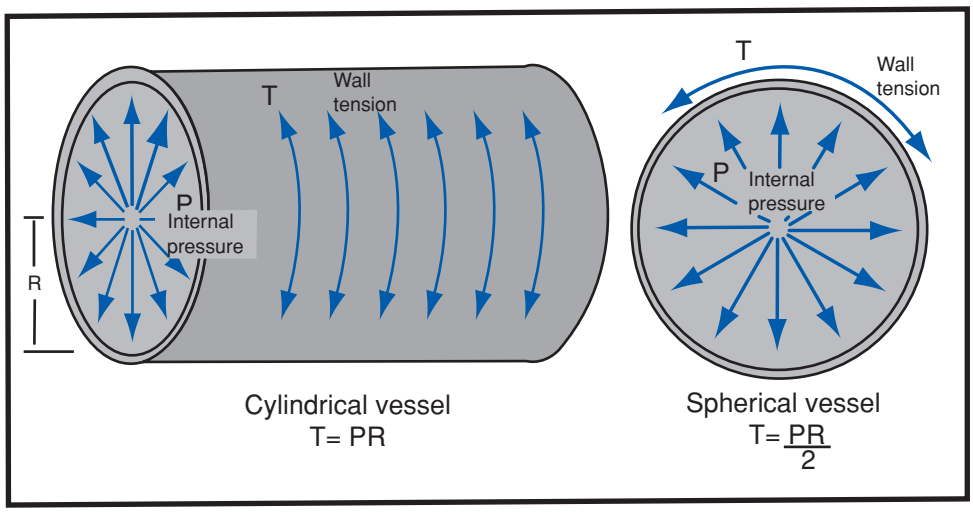


Figure 52-2. The law of Laplace. T = tension; P = pressure; R = radius. *(Illustration from HyperPhysics by Rod Nave, Georgia State University.)*

rupture, and 94% of these patients died.[21] The potential for complications of rupture or dissection is primarily dependent on size and the underlying etiology of the aneurysm.

Size

Based on the law of Laplace, wall tension increases as the radius of an aneurysm increases (tension = pressure x radius; Fig. 52-2). It is therefore intuitive that larger aneurysms have a greater risk of rupture. This was first established for abdominal aortic aneurysms by Szilagyi and associates in 1966.[73] Subsequent natural history studies have confirmed this finding and have found also that larger aneurysms have a higher rate of expansion.[74,75] Coady and coworkers[76] have written extensively on the natural history of thoracic aortic aneurysms. The incidence of acute dissection or rupture according to size in their cohort of patients is shown in Fig. 52-3. Logistic regression analysis revealed a 4.3-fold increased risk of rupture or dissection in an aneurysm 6.0 to 6.9 cm in diameter compared to an aneurysm 4.0 to 4.9 cm in diameter. Growth rates varied from 0.08 cm per year for aneurysms less than 4.0 cm to 0.16 cm per year for aneurysms greater than 8.0 cm in diameter. Mean growth rates as great as 0.42 cm per year have been reported in other series.[77,78] Dapunt and colleagues[57] also noted an increased rate of growth in smokers and patients with a history of hypertension. Davies and associates[79] demonstrated similar results in their evaluation of cumulative risk of negative outcomes based on thoracic aortic aneurysm size on initial presentation (Fig. 52-4).

The Influence of Etiology on Natural History

Marfan syndrome

Although size criteria are perhaps most important, the underlying etiology must be considered. Patients with Marfan syndrome have accelerated aneurysm growth and tend to rupture or dissect at smaller sizes.[79] This is particularly true for those with a family history of early complications.[79] The

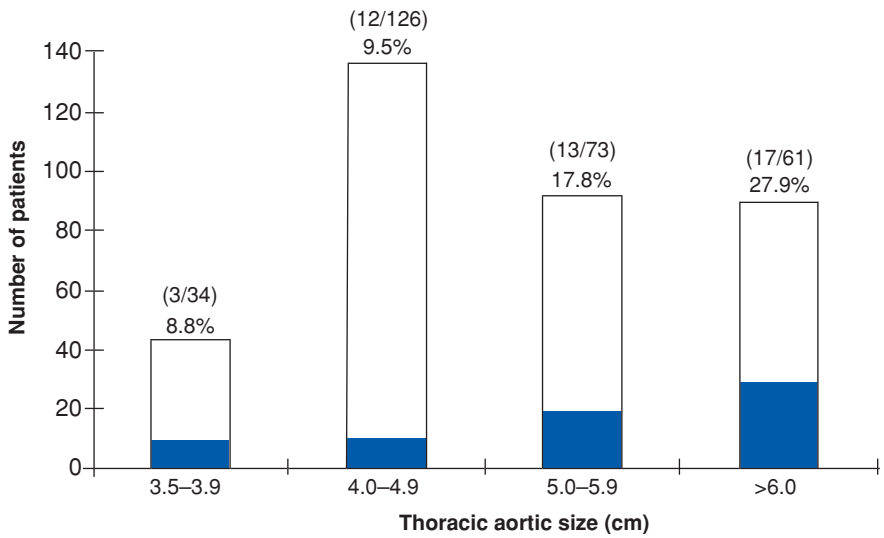


Figure 52-3. The incidence of acute dissection or rupture of thoracic aneurysms according to size. The height of the column corresponds to the total number of patients and the black area to the proportion of patients who suffered complications of dissection or rupture. *(Reproduced with permission from Coady et al.[76])*

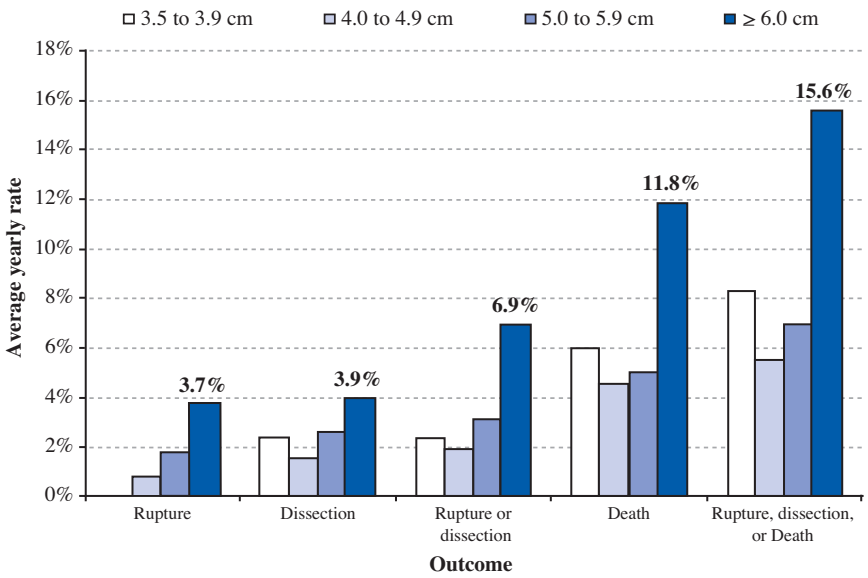


Figure 52-4. Average yearly rates of negative outcomes (rupture, dissection, and death). These estimates represent the average rate during the first 5 years after presentation. *(Reproduced with permission from Davies et al.[79])*

average age of death for untreated patients with Marfan syndrome is 32 years,[80] with complications of the aortic root being responsible for 60 to 80% of these deaths from aortic rupture, acute congestive heart failure from valvular incompetence, or acute aortic dissection.[47,81]

Familial aneurysms

The inheritance of aneurysmal disease without an associated phenotypic syndrome such as Marfan syndrome was first noted for abdominal aortic aneurysms.[82,83] In 1997 familial aggregation of thoracic aneurysms was noted by Biddinger and associates.[84] Coady and coworkers[85] estimated that 19% of their study population fit criteria for familial aneurysms by pedigree analysis. The primary mode of inheritance was autosomal dominant, but X-linked and recessive patterns were also evident in some cases. This subgroup had an annual growth rate almost double the growth rate for the entire population.

Aortic dissection

In chronic dissections, the barrier to rupture is the outer third of the media and the adventitia. Dissections are therefore associated with an accelerated rate of expansion and rupture. Comparisons between dissecting and nondissecting thoracic aneurysms of similar size have revealed as much as a sixfold greater growth rate for dissections.[23]

Syphilitic aneurysms

The average time from the diagnosis of advanced syphilis to cardiovascular symptoms is 10 to 20 years.[1] The average survival from the onset of cardiac symptoms is only six to eight months.[1] Saccular aneurysms, which are common in this disease, may have a more rapid rate of expansion and greater risk of rupture.[86] Dissection is less likely because of the scarring that occurs within the media.[32] Modern studies of growth rates and size at the time of rupture are not feasible because of the rarity of this condition.

CLINICAL PRESENTATION

Signs and Symptoms

A significant number of ascending aortic aneurysms are asymptomatic when diagnosed, being incidentally noted on chest x-ray or other imaging study.[26] Echocardiographic evaluation of aortic insufficiency is also a frequent mode of diagnosis. Between 25 and 75% of patients, however, present with chest pain that results in the diagnosis of an aneurysm.[26,87,88] Pain from the ascending aorta is usually localized to the anterior chest. The pain may be acute in onset signifying impending rupture, or a chronic gnawing pain from compression of the overlying sternum. Occasionally signs of superior vena cava or airway compression are present.[88] Less commonly, aneurysms of the ascending aorta or aortic root can rupture into the right atrium or the superior vena cava, presenting with high-output cardiac failure, or bleed into the lungs with ensuing hemoptysis. Hoarseness resulting from stretch injury of the left recurrent laryngeal nerve suggests involvement of the distal aortic arch or proximal descending thoracic aorta. In contrast, dissection of the ascending aorta presents with severe "tearing" pain in 75% of patients.[25,26]

Physical Examination

In the case of rupture, the patient will present in extremis. In a patient without rupture, the examination is often unremarkable. If the sinotubular ridge or aortic root is dilated, a widened pulse pressure or diastolic murmur signifying aortic

insufficiency may be noted. If dilation is isolated to the ascending aorta, however, the aneurysm can reach large dimensions without producing physical findings. A thorough vascular examination should be carried out to look for any concomitant peripheral vascular disease, carotid disease, or sequelae of distal embolization. Abdominal aortic aneurysms are present in 10 to 20% of patients with atherosclerotic involvement of an ascending aortic aneurysm,[25,89] and this should also be sought on physical examination. In rare cases, aneurysms may cause compression necrosis of the overlying sternum and ribs. Syphilitic aneurysms have been noted to erode through the chest wall and rupture externally.[1]

DIAGNOSTIC STUDIES

Electrocardiogram

With significant aortic insufficiency, left ventricular hypertrophy or strain is evident. Patients with generalized atherosclerosis may show evidence of concomitant coronary artery disease, or previous myocardial injury.

Chest Radiography

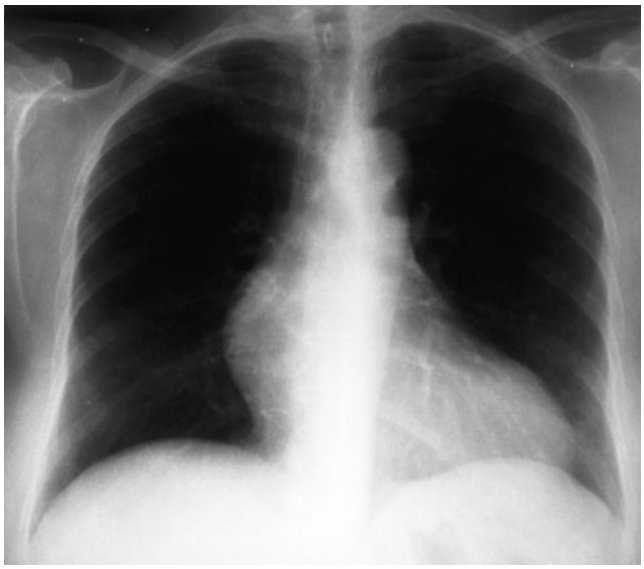
Many asymptomatic ascending aortic aneurysms are first detected on chest x-ray. The enlarged ascending aorta produces a convex contour of the right superior mediastinum (Fig. 52-5A). In the lateral view, there is loss of the retrosternal air space (Fig. 52-5B). Aneurysms confined to the aortic root can be obscured by the cardiac silhouette and may not be evident on chest radiograph.[90]

Echocardiography

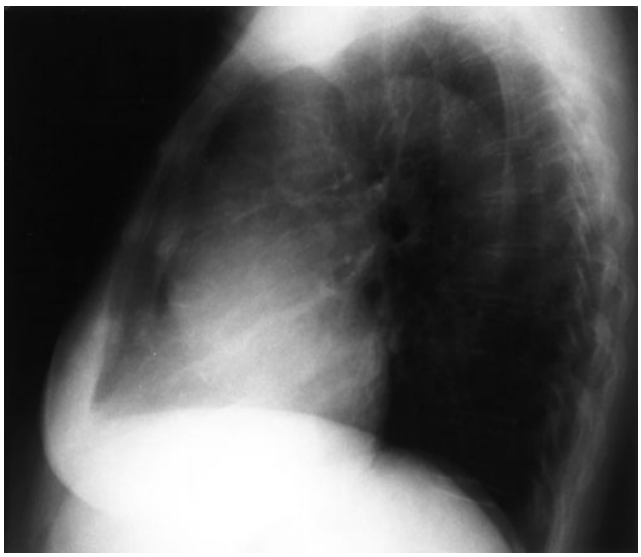
Transesophageal echocardiography (TEE) is a portable diagnostic tool that can be moved to the patient's bedside. This portability aids in diagnosis of acute aortic pathologies in the emergency department, operating room, and clinical suite. Ascending aortic aneurysms are the most common cause of isolated aortic insufficiency,[91] and therefore aneurysms are frequently detected during evaluation of a regurgitant aortic valve. TEE can accurately detect and differentiate between ascending aortic aneurysms, dissections, and intramural hematoma.[92] Imaging of the distal ascending aorta is obscured by air in the tracheobronchial tree, with up to 40% of its distal extent not well visualized.[93] Transthoracic echocardiography is far less reliable.[87] TEE is an invasive imaging modality and carries a small risk of esophageal perforation, respiratory compromise, and hemodynamic instability, which demands proper patient selection.

Aortography

Aortography provides precise delineation of the aortic lumen, and certain diseases have very characteristic arteriographic patterns. Annuloaortic ectasia has a "pear-shaped" morphology (Fig. 52-6) with prominent dilation



A



B

Figure 52-5. Posteroanterior and lateral chest radiograph of a patient with an ascending aortic aneurysm. The posteroanterior view (A) shows convexity of the right mediastinum, and the lateral view (B) shows loss of the normal retrosternal air space. *(Reproduced with permission from Downing SW, Kouchokos NT: Ascending aortic aneurysm, in Edmunds LH Jr (ed): Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997; p 1163.)*

of the aortic sinuses and less severe dilation of the ascending aorta tapering to normal caliber at the origin of the innominate artery. Pseudoaneurysms appear as saccular outpouchings with irregular contour.[94] Syphilitic aneurysms involving the aortic root are often associated with coronary ostial stenosis.[32]

One of the beneficial aspects of aortography is accurate demonstration of the relationship of the aneurysm to the arch vessels. Aortography also detects aortic regurgitation and cephalad displacement of the coronary ostia. In

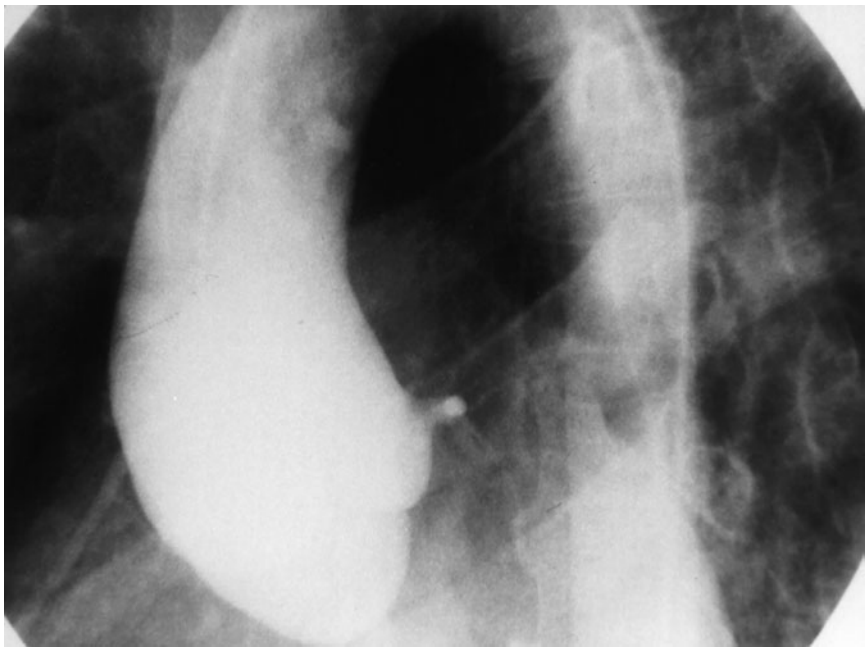


Figure 52-6. Aortic angiogram of a patient with classic annuloaortic ectasia. The aortic root is dilated and the ascending aorta tapers to a normal caliber at the origin of the innominate artery giving the classic "pear-shaped" morphology. *(Reproduced with permission from Downing SW, Kouchokos NT: Ascending aortic aneurysm, in Edmunds LH Jr (ed): Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997; p 1163.)*

patients over the age of 40 or with a pertinent history, the opportunity is afforded to check for coronary disease and left ventricular dysfunction. Disadvantages include contrast and radiation exposure, puncture site complications, underestimation of aneurysm size in the presence of laminar clot, and the likelihood of missing dissections.

Computed Tomography

Contrast-enhanced computed tomography (CT) is the most widely used noninvasive technique for imaging the thoracic aorta. CT scanning provides rapid and precise evaluation of the ascending aorta in regard to size, extent, and location of the disease process (Fig. 52-7). CT scanning detects areas of calcification, and accurately identifies dissections and mural thrombus. When laminar clot is present, CT scanning provides a more accurate assessment of aneurysm size than aortography. However, because structures are visualized in an axial view only, the diameter of a tortuous aorta can be grossly overestimated. Three-dimensional reconstruction of CT scans may prove useful in determining the proximal and distal extent of aortic disease relative to the arch vessels, which can aid the surgeon in operative planning.[88] Ideally, the entire thoracic and abdominal aorta should be examined for evidence of concomitant aneurysm disease in the arterial tree. The main disadvantage of CT scans is the need for contrast solution for optimal resolution, which may be contraindicated in those patients with renal insufficiency or a history of a dye allergy.

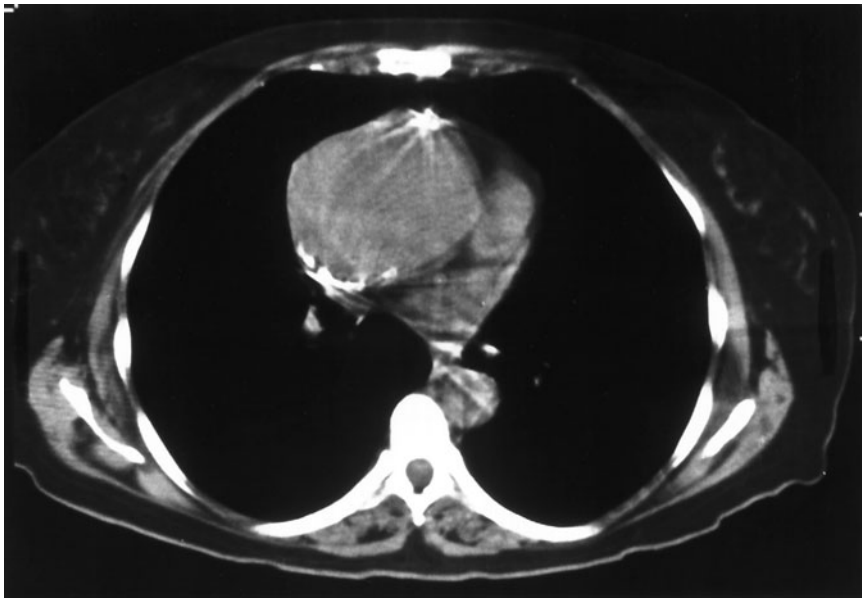


Figure 52-7. Computed tomographic scan of an 8-cm ascending aortic aneurysm. *(Reproduced with permission from Downing SW, Kouchokos NT: Ascending aortic aneurysm, in Edmunds LH Jr (ed): Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997; p 1163.)*

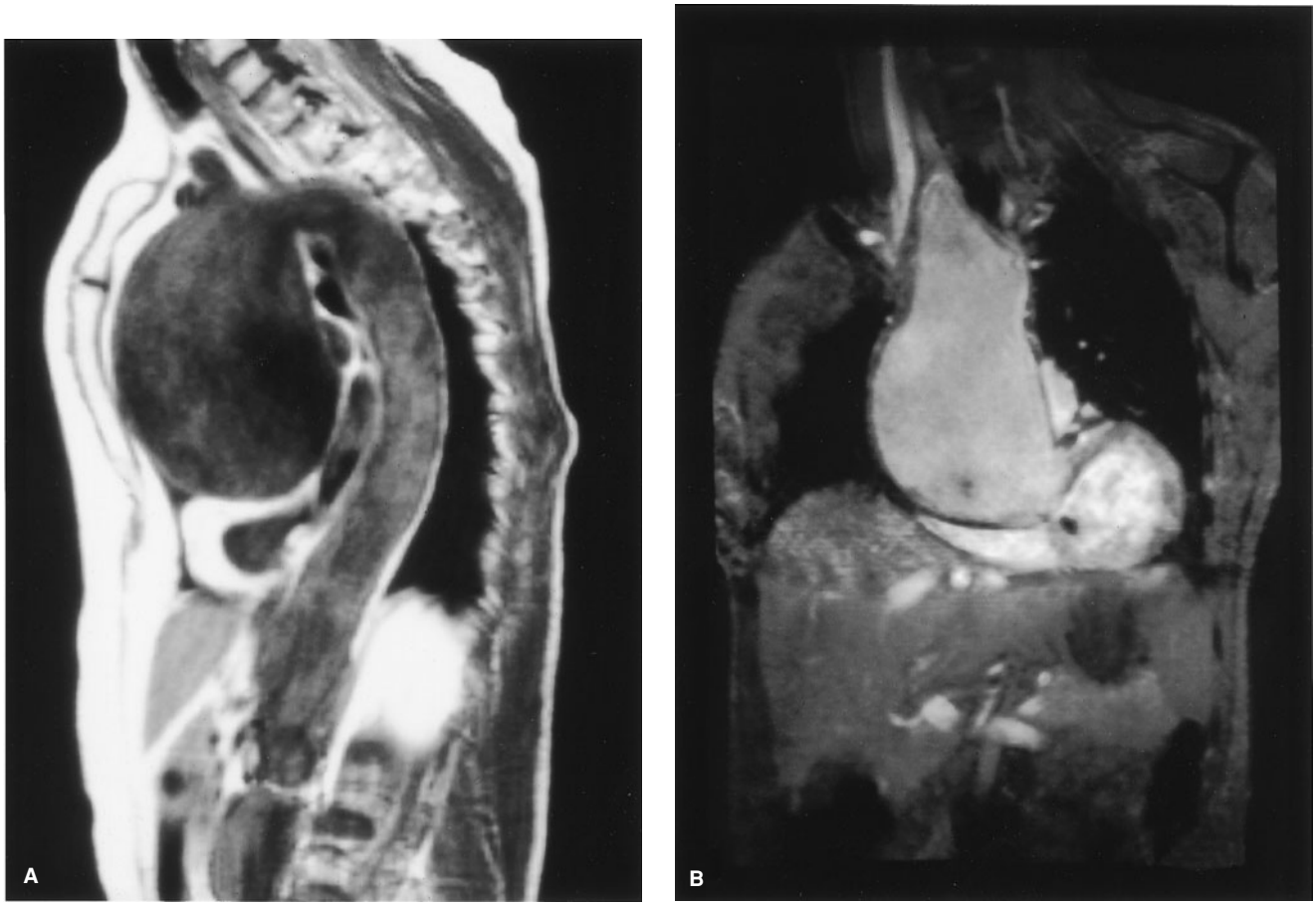


Figure 52-8. Magnetic resonance image of ascending aortic aneurysms demonstrating sagittal (A) and coronal (B) views. The origin of the innominate artery and its relationship to the distal portion of the aneurysm can be appreciated on the sagittal view. *(Images provided courtesy of Kent E. Yucel, MD.)*

Magnetic Resonance Imaging

The benefits of magnetic resonance imaging (MRI) over CT scanning include visualization in the sagittal and coronal planes (Fig. 52-8), enhanced three-dimensional imaging (Fig. 52-9), and the avoidance of contrast and radiation exposure. Cardiac imaging with MRI is evolving, and may provide evaluation of cardiac perfusion, myocardial function, and coronary and valve anatomy with a single modality in the future.[95–97] Contrast-enhanced MR angiography allows more precise measurements of the aorta and its major branches with images comparable to conventional angiography. Currently, however, MRI is expensive, less readily available, and more time consuming than CT scanning. In addition, current MRI monitors are relatively unsuitable for those patients connected to mechanical ventilators or hemodynamic monitoring equipment.

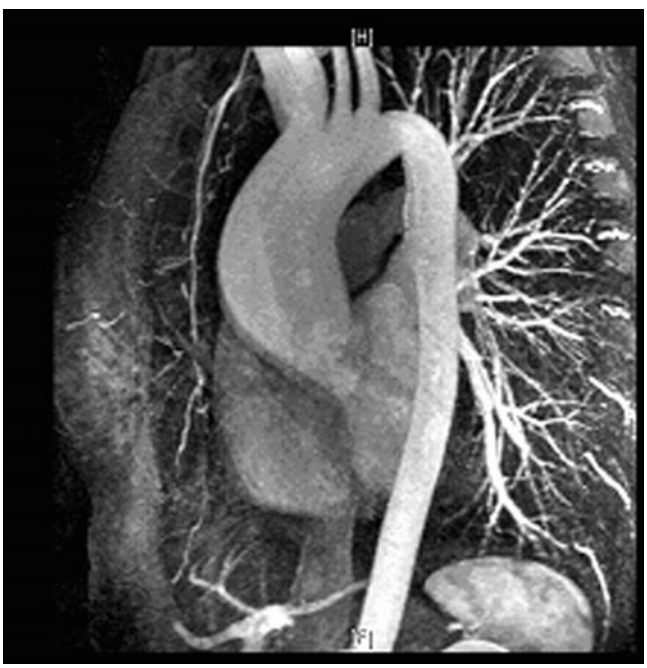


Figure 52-9. Three-dimensional magnetic resonance angiography imaging revealing an ascending aortic aneurysm extending into the proximal aortic arch. *(Image provided courtesy of R. Bolman, MD.)*

INDICATIONS FOR OPERATION

Symptoms

Emergent operation is indicated in the setting of acute ascending aortic dissection or rupture. Ascending aortic aneurysms rupture into the pericardial space and result in

death from acute cardiac tamponade. Aortic dissections may rupture or may compromise coronary or cerebral circulation. Operative mortality is significant in this setting, but death is certain in the case of rupture and probable in the case of acute dissection if not surgically addressed.

Symptomatic aortic insufficiency or stenosis may be the primary indication for operation. When replacing or repairing a diseased valve a decision must be made regarding the moderately dilated aorta. Michel and colleagues[98] reported that 25% of patients undergoing surgery for aortic insufficiency who had ascending aortic diameters greater than 4 cm required subsequent operation for aortic replacement. Prenger and associates[99] reported a 27% incidence of aortic dissection following aortic valve replacement in patients with aortic diameters greater than 5 cm. Based on these findings it is recommended that aortic diameters of 4 to 5 cm be dealt with at the time of aortic valve surgery. Further incentive for earlier surgery is the improved possibility of native valve preservation.

Size and Growth Rate

Because the diameter of an aneurysm strongly correlates with the risk of rupture or dissection, size has long been used as the criterion for elective surgical intervention. Size of the aneurysm at initial evaluation is the strongest predictor of risk of rupture. Although size criteria for the abdominal aorta have been well established and generally agreed upon, less of a consensus has emerged for the thoracic aorta. Variable growth rates and propensities for rupture in different regions of the thoracic aorta and with different underlying pathologies are perhaps to blame. The average size of rupture of the thoracic aorta reported in the literature is highly variable.[57,100,101] Coady and coworkers[76] report rupture or dissection at a median size of 5.9 cm in the ascending aorta (Fig. 52-10) and 7.2 cm in the descending aorta. Because

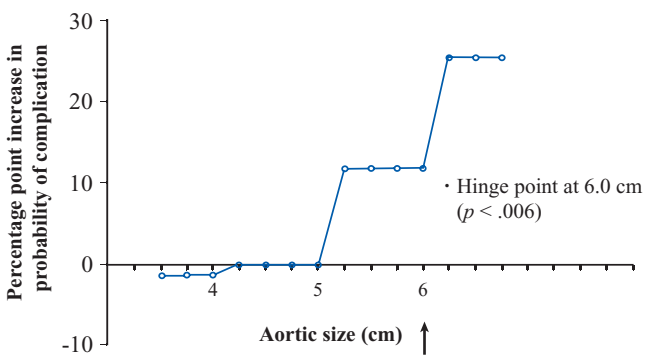


Figure 52-10. Logistic regression analysis of initial aneurysm size for risk of rupture or dissection. The probability of rupture or dissection is 25% higher in patients who present with aneurysms 6.0 cm or larger versus a comparison group with aneurysms 4.0 to 4.9 cm in diameter. Six centimeters appears to be a "hinge point" beyond which the risk of complications greatly increases. *(Reproduced with permission from Coady et al.[108])*

intervention at these diameters would have by definition resulted in rupture or dissection in 50% of patients, preemptive surgical therapy at 5.5 cm and 6.5 cm, respectively, for ascending and descending aneurysms seems appropriate.

As opposed to absolute size criteria, some surgeons prefer the use of ratios of measured to expected size. The expected size is based on the body surface area and age of the patient. The ratio indicating intervention is adjusted based on the underlying etiology. Ergin and colleagues[102] advocate a ratio of 1.5 for the average patient with an asymptomatic incidentally discovered ascending aortic aneurysm. This leads to intervention at a size of only 4.8 to 5.0 cm in an adult less than 40 years of age with a body surface area of 2 m^2. Because the ascending aorta normally increases in size with age, the diameter for intervention would be higher in a patient more than 40 years old.

The rate of expansion is also an important consideration. Reported mean growth rates of thoracic aneurysms vary from 0.10 to 0.42 cm per year.[56,77,79,103–105] The rate of expansion is usually greater in the descending aorta and in conditions with a weakened aortic wall, such as Marfan syndrome or chronic dissection.[76] Growth at a rate of greater than 1.0 cm per year is certainly an accepted indication for surgical intervention,[57] but more often the rate of dilation is used by the surgeon as supplementary information that helps to guide the timing of surgery rather than serve as an absolute indication.

The Influence of Etiology

Patients with Marfan syndrome or with familial aneurysms, particularly when there is a history of early dissection or rupture, should undergo earlier intervention. Gott and associates[106,107] recommend intervention in patients with Marfan syndrome at an ascending aortic diameter of 5.0 to 6.0 cm. Coady and coworkers[108] recommend intervention at 5.0 cm. Ergin and colleagues[102] recommend a ratio of measured diameter to predicted size of 1.3. Patients with chronic dissection should be considered to have similar intervention criteria as those with Marfan syndrome. Patients with bicuspid and unicuspid aortic valves are probably at intermediate risk[109] and Ergin and associates[102] recommend intervention at a ratio of 1.4 in these patients. Pseudoaneurysms are at a high risk of rupture and should be treated when discovered. In summary, the overall assessment of appropriate size of ascending aortic aneurysm to consider surgical repair is based on a paradigm that considers both size and etiology (Table 52-1).

PREOPERATIVE PREPARATION

A careful preoperative evaluation of the patient is important to minimize the risks of surgery. Nearly one-third of patients undergoing surgery for thoracic aortic disease have chronic obstructive pulmonary disease.[89] Patients with suspect pulmonary function should have spirometery and room air

Table 52–1.

Current Guidelines For Surgery

Adult age <40 years BSA 2 m^2	Diameter (cm)	Ratio
Marfan's (positive family history	>4.3	1.3
Chronic dissections	>4.3	1.3
Bicuspid value with dysfunction	>4.5	1.4
Degenerative with aortic insufficiency	>4.8	1.5
Degenerative without aortic insufficiency	>4.8	1.5
Other cardiac surgry	>4.8	1.5

AI = aortic insufficiency; BSA = body surface area.
Source: Reprinted with permission from Ergin et al.[102]

arterial blood gases. Smoking cessation, antibiotic treatment of chronic bronchitis, and chest physiotherapy may prove beneficial in elective situations. Normal renal function should be ensured with the appropriate blood work, and abnormal results should prompt further investigation. Because unaddressed severe carotid disease is a risk factor for stroke during ascending aortic operations,[110] patients over the age of 65 should have duplex imaging of their carotids. Younger patients with peripheral vascular disease, extensive coronary artery disease, carotid bruits, or history suspicious for cerebral ischemia should be investigated as well.[111] Abdominal aortic aneurysms occur in 10 to 20% of patients with ascending aortic aneurysms.[25,89] Patients with "atherosclerotic aneurysms" that extend into the aortic arch have a greater than 50% probability of having distal thoracic or abdominal aortic aneurysms.[89] CT or MRI of the abdominal aorta is indicated if disease is suspected.

CHOICE OF PROCEDURE

The specific procedure that is performed depends on the distal extent of aortic involvement, condition of the aortic root and the aortic valve (Fig. 52-11), underlying pathology, life expectancy of the patient, desired anticoagulation status, and surgeon preference. Specific procedures and their indications are listed in Table 52-2.

Ascending Aortic Aneurysms

Ascending aortic aneurysms with normal sinuses and aortic annulus require only replacement of the ascending aorta from the sinotubular ridge to the origin of the innominate artery with a Dacron tube graft. If the aortic valve is diseased,

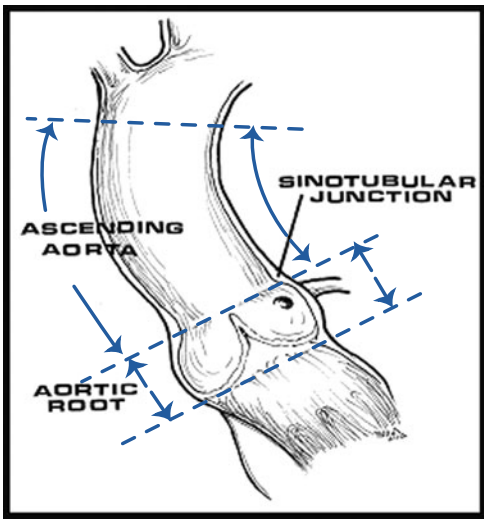


Figure 52-11. Illustration demonstrating the relationship of the aortic root, sinotubular junction, and ascending aorta. *(Illustration provided by R. Bolman, MD.)*

this can be replaced separately. The sinuses in patients with Marfan syndrome should not be preserved because of the frequent need for reoperation (Fig. 52-12).[112,113]

Annuloaortic Ectasia

Composite valve-graft conduit

Patients who have significant dilation of the aortic root in addition to an aneurysm of the ascending aorta or patients with Marfan syndrome should undergo replacement of the ascending aorta and root. This is usually done with a composite graft consisting of a mechanical valve inserted into a collagen- or gelatin-impregnated Dacron graft that comes preassembled. The coronary arteries are reimplanted as buttons.

Aortic allograft

The ascending aorta and root can be replaced with an aortic allograft with coronary reimplantation.[114] Accepted indications include patients with endocarditis, women anticipating pregnancy, young adults with active lifestyles, or patients with any other contraindications to anticoagulation.[115]

Pulmonary autografts (ross procedure)

A pulmonary autograft can be used to replace the aortic root and proximal ascending aorta. More distal replacement of the ascending aorta requires addition of a Dacron graft. The Ross procedure is most commonly performed for congenital surgery because of the proposed growth potential of the autograft. The use of the Ross procedure in adults with aneurysmal disease is more controversial. Potential indications include young adults with active lifestyles and life expectancies exceeding 15 to 20 years, women anticipating pregnancy, or patients with any contraindication to

Table 52–2.

Specific Procedures and Indications

Procedure	Potential indications
Simple tube graft*	Ascending aortic aneurysm with normal aortic root May correct central AI resulting from dilation of the ST junction
Composite valve-graft conduit	Involvement of ascending aorta and the root with aortic valve that cannot be spared
Separate ascending aorta-aortic valve replacement*	Ascending aortic aneurysm with normal root and aortic valve that requires replacement
Aortic allograft	Endocarditis with root destruction or infection of previous composite graft Root replacement for younger patients with active lifestyle or patients with contraindications to warfarin
Pulmonary autograft†	Root replacement for young patients who will benefit from growth potential of autograft Root replacement for younger patients with active lifestyle or patients with contraindications to warfarin
Aortic valve-spring procedure Reimplantation Root remodeling	Diseased ascending aorta and root with grossly normal aortic valves
External wrapping of the ascending aorta	Debilitated patients with limited survival who may not tolerate more extensive procedures

** Sparing the aortic root is contraindicated in Marfan syndrome.*
† The use of a pulmonary autograft is contraindicated in Marfan syndrome AI = aortic insufficiency; ST = sinotubular junction.

warfarin therapy.[115] The Ross procedure is contraindicated in patients with Marfan syndrome or inherited weakness of the aortic wall that may affect durability of the autograft.[115,116]

Valve-sparing procedures

If the aortic valve leaflets are grossly normal and aortic insufficiency is secondary to dilation of the sinotubular ridge or aortic root, then the native valve can often be spared.[117,118] Yacoub and associates have been able to apply valve-sparing techniques in almost 80% of patients operated on for ascending aortic aneurysms.[119] A variety of procedures are used to preserve the aortic valve. Reduction of the diameter of the sinotubular ridge via ascending aorta replacement[120] may be all that is required to correct central insufficiency. If the aortic root is involved, it may be completely replaced by inserting the

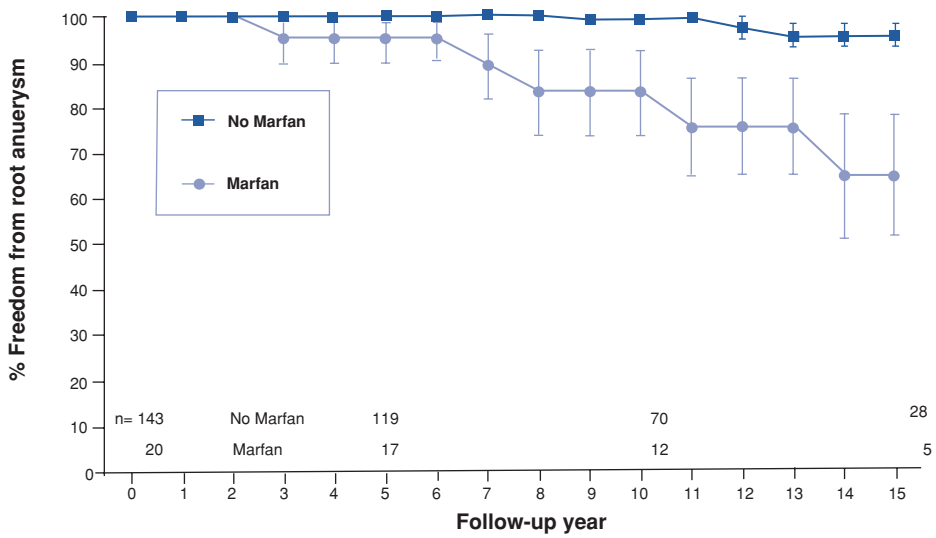


Figure 52-12. Actuarial estimate of freedom from late aortic root aneurysm for patients with and without Marfan syndrome who have undergone ascending aortic operations ($p < .0001$). *(Reproduced with permission from Yun KL, Miller DC: Ascending aortic aneurysm and aortic valve disease: What is the most optimal surgical technique? Semin Thorac Cardiovasc Surg 1997; 9:233.)*

scalloped native valve into a Dacron graft,[121] or dilated sinuses may be individually remodeled with tongues of the proximal Dacron graft.[122] If significant annular dilation is present, an aortic annuloplasty can be performed with the external application of a strip of graft material.[123] The application of valve-sparing procedures to patients with Marfan syndrome is controversial, as the durability of the leaflets is in question.[124] These procedures are discussed in detail in Chapter 37.

Alternative procedures

In older patients who are at high risk, or who have limited life expectancy, external wrapping of the aorta or separate valve and ascending aorta replacement may be appropriate without addressing the aortic root.[103,113,125]

Management of Associated Conditions

Coronary artery disease

Twenty-five percent of patients undergoing surgery for ascending aortic aneurysms will have concomitant coronary artery disease.[89] These patients should have appropriate bypass grafting performed at the time of ascending aneurysm surgery.

Mitral valve disease

Mitral valve disease is frequently encountered in patients with aortic aneurysms. This is particularly true for patients with Marfan syndrome, in whom the incidence approaches 30%.[48] Patients who have evidence of moderate to severe mitral regurgitation should undergo mitral valve repair or replacement at the time of aortic replacement.[68,126] Gilinov and associates[127] reported results of mitral valve repair in patients with Marfan syndrome, many of whom also had simultaneous replacement of the aortic root. They observed an 88% actuarial rate of freedom from significant mitral regurgitation at 5 years.

OPERATIVE TECHNIQUE

General

Monitoring and anesthesia

Venous access consists of two large-bore peripheral lines and a central line. We monitor filling pressures and cardiac output with a pulmonary artery catheter. A radial artery line provides blood pressure monitoring and determination of activated clotting times. Systemic temperature is monitored with nasopharyngeal and bladder probes. Transesophageal echocardiographic assessment of myocardial and valvular function is routine. Anesthesia is maintained with isoflurane and intravenous fentanyl.

Incision

A median sternotomy is the preferred incision. Extension into the left fourth or fifth interspace facilitates exposure of the distal aortic arch or descending aorta when required.

Perfusion

Cannulation is performed following heparinization (350 U/kg) and confirmation of an activated clotting time greater than 450 seconds. If the distal ascending aorta is not involved, this region or the proximal arch is cannulated. The aortic cannulation site must allow enough room proximally for the cross-clamp and a sufficient cuff of aortic tissue to sew to, while still allowing all diseased aorta to be resected. Epiaortic ultrasound assists in finding safe areas for clamping and cannulation. If the arch is involved and circulatory arrest will be required, either the right axillary artery, the femoral artery, or the aneurysm itself is cannulated. Before retrograde perfusion of the femoral artery is considered, however, TEE assessment of the descending aorta is performed. Venous cannulation is performed with a 21F or 24F two-stage cannula in the right atrial appendage. The superior and inferior vena cava are cannulated separately if circulatory arrest or mitral valve procedures will be required. This bicaval cannulation allows for retrograde cerebral perfusion and a transseptal approach to the mitral valve. The superior vena cava cannula should be placed above the azygos vein for retrograde cerebral perfusion. Flow during retrograde cerebral perfusion should be approximately 200 to 300 mL/min to maintain a jugular venous pressure of 20 to 25 mm Hg. Carbon dioxide insufflation into the pericardial well is routinely used for any procedure that requires opening the left heart.

Right axillary cannulation provides the benefit of allowing one arterial perfusion site for the entire operation and permitting a method for cerebral perfusion by the use of selective antegrade cerebral perfusion (SACP). Using this method, a low flow of approximately 10 mL/kg through the right axillary artery is initiated at the time of systemic circulatory arrest. A snare or clamp is placed on the innominate artery and cerebral perfusion is via the right carotid and right vertebral artery (Fig. 52-13).

The cardiopulmonary bypass circuit is primed with lactated Ringer solution and 25 g of mannitol. No glucose is added to the prime to prevent exacerbation of neurologic injury.[128] The cannulas are attached, and low-flow cardiopulmonary bypass is initiated. A left ventricular vent is inserted via the right superior pulmonary vein and a balloon-tipped catheter is inserted into the coronary sinus for retrograde cardioplegia delivery. Cardiopulmonary bypass flow is increased to 2.2 to 2.5 L/min/m^2 and moderate systemic hypothermia (28°C) and hemodilution (hematocrit 15 to 25%) are established.

Myocardial protection

Cold blood hyperkalemic cardioplegia (4°C) is given antegrade into the aortic root at a rate of 300 mL/min for 2 minutes and then retrograde at a rate of 200 mL/min for an additional 2 minutes. A cooling jacket may be used to facilitate this process. If the aortic valve is grossly incompetent, and prompt arrest is not achieved with retrograde cardioplegia, the aorta is opened and the coronary ostia are cannulated directly. During the procedure, retrograde cardioplegia is administered every 20 minutes.

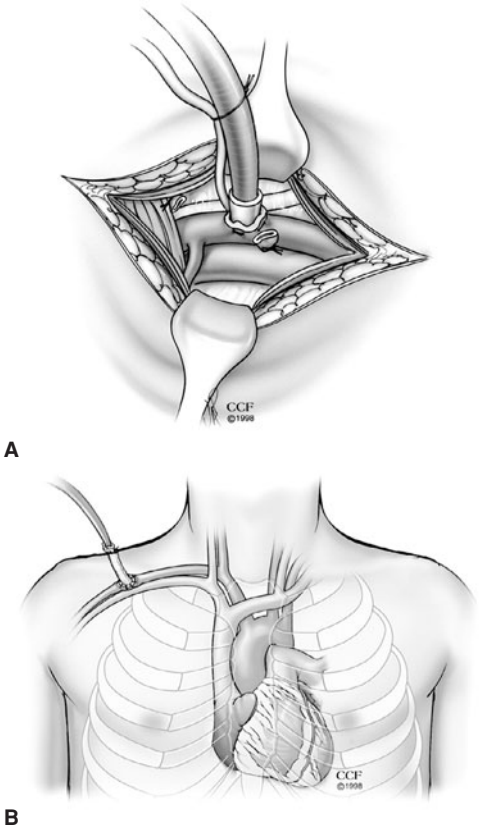


Figure 52-13. (A) Direct cannulation of axillary artery with right-angle arterial cannula (note division of crossing vein). (B) Cannulation of axillary artery with a side graft. A straight arterial cannula is inserted into graft. *(Reprinted with permission from Sabik JF, Nemeh H, Lytle BW, et al: Cannulation of the axillary artery with a side graft reduces morbidity. Ann Thorac Surg 2004; 77:1315.)*

Choice of graft

Woven double velour Dacron grafts impregnated with collagen or gelatin are relatively impervious to blood and have excellent handling characteristics. If root replacement is required, prefabricated composite grafts with mechanical valves are available. Bioprosthetic valves can be inserted into a Dacron graft if desired. The indications for pulmonary autograft or aortic allograft use have been previously discussed.

Specific Operative Techniques

Replacement of the ascending aorta

After cardiopulmonary bypass is established the aorta is clamped just proximal to the innominate artery, and the heart is arrested with cold blood cardioplegia. The aorta is transected below the clamp leaving a sufficient cuff for subsequent anastomosis (Fig. 52-14A). The proximal aorta is then transected just above the commissures. An appropriately sized Dacron graft is selected and sewn to the distal aorta with a continuous 3-0 or 4-0 polypropylene suture, incorporating a strip of felt (Fig. 52-14B). If required, the aortic valve is replaced at this time (Figs. 52-14C and 52-14D). The proximal anastomosis is performed in the same fashion after the graft is cut to the appropriate length (Figs. 52-14E and 52-14F). The graft is de-aired and the patient is weaned from cardiopulmonary bypass. After decannulation and protamine administration, suture line hemostasis is ensured.

Replacement of the ascending aorta and aortic root with a composite valve-graft conduit

The Bentall operation has been considered the gold standard for treatment of combined ascending aortic aneurysm disease and aortic valve pathology.[129] After establishing cardiopulmonary bypass, the aorta is clamped proximal to the innominate artery and the heart is arrested with cold blood cardioplegia. The aorta is transected beneath the clamp, ensuring an adequate cuff of aortic tissue. Proximally the aortic root is excised leaving only buttons of aortic tissue surrounding each of the coronary arteries (Fig. 52-15A). The coronaries are mobilized for 1 to 2 cm to prevent tension during reimplantation. A composite graft is selected based on the size of the aortic annulus. The sewing ring of the composite graft is sutured to the annulus with 2-0 pledgeted polyester mattress sutures placed immediately adjacent to each other (Fig 52-15B). The adjacent placement of sutures and the selection of a conduit that snugly fits within the annulus help to ensure hemostasis. A second suture line with a 4-0 running polypropylene suture can be used to approximate the aortic remnant to the newly secured valved conduit sewing ring to aid in hemostasis. Openings for coronary reimplantation are made in the appropriate position in the Dacron graft with an ophthalmic cautery (Fig. 52-15C). First the left and then the right coronary arteries are attached using 4-0 or 5-0 polypropylene suture in continuous fashion incorporating a thin strip of felt (Fig. 52-15D). The distal anastomosis is then performed with a continuous 3-0 or 4-0 polypropylene suture also incorporating a strip of felt. The graft is vented with a needle and the left atrium and ventricle are de-aired. After the patient is decannulated and protamine has been administered, suture line hemostasis is scrutinized.

Replacement of the ascending aorta and aortic root with an allograft or autograft

The muscular tissue at the base of the conduit is sutured to the aortic annulus with a continuous or interrupted 4-0 polypropylene or braided synthetic suture. The suture line is reinforced with a strip of Dacron or pericardium. Coronary ostia are created and coronary buttons are inserted with a continuous 4-0 or 5-0 polypropylene suture. Extension with a Dacron tube graft may be required to successfully replace the entire diseased aorta.

Open technique for distal anastomosis

The distal aortic anastomosis may need to be sewn under circulatory arrest as an open technique if clamping of the distal

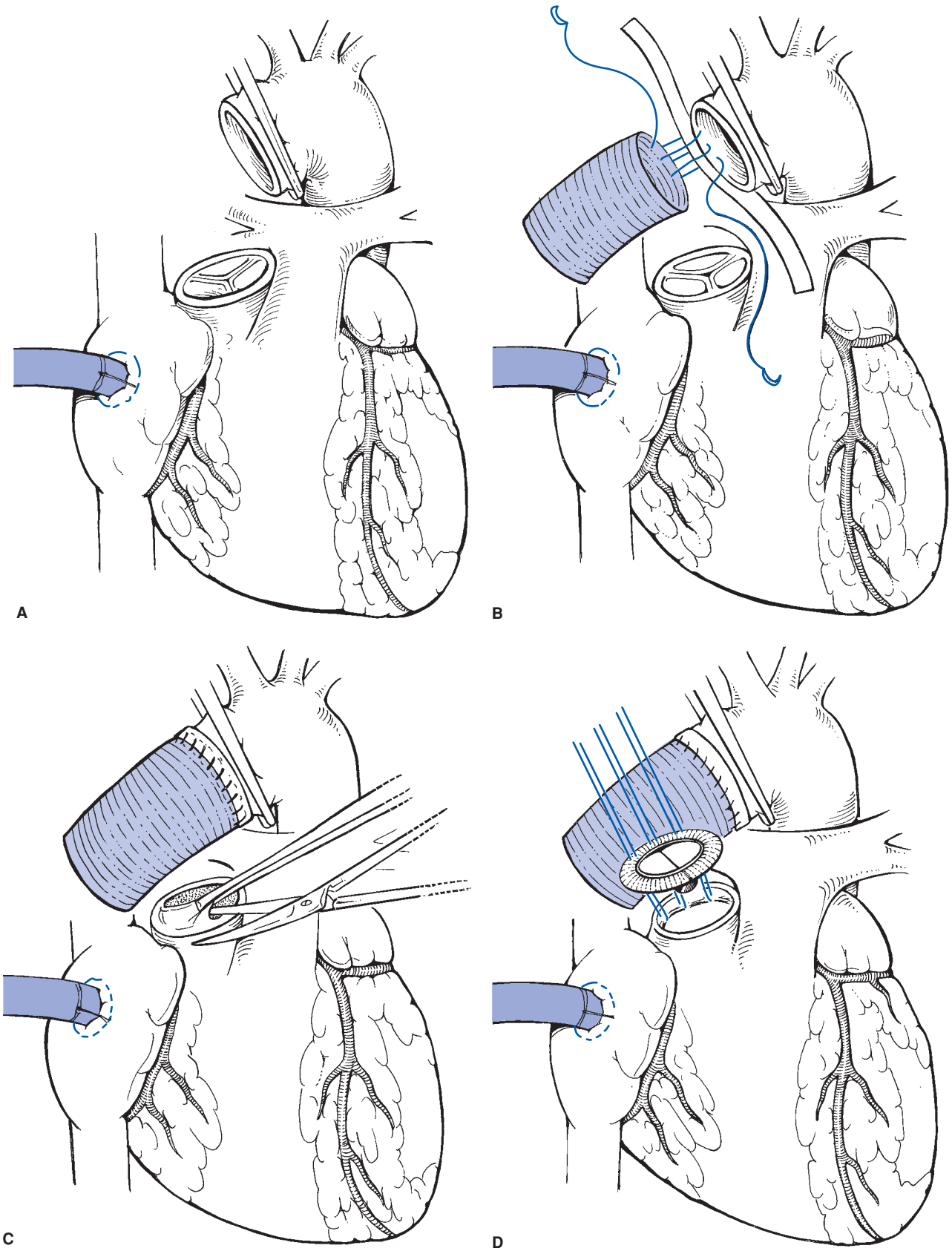


Figure 52-14. Illustration of simple aortic tube graft placement with separate replacement of the aortic valve. (A) The aorta is clamped proximal to the innominate artery (the aortic perfusion cannula is not shown) and the diseased aorta is resected down to just above the aortic valve commissures. (B) A Dacron graft is sewn to the distal aorta with a 3-0 or 4-0 polypropylene suture reinforced with a strip of Teflon felt. (C) If aortic valve replacement is indicated, the diseased valve is excised. (D) The valve is replaced with the valve of the surgeon's choice. *(Continued)*

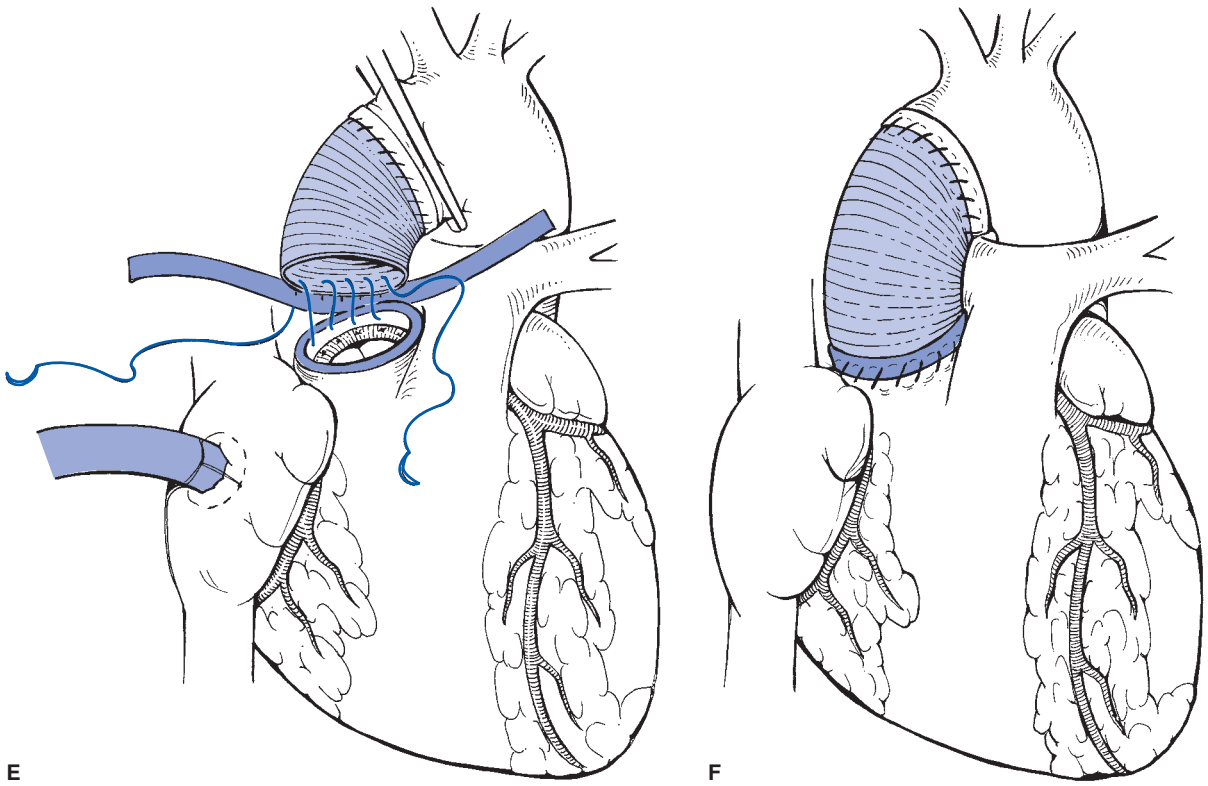


Figure 52-14. (*Continued*) (E, F) The graft is sewn to the proximal aorta with 3-0 or 4-0 polypropylene reinforcing the aortic tissue with a strip of Teflon felt. *(Reproduced with permission from Downing SW, Kouchokos NT: Ascending aortic aneurysm, in Edmunds LH Jr (ed): Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997; p 1163.)*

ascending aorta is not safe, or if partial or complete arch replacement is indicated. Clamping may be dangerous because of atherosclerotic disease or clot, or may not be possible because of the distal extent of the aneurysm. Cardiopulmonary bypass is initiated with right axillary artery cannulation, femoral artery cannulation, or direct cannulation of the ascending aneurysm, depending on the indication for circulatory arrest. The typical cardiopulmonary bypass setup for a case requiring circulatory arrest and retrograde cerebral perfusion is shown in Fig. 52-16. Central nervous system protection is enhanced by maintaining the blood glucose below 200 mg/dL, as well as by the administration of methylprednisolone (7 mg/kg) and thiopental (7 to 15 mg/kg). Mannitol (0.3 to 0.4 g/kg) and furosemide (100 mg) are given for renal preservation. Once the nasopharyngeal temperature reaches 15°C and the electroencephalogram has been isoelectric for 5 minutes, the patient is placed in Trendelenburg position and the circulation arrested. Approximately 25% of the patient's volume is drained into the venous reservoir.

The aorta is divided distally in a region dictated by the distal extent of disease. If the aneurysm ends at the takeoff of the innominate artery, the aorta can be transected here and the graft sewn, leaving the arch intact. If the aneurysm extends to the proximal undersurface of the arch, the distal end of the graft is beveled to conform to the resected surface of the arch (Fig. 52-16B). If the arch in the region of the origin of the brachiocephalic vessels is involved, then the aorta is divided distal to the origin of the left subclavian artery. The distal anastomosis is performed with a running 3-0 polypropylene suture reinforced with a felt strip. An elliptical portion of the graft is then excised that corresponds to a single island of aortic tissue that has been fashioned around the origin of the brachiocephalic vessels. This anastomosis is performed with felt-enforced running 3-0 polypropylene sutures as well. During this anastomosis, either selective antegrade cerebral perfusion (SACP) or slow retrograde perfusion of the superior vena cava is performed to remove any air or particulate debris (see Fig. 52-16B). Additionally, SACP may be used for the majority of the systemic circulatory arrest period with retrograde perfusion used at the end of circulatory arrest to allow a washout of any debris in the arch vessels. Antegrade perfusion is then initiated via direct cannulation of the graft, insertion of a cannula into a previously placed 8-mm side graft, or reinstitution of full antegrade perfusion through the original right axillary cannula (Fig. 52-16C). Femoral perfusion is not resumed in order to prevent cerebral embolization of distal aortic debris that may have occurred during previous manipulations.

The patient is rewarmed, and any additional procedures that are required such as coronary revascularization or mitral valve interventions are performed now that cerebral

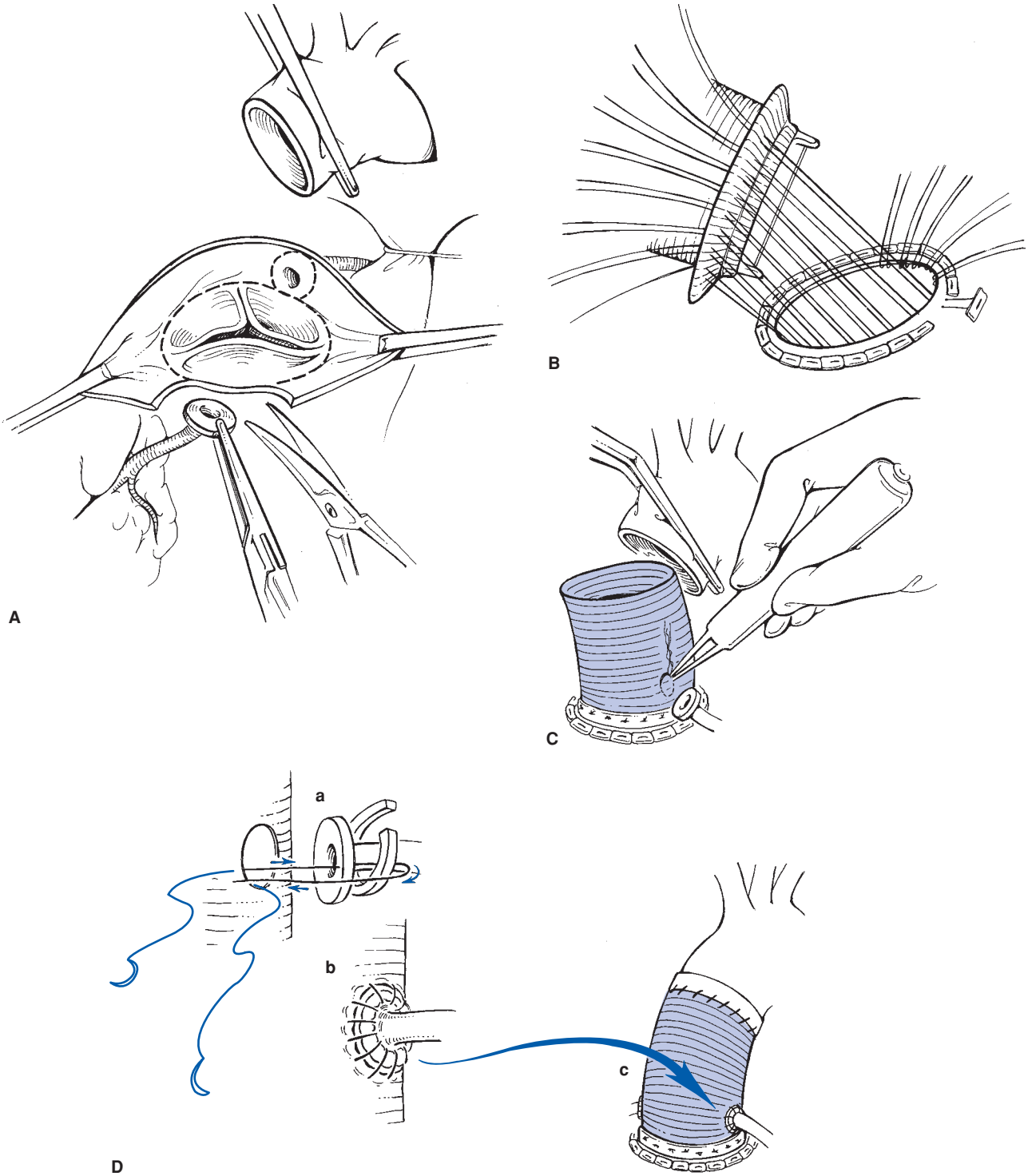


Figure 52-15. Illustration of insertion of a composite valve-graft conduit with coronary artery reimplantation. (A) A full-thickness button of aortic wall adjacent to each coronary ostium is fashioned. The aortic valve and sinuses are then excised. (B) Pledgeted 2-0 braided polyester sutures are placed in the supra-annular position and immediately adjacent to one another to ensure a watertight closure. The sutures are placed in the upper half of the sewing ring, helping to seat the valve deep within the aortic annulus. Note that no knots or suture material are exposed to the bloodstream. (C) Ophthalmic cautery is used to create an orifice in the graft in the appropriate position for left coronary reimplantation. (D) The left coronary anastomosis is performed first with a continuous 4-0 or 5-0 polypropylene suture incorporating a thin strip of felt. The right coronary anastomosis is then performed in a similar fashion. *(Reproduced with permission from Downing SW, Kouchokos NT: Ascending aortic aneurysm, in Edmunds LH Jr (ed): Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997; p 1163.)*

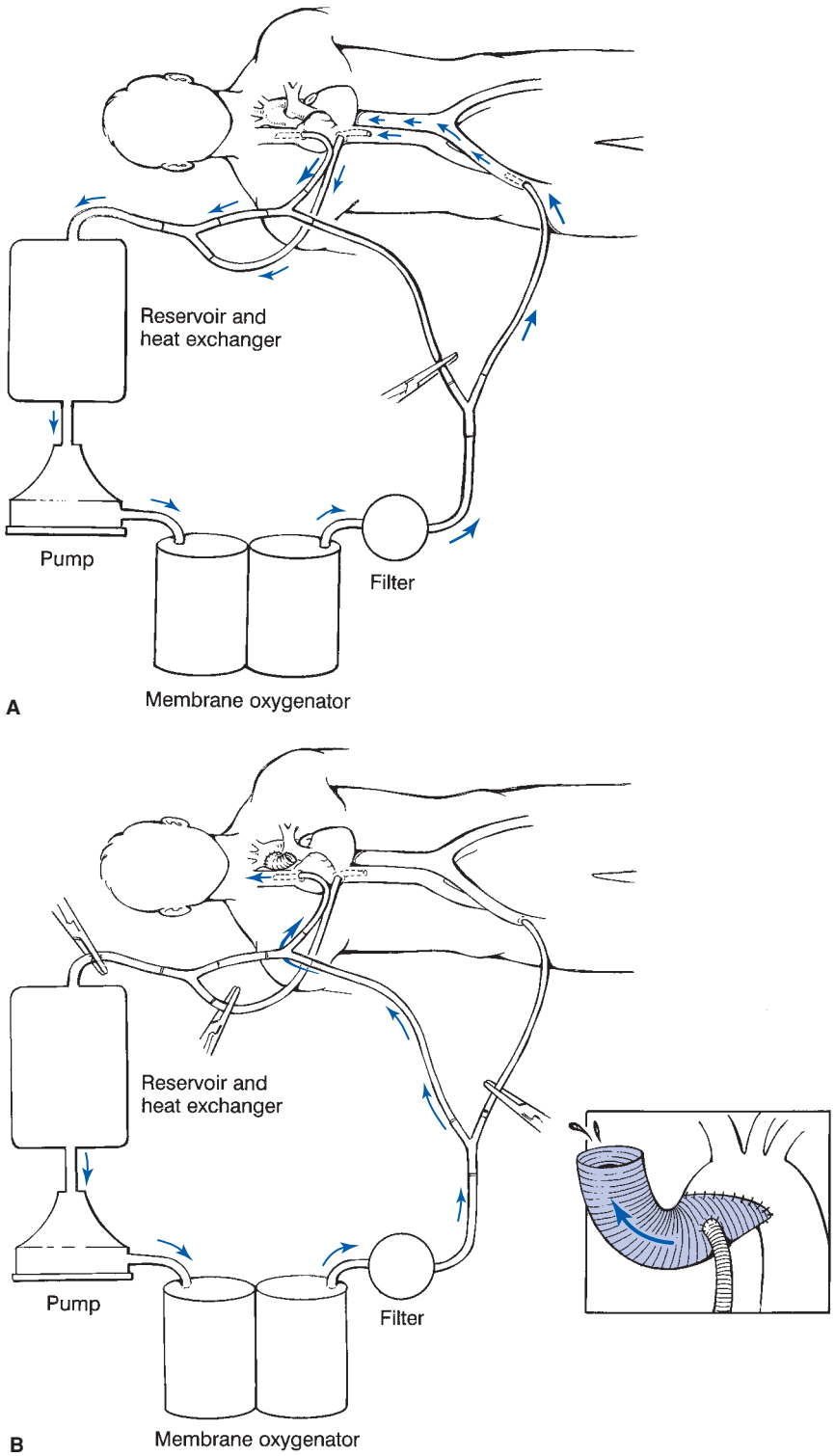


Figure 52-16. Schematic representation of the cardiopulmonary bypass circuit used for circulatory arrest when a portion or all of the aortic arch is to be replaced, or when it is unsafe to clamp the ascending aorta. (A) Cardiopulmonary bypass is established using two vena cava cannulas and a femoral artery cannula. A shunt connecting the venous and arterial lines is clamped. (B) The arterial and inferior vena caval lines are clamped and the shunt is opened, allowing retrograde cerebral perfusion of cold oxygenated blood through the superior vena cava cannula. Air and atherosclerotic debris are evacuated from the brachiocephalic arteries (inset). A separate 8-mm Dacron graft is sewn to the side of the Dacron graft to allow antegrade reperfusion of the brain once the distal anastomosis is done.

circulation has been restored. The proximal graft is sewn to the ascending aorta just above the sinotubular ridge or the aortic annulus in the case of composite graft placement. Thorough de-airing is performed and the patient is weaned from cardiopulmonary bypass. After protamine, suture lines are inspected closely.

Cabrol technique for reestablishing coronary flow

Avoidance of tension at the site of coronary reimplantation after aortic root replacement is essential to prevent postoperative bleeding and pseudoaneurysm formation. In the Cabrol technique, a single 6- to 8-mm Dacron graft is anastomosed end to end to the coronary arteries and

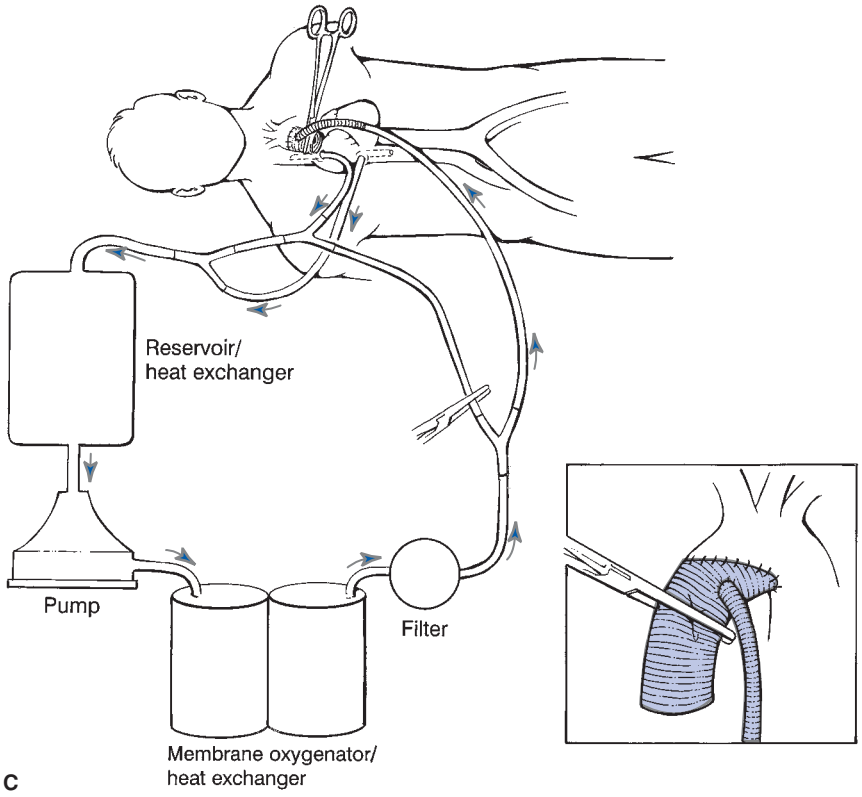


Figure 52-16. (*Continued*) (C) Cardiopulmonary bypass is reestablished in an antegrade fashion. The femoral arterial cannula is removed and the shunt is occluded. *(Reproduced with permission from Downing SW, Kouchokos NT: Ascending aortic aneurysm, in Edmunds LH Jr (ed): Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997; p 1163.)*

then the mid-segment of the coronary graft is anastomosed side to side to the aortic graft (Fig. 52-17). This technique is often required when the coronary ostia are low or when there is scarring from a previous operation preventing adequate mobilization. Oversizing of the Cabrol side arm above 8 mm should be avoided to avoid potential stasis and risk of postoperative thrombosis. Tension on the left coronary anastomosis is more common, and a small Dacron interposition graft may be required on this side in isolation in certain cases.

Reoperation on the ascending aorta and aortic root

Reoperative surgery on the ascending aorta and aortic root can be particularly challenging but is becoming more frequent. Because of improved outcomes,[68,71,110,130,131] the criteria for treatment of ascending aortic disease have been liberalized to include more elderly patients and more patients who have had previous cardiac surgery.[132,133] Increasing use of allografts, pulmonary autografts, and valve-preserving techniques may also result in an increased need for subsequent reintervention as these patients age. Indications for reoperation include aortic insufficiency, development of aneurysms or dissections in remaining segments of the thoracic aorta, false aneurysms, prosthetic valve malfunction or infection, or degeneration of biologic prostheses.[132]

To maximize safety, preemptive peripheral exposure or cannulation is required either through right axillary artery/femoral venous cannulation or through femoral artery/femoral venous cannulation. In the case of large pseudoaneurysms or grafts tethered to the posterior sternal wall, significant blood loss may be unavoidable upon entry. In such situations it is necessary to go on "pump-sucker bypass" until structures are dissected out and bleeding is controlled. Fifty percent of patients undergoing reoperation have significant aortic insufficiency, making myocardial preservation more challenging. In such cases, the perfusate temperature must not be reduced until exposure is sufficient to allow either clamping of the aorta or venting in order to prevent fibrillation and distension of the left ventricle and direct antegrade perfusion and retrograde perfusion of cardioplegia must be administered. Reimplantation of coronary buttons in the case of root replacement is often not possible without use of a modified Cabrol technique or an interposition graft.

Management of Complications

Bleeding

Woven Dacron grafts impregnated with collagen or gelatin are relatively impervious to blood and have reduced blood loss following replacement of the ascending aorta. Anastomotic bleeding is lessened with the use of Teflon pledgets at the aortic and coronary anastomoses. When composite valve-graft insertion is indicated, choosing a valve size that snugly fits the annulus and placing mattress stitches immediately adjacent to each other are helpful. Tension must be avoided at the sites of coronary reimplantation, as this is a frequent site of bleeding. The modified Cabrol method or an

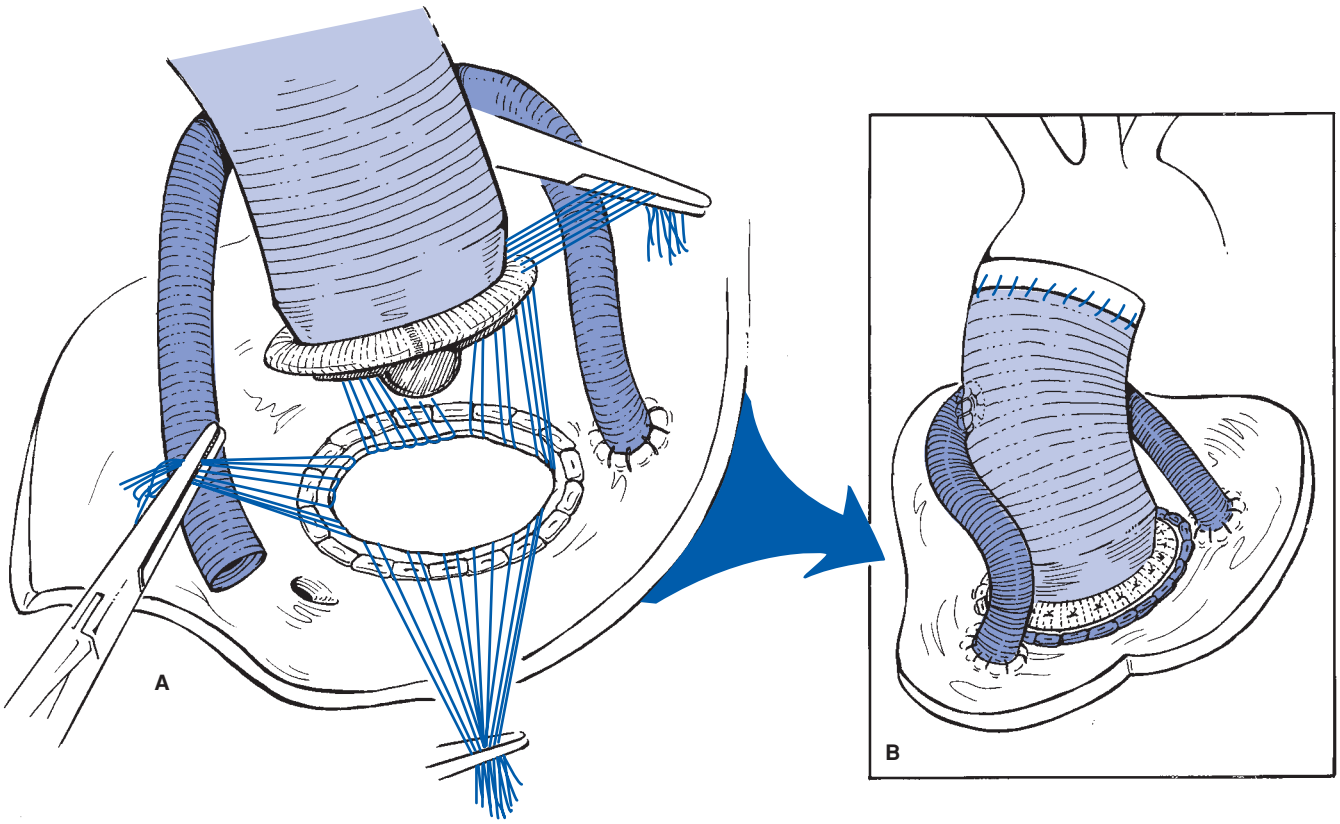


Figure 52-17. Classic Cabrol technique for coronary reimplantation. (A) An 8- to 10-mm Dacron tube graft is anastomosed end-to-end to the aortic tissue surrounding the left and right coronary ostia. (B) An opening is made in the mid-portion of the coronary graft and in an appropriate position in the aortic graft and an anastomosis is formed. The modified Cabrol technique involves the formation of individual coronary buttons allowing the small-caliber Dacron graft to be sewn to the full thickness of the aortic tissue surrounding the coronary ostia. *(Reproduced with permission from Downing SW, Kouchokos NT: Ascending aortic aneurysm, in Edmunds LH Jr (ed): Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997; p 1163.)*

interposition graft should be used when any tension is present. The inclusion technique of graft insertion is associated with an increased incidence of bleeding and pseudoaneurysm formation and has largely been abandoned.[68,134,135] All coronary and aortic anastomoses should be sewn to the full thickness of the aorta, and wrapping of the graft with residual aorta is not indicated. After the administration of protamine, all anastomoses must be evaluated closely.

Suspected coagulopathy should be documented by laboratory tests and treated accordingly. In cases of refractory coagulopathy, the anastomosis can be wrapped tightly with a small segment of Dacron to reduce tension on the suture line and reduce needle hole bleeding. Homologous blood donation can be avoided in a significant number of patients with the use of blood conservation techniques such as Cell Savers, autologous blood donation, plateletpheresis, the reinfusion of chest tube drainage, and the use of antifibrinolytics.[71]

Stroke

Neurologic injury following proximal aortic surgery remains a significant cause of morbidity and mortality.[136] Embolization of atherosclerotic debris or thrombus from the ascending aorta and arch produces focal neurologic deficits. Diffuse injury can be attributed to microemboli of air or cellular debris, insufficient or uneven cooling, and a prolonged circulatory arrest period. After circulatory arrest periods exceeding 40 minutes the incidence of stroke greatly increases.[137] Profound hypothermia may itself be injurious to the central nervous system without associated circulatory arrest.[137]

Stroke due to embolization is diminished when the aorta is evaluated via epiaortic ultrasound or other imaging modality to detect atherosclerotic plaques and thrombus. This allows appropriate adjustments to be made in clamping and cannulation strategies.[138] The utility of retrograde cerebral perfusion as an adjunct to hypothermic circulatory arrest is controversial, but some groups report an increase in the safe period of circulatory arrest.[139–141] Laboratory evidence suggests that the primary benefits of retrograde cerebral perfusion are flushing of embolic material and perhaps more homogeneous cooling, rather than effective nutrient delivery, which is far superior with antegrade circulation.[142] Resumption of antegrade circulation through the graft once

the distal aortic anastomosis is complete, rather than retrograde via the femoral vessels, after a period of circulatory arrest avoids embolization of distal aortic debris. Patients with severe carotid artery occlusive disease are at increased risk of stroke during ascending aortic procedures,[110] and patients older than 65, those with peripheral vascular disease, or those with pertinent histories should be evaluated.

Pulmonary dysfunction

Cardiopulmonary bypass is known to cause alterations in pulmonary function as evidenced by changes in alveolar-arterial oxygen gradients, pulmonary vascular resistance, pulmonary compliance, and intrapulmonary shunting. Usually these changes are subclinical, but a full-blown adult respiratory distress–like syndrome is reported in 0.5 to 1.7% of patients following cardiopulmonary bypass.[143] The specific cause is the subject of much investigation and debate, but it is generally accepted that exposure of blood elements to the foreign surface of the cardiopulmonary circuit results in the activation of inflammatory cells and the complement cascade resulting in pulmonary injury.[143] The duration of cardiopulmonary bypass, urgency of the procedure, and general condition of the patient may roughly correlate with the occurrence and severity of pulmonary dysfunction, but it can be unpredictable.[144]

Treatment is supportive, with early diagnosis and treatment of any subsequent pulmonary infections. Preventive measures may include preoperative optimization of pulmonary function, minimization of pump time, judicious use of blood products, heparin-coated bypass circuits,[145,146] and leukocyte depletion.[147,148]

Postoperative coronary insufficiency

Coronary insufficiency is uncommon in the postoperative period, but may occur following root replacement and coronary reimplantation. Ischemia may be due to kinking of a Dacron or saphenous vein interposition graft. Coronaries implanted under tension, or aortic suture lines, may bleed resulting in compression from an expanding hematoma. Suspicion of coronary insufficiency must be promptly evaluated with angiography and/or reoperation.

RESULTS OF OPERATION

Perioperative Morbidity

The primary causes of significant morbidity in the early postoperative period are neurologic injury and bleeding. Stroke has been reported in 1.8 to 5.9% of patients in various series.[71,89,131,149–151] Antegrade reperfusion following completion of the distal aortic anastomosis[71] and the use of retrograde cerebral perfusion[138,139] may lower the risk of stroke in patients requiring circulatory arrest. Postoperative bleeding requiring reoperation ranges from 2.4 to 11.1%.[68,71,131,149–152] The use of the exclusion technique of graft insertion and blood-impervious grafts has resulted in lower bleeding rates in more recent series. Ten to eighteen percent of patients require prolonged mechanical ventilation,[71,151] and 18 to 25% require prolonged (more than 6 hours) inotropic support.[68,151] Postoperative myocardial infarction, reported in up to 2.5%, may be related to technical problems with coronary reimplantation.[71,131,149]

Perioperative Mortality

Contemporary surgical series on ascending aortic disease using modern grafting techniques and methods of cerebral and myocardial protection report hospital mortality rates of 1.7 to 17.1%.[44,71,102,130,131,152–155] Comparison of outcomes is difficult, however, because of heterogeneity of patients. Some series do not include dissection,[131] and the proportion of emergent operations, reoperations, and arch replacements is highly variable. The most common cause of early death is clearly cardiac failure. Other frequent causes of early death include stroke, bleeding, and pulmonary insufficiency.[68,89,130,149–151]

Risk Factors for Hospital Mortality

Emergent operation after the onset of acute dissection or rupture is the clearest risk factor for early death.[89,102,149] Risk of death following elective intervention is increased by increasing New York Heart Association classification,[130,149,156] increasing age,[89,102,150,151,156] prolonged cardiopulmonary bypass time,[68,149,150] dissection,[130] previous cardiac surgery,[89,151] and need for concomitant coronary revascularization.[149,151] Major risk factors are shown in Table 52-3.

Table 52–3.

Independent Predictors of Early Mortality

Risk factor	*p* Value (range)
Emergent operation	000–.0017
New York Heart Association functional class	.0001–.015
Age	.01–.045
Cardiopulmonary bypass time	<.001–.018
Dissection	<.001–.04
Concomitant coronary artery bypass graft	.001–.0014
Previous cardiac operation	<.001–.0068
Arch replacement	<.001
Reoperation for bleed	.0009–.032

Only risk factors found to be predictive on multivariate analysis are reported. Some of the reported risk factors were not significant in some series. Data are from the following references: 41,61,80,119,137,138,139,141,142,143.

Late Mortality

Reported actuarial survival, like early mortality, is variable and dependent on the patient cohort. Survival rates are 81 to 95% at 1 year,[89,149] 73 to 92% at 5 years,[89,102,130,149] 60 to 73% at 8 to 10 years,[102,130,151] and 48 to 67% at 12 to 14 years.[68,130,157] Predictors of late mortality include elevated New York Heart Association class,[68,151] requirement for arch reconstruction,[151] Marfan syndrome,[68] and extent of distal disease.[89,149] The most common cause of late death is cardiac, but distal aortic disease accounted for 32% of late deaths in one series.[89]

Reoperation

Reoperations may be required because of pseudoaneurysm formation, valve thrombosis or endocarditis, progression of disease in the native valve or remaining aortic segments, or degeneration of a bioprosthesis. Reported mortality for reoperative ascending aortic surgery varies between 6 and 22%, but has been reported as low as 3% for elective reoperations[133] and as high as 100% for emergent reoperations.[158] Predictors of poor outcome have included emergent reoperation, requirement for arch replacement, preoperative functional class III/IV, and duration of cardiopulmonary bypass.[132,133] Freedom from reoperation is 86 to 90% at 9 to 10 years.[130,151] Predictors of late reoperation have included Marfan syndrome (Fig. 52-18), the inclusion cylinder technique (Fig. 52-19),[68,159] and chronic dissection. Surveillance of patients who have undergone previous aortic surgery to minimize the need for urgent reoperations and appropriate resection of all diseased aortic tissue at the time of original operation will improve outcomes. In one series it was estimated that nearly 60% of redo aortic cases were required because of inadequate repair during previous operations.[132] Since the majority of these inadequate repairs involve residual aneurysm disease remaining at the distal ascending aorta or in the arch, some surgeons have advocated the routine use of hypothermic circulatory arrest (HCA) with the removal of the aortic cross-clamp to ensure complete resection of all diseased aorta.[160] Other groups have stressed the increased incidence of transient neurologic complications with the routine use of HCA and limit HCA to only those patients with aneurysms of the arch.[161,162]

Thromboembolism

Major thromboembolic events following replacement of the aortic root with a composite graft are currently uncommon. Unlike simple aortic valve replacement, suture material and pledgets are excluded from the bloodstream. Freedom from thromboembolism was 82 to 83% at 10 to 12 years in two older series.[68,150] The incidence in more recent series is considerably lower.[71] Gott and associates[130] reported an incidence of only 0.42 thromboembolic events per 100 patient years.

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis is not reported in some series, but was the most common late complication occurring after root replacement reported by Gott and colleagues.[130] The actuarial freedom from endocarditis in 270 patients was 88% at 14 years.

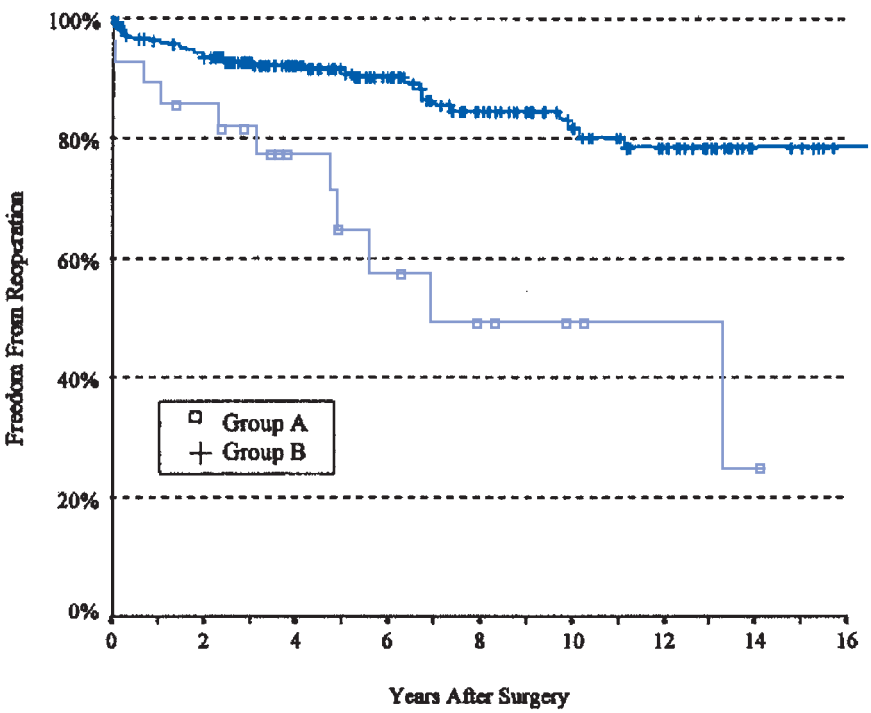


Figure 52-18. Freedom from reoperation (Kaplan-Meier) of patients with Marfan syndrome (group A) versus those without fibrillinopathic etiologies (group B). *(Reproduced with permission from Detter et al.[44])*

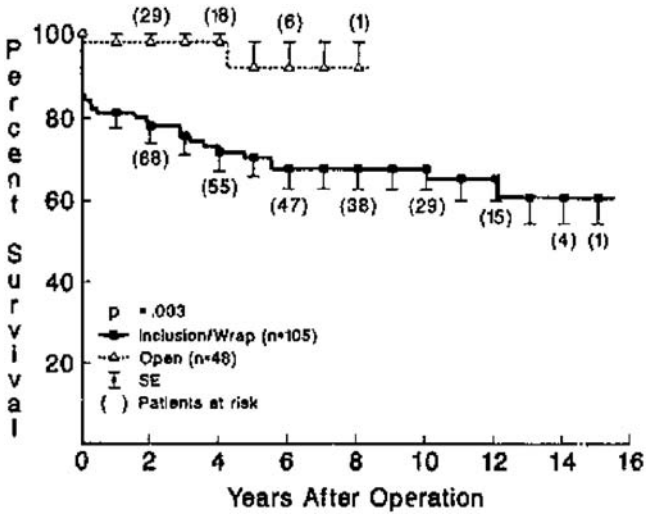


Figure 52-19. Actuarial freedom from reoperation on the ascending aorta or aortic valve. Patients are divided into those who had inclusion versus exclusion grafting techniques. *(Reproduced with permission from Kouchoukos et al.[68])*

Results of Operation in Patients with Marfan Syndrome

Gott and associates[106] reviewed the experience of 10 surgical centers with regard to root replacement in 675 patients with Marfan syndrome from 1968 to 1996. The 30-day mortality was 3.3%, but was only 1.5% for elective repair. Emergency surgery resulted in a 30-day mortality of nearly 12%. The survival rate was 93% at 1 year, 84% at 5 years, 75% at 10 years, and 59% at 20 years. Complications related to the residual thoracic aorta and arrhythmias were the leading causes of death. The most frequent late complication was thromboembolism. Advanced New York Heart Association class at the time of original operation was the only predictor of late death. This very complete multicenter review demonstrates that root replacement in Marfan syndrome can be performed with a low mortality and good long-term survival. Kaplan-Meier survival analysis is shown in Fig. 52-20.

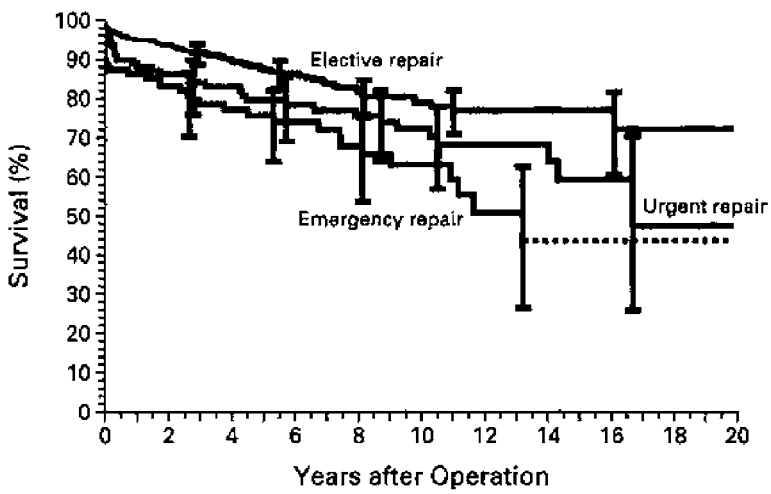
LONG-TERM SURVEILLANCE AFTER ASCENDING AORTIC OPERATIONS

All patients who have undergone thoracic aortic surgery must have long-term follow-up. Residual aortic tissue is often not normal and patients are prone to subsequent development of dissections or aneurysms. Pseudoaneurysms are frequently asymptomatic in the early stages and may initially present as periprosthetic hematomas.[163] A significant proportion of patients will require reoperation, and emergent operation is associated with a very high mortality. Periodic CT or MRI is ideal for assessing progression of disease in the residual aorta and for discovering the development of complications. Patients at increased risk of reoperation, such as those with Marfan syndrome, familial aneurysms, or dissections, require more vigilant follow-up.

THE INFECTED AORTIC GRAFT

Incidence

Graft infections are reported in 0.9 to 1.9% of patients following surgery of the thoracic aorta[164,165] and are associated with a mortality rate ranging from 25 to 75%.[165,166] Most graft infections become evident in the first month after operation[166,167] but may occur years after graft insertion.[168]



No. at Risk											
Elective repair	455	381	294	204	141	97	64	42	17	4	1
Urgent repair	117	88	74	62	53	41	23	16	8	4	3
Emergency repair	103	73	57	41	31	21	10	4	3	2	0

Figure 52-20. Kaplan-Meier survival analysis for 675 patients with Marfan syndrome from 10 different surgical centers according to the urgency of the procedure. *(Reproduced with permission from Gott et al.[106])*

Risk Factors

The risk of infection with any graft is increased with breaks in sterile technique and postoperative infectious complications. In one series 55% of patients had previous significant infectious complications, including wound infection, line sepsis, pneumonia, empyema, or septicemia.[168] The ascending aortic graft may be particularly vulnerable because of proximity to the wound and poor natural tissue coverage. The major infectious agents are *Staphylococcus aureus, S. epidermidis*, and less commonly *Pseudomonas*.[166–168] Infections may also be polymicrobial, fungal, or indeterminate.

Diagnosis

The majority of patients present with clinical signs of infection such as fever, chills, and elevated white blood cell count.[167–169] CT or MRI may demonstrate fluid collections or air in the periprosthetic space, but these are nonspecific findings, particularly in the early postoperative period. Confirmation of infection may require CT-guided aspiration of suspicious fluid collections. Associated pseudoaneurysms are detected by aortography or transesophageal echocardiography. Nuclear imaging techniques are endorsed by some,[170] but can be nonspecific for infection versus normal postoperative inflammation.[168]

Treatment

The traditional treatment of infected ascending aortic grafts, originally described by Hargrove and Edmunds in 1984,[165] includes removal of the infected prosthetic material, aggressive tissue débridement, local irrigation, systemic antibiotic therapy, replacement of the infected conduit, and utilization of autologous tissue to surround the new conduit and obliterate dead space. Most surgeons prefer replacement of the infected graft with a cryopreserved homograft, as it may be more resistant to subsequent infection.[171–173] The ideal autogenous tissue filler is the greater omentum because of its physical properties and its proposed ability to help combat infection.[174] In some cases small pseudoaneurysms have been resected and the graft locally repaired,[168] although this is controversial. Mortality rates remain substantial despite these aggressive measures.[168]

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CHAPTER 53

Aneurysms of the Aortic Arch

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The unique considerations in approaching aortic arch (AA) surgery concern cerebral protection. The question of how best to protect the brain while providing surgical access to the cerebral vessels is still a subject of controversy and research. The issues of concern in brain protection involve both minimizing global ischemia during the mandatory arrest of the circulation during AA surgery and preventing embolization of air and atheromatous debris from the often very diseased arch during the repair. Thus, cerebral protection methods are a major focus of discussion in this chapter, which describes in considerable detail the history and rationale for the use of hypothermic circulatory arrest, selective antegrade perfusion, and retrograde cerebral perfusion for prevention of global ischemia. It also discusses use of axillary artery cannulation and of a branched graft technique to minimize possible embolic damage.

SURGICAL INDICATIONS

There are urgent and elective indications for AA surgery. Urgent indications include rupture of an atherosclerotic aneurysm, rupture of the false lumen of a type A aortic dissection, type A dissection with extensive intimal tears in the arch, and mycotic arch aneurysms. Elective indications include arch aneurysms greater than 6 cm, saccular aneurysms with rapid enlargement (>1 cm/y) or symptoms (pain or hoarseness). Smaller aneurysms of 5 cm should be considered for repair in patients with Marfan syndrome or a family history of rupture or dissection.

PREOPERATIVE EVALUATION

Medical history and routine laboratory studies are important in evaluating possible symptoms due to the aneurysm and identifying comorbidities in these often elderly patients. A family history of a ruptured aneurysm is not uncommon, and aids in the decision to recommend surgery.[1] Comorbidities may influence and alter the operative approach, allow anticipation and possibly prevention of intraoperative or postoperative complications, or may contraindicate operation altogether.

Evaluation of an AA aneurysm requires a contrast-enhanced computed tomographic (CT) scan of the entire aorta. With new multidetector CT scans, the entire aorta can be imaged rapidly with reduced contrast and three-dimensional reconstructions. However, with advances in magnetic resonance imaging (MRI), equally detailed images can be obtained, and MRI is becoming the preferred modality for imaging by some surgeons.[2] Disadvantages of MRI are the duration of the examination and the cost; however, in patients with renal dysfunction, MRI is preferable, as the contrast agents are not nephrotoxic. Angiograms are not routinely required to visualize the lesion. Usually coronary angiography is indicated and visualization of the brachiocephalic vessels can be done with very little additional risk.

Cardiac Status and Management of Coronary Artery Disease

All patients require a preoperative echocardiogram to assess left ventricular function (LVF) and to exclude significant valvular heart disease. In patients with aneurysms of the ascending aorta in whom a Bentall procedure may be required, coronary arteriography is carried out to delineate the anatomy of the proximal coronary arteries. All patients over the age of 40 require routine coronary arteriography. Younger patients with coronary risk factors such as abnormal electrocardiogram, history of angina or smoking, or strong family history should also undergo coronary angiography.

If significant coronary artery disease (CAD) is present, coronary artery bypass surgery (CABS) or angioplasty is considered. If amenable to angioplasty, this is done with bare-metal stents several weeks before aneurysm surgery to prevent

possible stent thrombosis, since thrombotic complications have been observed when surgery involving administration of heparin and protamine is carried out sooner after angioplasty[3] or with discontinuation of antiplatelet therapy for drug-eluting stents.[4] If the aneurysm can be resected by a median sternotomy, or if the coronary arteries that require bypass are easily accessible through a left thoracotomy, coronary artery bypass grafting (CABG) can be done at the time of aneurysm repair. If the aneurysm is very extensive, or if access to the relevant coronary arteries will be difficult through an incision that is optimal for aneurysm resection, CABS is undertaken in a separate procedure several weeks prior to aneurysm repair.

If severe respiratory dysfunction is suspected on the basis of pulmonary function tests, or if there is a history of limited exercise tolerance, pulmonary consultation is requested. Active pulmonary infection is treated prior to surgery. Patients are urged to stop smoking for at least a month before operation and may require pulmonary rehabilitation. Pulmonary dysfunction increases operative risk and prolongs recovery, but chronic lung disease is not necessarily a contraindication to surgery unless oxygen dependence or significant carbon dioxide retention are present.

Cerebral Vessels and Prevention of Stroke

A carotid and vertebral duplex ultrasound is requested if there is a history of transient ischemic attacks or strokes, or if carotid bruits are present. In patients identified as having an aberrant left vertebral artery exiting the arch directly, documentation of the size and patency of the right vertebral artery is essential to guide operative strategy in complete arch replacement. Since emboli are likely to arise from the diseased aorta in the presence of an arch aneurysm, a history of a focal cerebral insult is not a contraindication to surgery. In patients with such a history, a CT scan of the brain is carried out preoperatively; this enables detection of silent fresh cerebral infarcts, which necessitate postponement of surgery in most instances. The preoperative CT scan is also invaluable for identification of old and new lesions, and may be helpful in determining prognosis if focal neurologic symptoms occur postoperatively. Rather than attempt to identify those patients most at risk for intraoperative and postoperative cerebral embolization because of extensive friable atherosclerotic debris in the ascending aorta and arch, we assume that all patients with arch aneurysms have a very high risk of embolization and take all possible steps to minimize their occurrence. Reasonably accurate preoperative identification of those patients at highest risk is possible using transesophageal echocardiography (TEE), high-resolution CT angiography, and even better visualization of the ascending aorta and arch is possible using epiaortic ultrasound intraoperatively (12-MHz probe).[5–7]

Cannulation Sites

For arterial cannulation in the management of arch aneurysms, we use the right axillary artery almost exclusively.[8] The axillary artery is usually soft and rarely involved in the generalized atherosclerotic process or dissected in a type A dissection. Its use avoids retrograde perfusion through a diseased abdominal and descending thoracic aorta and hence retrograde embolization. Axillary cannulation reduces the turbulent flow patterns in the arch and intraluminal atherosclerotic debris associated with ascending aortic cannulation.[9–12] In aortic dissection surgery the risk of malperfusion is lower than with other cannulation techniques and its use has been associated with improved outcomes.[13,14] Another advantage of axillary artery cannulation is its usefulness for selective antegrade cerebral perfusion during arch reconstruction.

The femoral vessels are still commonly used for cannulation. However, these are often calcified and atherosclerotic, and associated with the inherent risk of local dissection, retrograde dissection, and cerebral embolization. Cannulation can also be carried out in the ascending aorta using intraoperative epiaortic ultrasound to select a site free of atheroma in a segment of aorta adjacent to or even included in the anticipated resection; the perfusion cannula can subsequently be moved to the graft during the procedure. Despite the accuracy of epiaortic ultrasound, we are still concerned about using the aorta as a cannulation site and prefer to use the right axillary artery. Our preference is direct axillary cannulation with a right angle wire-reinforced arterial cannula (Edwards Lifesciences, Irvine, CA). The cannula is inserted through a transverse arteriotomy. In a few patients the right arm is potentially ischemic, therefore the period of cannulation should be limited and the cannula removed and the artery repaired prior to protamine administration. Many surgeons prefer the side branch technique with an 8 or 10 mm graft attached to the artery with a 5-0 polypropylene suture through a longitudinal arteriotomy.[11] In patients with very small axillary arteries, transsecting the artery and sewing a 6 mm graft end to end, and then cannulating the graft with a smaller straight femoral arterial cannula works well, avoiding less desirable cannulation sites.

ANESTHESIA AND MONITORING

In general, anesthesia for repair of AA aneurysms is no different from that for conventional open heart surgery, which relies primarily on the use of high doses of narcotics. Routine hemodynamic monitoring includes a Swan-Ganz catheter, a jugular venous bulb catheter if possible, and left radial and femoral arterial catheters. Transesophageal echocardiography is used to monitor LVF and distention, to confirm adequate flow in the arch and arch vessels, and to guard against malperfusion. Although we do not rely on electroencephalographic (EEG) surveillance, it is still used by some surgeons to determine maximum cerebral metabolic suppression in conjunction with hypothermic circulatory arrest, and to assess adequacy of cerebral protection.

Cerebral oximetry confirms the adequacy of cerebral perfusion and oxygenation. The baseline and trend may be more important than the actual number when assessing cerebral blood flow. With individual catheters for selective cerebral perfusion, acute changes may indicate catheter migration

(into the right subclavian artery), catheter obstruction, or dislodgment.[15,16] Any asymmetrical decline should prompt a thorough assessment to determine sufficient cerebral flow. If unilateral selective cerebral perfusion from the right axillary is used for cerebral protection, cerebral oximetry of the contralateral hemisphere may indicate the need for an additional catheter in the left common carotid artery in patients without sufficient collaterals.[17,18] Cerebral oximetry may not detect cerebral embolic events.[19] Transcranial Doppler is more sensitive in detecting embolic events and confirming cerebral blood flow, but is more operator-dependent and may not be available in emergent situations (CPB).[20]

We no longer administer barbiturates because at the doses recommended to enhance cerebral protection, they significantly depress myocardial function, and also because there are conflicting laboratory data with regard to their effectiveness in the presence of hypothermia.[21] We give 2 g of methylprednisolone at the beginning of the case before the start of perfusion, where use of hypothermic circulatory arrest (HCA) is anticipated. If HCA exceeds 30 minutes, we continue to administer steroids for 48 hours postoperatively (125 mg every 6 hours for 24 hours, then 125 mg every 12 hours for 24 hours).

In patients in whom a thoracotomy is utilized, use of a double-lumen tube that permits selective ventilation of the right lung is helpful if substantial dissection and mobilization of the descending thoracic aorta is necessary before institution of cardiopulmonary bypass (CPB).

Perfusion

The routine perfusion protocol for intracardiac operations is also utilized for repair of arch aneurysms. When initiating cardiopulmonary bypass via the axillary artery, perfusion is begun, while slowly watching for retrograde dissection and adequacy of flow. Transesophageal echocardiography is helpful in cases of dissection to avoid malperfusion. With right axillary artery cannulation, the site of arterial perfusion is constant and allows retrograde flushing of the brachiocephalic vessels. For distal aortic arch reconstruction, a Y connector in the arterial line enables a second antegrade perfusion catheter to be used if needed. Distal arch descending aneurysms require transfer of the perfusion cannula from the femoral artery to the proximal graft following deep HCA.

Although some controversy exists about whether pH during cooling should be maintained according to alpha-stat or pH-stat principles, we continue to utilize values uncorrected for temperature, the alpha-stat approach. The continued use of alpha-stat management for selective cerebral perfusion in adult patients may be beneficial by preserving cerebral autoregulation, maintaining metabolic suppression, and reducing the risk of cerebral embolization.[22] In patients with previous strokes, experimental studies reveal the damaged brain's susceptibility to ischemia during selective cerebral perfusion.[23] The use of pH-stat management may be marginally beneficial in this subset of patients.[24] However, further studies are necessary.

Currently our technique for selective cerebral perfusion (SCP) is alpha-stat management, a perfusate temperature between 15 and 20°C, a hematocrit of 25 to 30%, and flows of 10 mL/kg/min with a mean arterial pressure (MAP) of 40 to 60 mm Hg. Overperfusion has been shown to be as detrimental as underperfusion in a canine model.[25]

We rely on a long duration of cooling, a low esophageal temperature, a high jugular venous oxygen saturation, and topical hypothermia to ensure adequate cerebral protection during HCA.

OPERATIVE TECHNIQUES

Incision

In >90% of AA cases, an extended median sternotomy is used. This incision gives access to the ascending aorta, the arch, and the proximal descending thoracic aorta as far as 5 cm beyond the origin of the left subclavian artery. The conventional median sternotomy is extended along the border of the sternocleidomastoid muscle on the left side of the neck. The strap muscles of the left side of the neck may be incised, and the innominate vein is mobilized and preserved but can be divided if necessary.

If the anticipated surgical procedure involves both intracardiac pathology and/or extensive resection of the ascending aorta and the arch, as well as resection of aorta beyond the proximal descending thoracic aorta, some surgeons advocate a thoracosternotomy or bilateral thoracotomy incision.[26–29] This incision is a bilateral anterior thoracotomy in the third or fourth intercostal space joined by dividing the sternum. It gives excellent exposure to the entire ascending aorta, arch, and most of the descending aorta. However, it may have a deleterious effect on pulmonary function, and puts both phrenic nerves at risk. We have preferred to carry out the repair in this situation in two stages using the elephant trunk approach,[30–32] and to reserve the thoracosternotomy incision for some reoperations and patients requiring emergent correction of simultaneous cardiac and aortic arch/descending aortic pathology. In patients with a lesion primarily in the descending aorta that extends no farther proximally than the distal arch, a left lateral thoracotomy in the fourth or fifth intercostal space is the incision of choice; this can be extended inferiorly across the costochondral site if necessary.

Cooling and Rewarming

We lower the perfusate temperature to 10°C, and monitor both bladder and esophageal (or tympanic) temperatures. After HCA, we utilize a period of hypothermic reperfusion, since our laboratory data have shown that this may be beneficial.[33] During rewarming, we never raise blood temperature above 37°C, and we avoid creating a gradient exceeding 10°C between blood and esophagus. Warming is discontinued when the patient reaches an esophageal (or tympanic) temperature higher than 35°C, and a bladder temperature of 30 to 32°C. We prefer the patient to rewarm gradually in the intensive care unit following closure.

Graft and Suture Materials

We use collagen-impregnated grafts. We excise the aneurysmal portion of the aorta completely and carry out a full-thickness anastomosis to the remaining normal aorta. We use Teflon felt on the outside of the aortic wall for reinforcement, and place the graft within the cuff of the aorta. Although some surgeons feel that reinforcing anastomoses with Teflon felt is not necessary, pseudoaneurysms are extremely rare with this technique.[34] Most anastomoses are carried out using 3-0 polypropylene, but 2-0 polypropylene is used for suturing one large graft to another because the lifetime integrity of a graft-to-graft anastomosis depends on the sutures.

Myocardial Protection

We use antegrade blood for cardioplegia if the coronary ostia are readily accessible, supplemented with retrograde perfusion. Otherwise, 60 mEq of potassium is infused into the pump over 1 to 2 minutes just prior to circulatory arrest; this effectively converts ventricular fibrillation to asystole. For the remainder of the procedure, we rely on total body hypothermia—supplemented with antegrade and retrograde blood cardioplegia and topical cooling—for myocardial protection.

Prevention of Paraplegia

Although the possible development of paraplegia is not a major concern with most operations involving the AA, it is a consideration with procedures involving the descending thoracic and thoracoabdominal aorta. In these patients, some protection of the spinal cord is afforded by the use of total body hypothermia, but additional safeguards are warranted including cerebrospinal fluid drainage and when indicated, distal perfusion. During operations for resection of the distal arch plus a significant portion of the descending aorta, we routinely monitor somatosensory evoked potentials (SSEPs). Motor evoked potentials (MEPs) have recently been introduced and may provide superior monitoring of anterior cord integrity.[35,36] Intercostal vessels are sacrificed gradually prior to institution of CPB: each vessel is clamped initially, and the vessel is sacrificed only if no changes in MEPs and SSEPs are seen for more than 10 minutes after their temporary occlusion.[37,38] MEP and SSEP monitoring is continued until the patient exits the operating room, confirming the return of signals and spinal cord integrity. Mean arterial pressure is maintained in the range of 80 to 100 mm Hg, or possibly a higher level determined by intraoperative evoked potential changes. Thereafter, function of the lower extremities is assessed clinically on an hourly basis, for a total of 72 hours of postoperative monitoring. If deterioration in motor function of the lower extremities is seen, blood pressure is increased, and intrathecal pressure is decreased by withdrawal of cerebrospinal fluid. These maneuvers to increase spinal cord perfusion pressure have proven successful in reversing the manifestations of late-onset paraparesis in the majority of our patients,[38] and also have been effective in the hands of others.[39–41]

Prevention of End-Organ Ischemia

End-organ complications are rare with our techniques due to the use of deep hypothermia. As antegrade selective cerebral perfusion has gained popularity, surgeons are performing arch surgery at moderate hypothermia (20 to 28°C). Caution needs to be taken at these temperatures, since end organs are more vulnerable to ischemia. In order to limit lower body ischemia, thoracoabdominal perfusion during antegrade cerebral perfusion has been recommended via the femoral artery while clamping the proximal descending aorta, or by antegrade perfusion through an endoluminal balloon cannula placed in the descending aorta or side-arm graft placed to the arch graft.[42,43]

Control of Hemorrhage

Most current aortic surgery is carried out using antifibrinolytic agents to inhibit bleeding. We routinely use epsilon-aminocaproic acid, but others have reported that tranexamic acid is as effective. Aprotinin remains controversial but its use is increasing. Some surgeons have observed an untoward incidence of renal dysfunction and intravascular thrombosis when using this protease inhibitor in conjunction with HCA,[44,45] but others feel that the drug is safe if adequate doses of heparin are used concurrently. The demonstration of benefit associated with use of aprotinin with HCA has not been consistent.[46,47] Severe allergic reactions to aprotinin have been reported.[48] In simple cases involving only a short interval of hypothermia, such as ascending aortic and hemiarch replacement, blood and clotting factors are usually not required. If an interval of HCA longer than 30 minutes or duration of perfusion exceeding 3 hours is anticipated, 2 to 4 units of fresh frozen plasma and 5 to 10 units of platelets are brought to the operating room at the end of perfusion. These are infused if any question arises concerning the adequacy of hemostasis after protamine is given. Rarely in reoperative aortic surgery, acute dissections, and in patients with preoperative coagulopathy is mediastinal packing required to control bleeding. Alternatively, a Cabrol fistula is created in the superior mediastinum to shunt shed blood into the right atrium.[49] If this fails activated recombinant factor VIIa is indicated as rescue therapy for patients with refractory nonsurgical postoperative hemorrhage.[50,51]

Use of Glue

European surgeons have enthusiastically used gelatin resorcinol formaldehyde (GRF) and other biological glues, predominantly in strengthening aortic tissue after aortic dissection. Excellent results have been reported with the use of these glues in acute type A dissection.[52] Recently, however, there has been concern that the formaldehyde component of the GRF glue may be toxic to the aortic media and cause tissue necrosis, leading to late redissection and pseudoaneurysm formation.[53,54] We have not found GRF glue to be necessary. Due to the concerns about GRF glue, Bioglue (CryoLife, Inc., Kennesaw, GA) composed of bovine serum

albumin and glutaraldehyde gained popularity as an agent to strengthen friable tissues, particularly in acute aortic dissection.[55] It has been widely used as a sealant along suture lines. Recent evidence suggests that it should be used with caution, as it has been shown to leak through needle holes and embolize. Equally worrisome are the reports of localized tissue toxicity.[56–59] In most scenarios we find glues unnecessary.

Treatment of Infected Grafts and Mycotic Aneurysms

In patients in whom a previously inserted graft has become infected, or if a mycotic aneurysm is suspected, our initial strategy is to treat the patient for several days with specific intravenous antibiotics when the organism is known, and with broad-spectrum antibiotics otherwise. At the time of surgery, the entire infected aneurysm or graft is removed and replaced with a new graft. Often the organism causing the infection can be cultured from the resected specimen. Intravenous antibiotics are continued for at least 6 weeks, and if a suitable agent can be found, oral antibiotic therapy is instituted for an additional 3 to 6 months. In cases of a frankly purulent operating field, the chest may be left open, mediastinal washout occurs within 24 to 48 hours, and then pectoralis major or omentum may be brought into the wound and wrapped around the implanted prosthetic graft. A vacuum-assisted closure dressing is applied and the mediastinum closed when signs of sepsis have resolved. Others report the successful use of cryopreserved homografts in this setting.[26,27] C-reactive protein is a useful biochemical marker to help guide the length of antibiotic therapy and determine resolution of inflammation.[60–62]

CEREBRAL PROTECTION TECHNIQUES

Hypothermic Circulatory Arrest

Historical and theoretical considerations

Hypothermic circulatory arrest was first introduced in the early days of open heart surgery as an alternative to extracorporeal circulation. In the 1960s, isolated case reports described the use of HCA in repair of AA aneurysms.[63,64] The merit of HCA as a technique for correction of complex congenital heart lesions in infants was advocated by Barrat-Boyes and associates.[65] This prompted renewed interest in its use in adults with aneurysms of the AA. The first series of such cases was reported by Griepp and colleagues.[66]

Since that time, the efficacy of HCA in protecting the brain in adults with aortic aneurysms has been widely accepted. However, increasing utilization of HCA also revealed some of its limitations and raised concerns about its safety, especially when longer durations are required. A combination of hypothermia and circulatory arrest with selective antegrade cerebral perfusion may allow one to take optimal advantage of the benefits of both cerebral protection strategies.

The basis for the initial enthusiasm for the use of hypothermia to protect the brain during circulatory arrest was a series of investigations in adult dogs that documented profound inhibition of cerebral metabolism with lowering of brain temperature.[67] Using a ratio of normothermic metabolic rate and hypothermic metabolic rate at various temperatures, Michenfelder and Milde postulated that complete arrest of the cerebral circulation for as long as 30 minutes at 18°C would not result in any permanent neurologic injury, and in subsequent experiments they provided evidence indicating that periods of HCA as long as 60 minutes should be safe.[68]

Subsequent laboratory investigations in puppies[69] and piglets,[70] however, showed that suppression of cerebral metabolic function by hypothermia is less complete than that predicted by the formula proposed by Michenfelder. In puppies, cerebral metabolic rate is reduced only to 40% of control levels at 18°C, and HCA for 60 minutes at 18°C results in detectable early behavioral dysfunction following surgery and in quantitative EEG changes.[69,71] More prolonged HCA at 20°C in young piglets produces unequivocal behavioral sequelae as well as histologic evidence of cerebral damage.[72] HCA for even short intervals is followed by severe cerebral vasoconstriction that may last for hours. During this period, normal levels of cerebral metabolism are maintained by means of increased oxygen extraction, and the animals are vulnerable to hypoxic insults.[71,73–75] A period of cold reperfusion has been shown to reduce intracranial pressure during the recovery phase following HCA.[33] In this and other experimental studies, high intracranial pressure correlates with delayed neurologic recovery and subsequent cerebral histopathologic abnormalities. Oxygen saturation data also imply that cerebral blood flow several hours postoperatively is better following cold reperfusion, suggesting improved recovery from HCA.

In a review of 200 adults who underwent HCA during operations on the thoracic aorta, our group found that 19% of the patients had temporary neurologic dysfunction (TND) postoperatively, with varying degrees of obtundation, confusion, agitation, or transient parkinsonism. Occurrence of these symptoms correlated significantly with age and duration of HCA; the interval of HCA averaged 47 minutes in patients with symptoms of TND, and was 33 minutes in those without symptoms. Duration of HCA did not correlate with mortality or with permanent neurologic injury, which was usually focal, and was significantly more frequent in older patients and in those with obvious atheromatous debris in the arch or descending aorta at the time of operation.

More sensitive neuropsychologic testing after deep hypothermic circulatory arrest showed that HCA duration of more than 25 minutes and advanced age were significant predictors of poor performance in examinations of memory and fine motor function.[76] Impairment of memory function may be related to injury of the hippocampus, which is particularly sensitive to ischemic injury because of its high metabolic rate.[77] Patients with impaired neurocognitive function several weeks postoperatively were significantly more likely to have manifested TND immediately postoperatively.

Therefore, TND is a reflection of subtle brain injury, possibly as a result of inadequate cerebral protection. Based on these findings, a duration of circulatory arrest exceeding 25 minutes must be considered a risk factor for long-term albeit subtle deficits in cognitive function.

Past projections of the theoretical safe duration of circulatory arrest based on rates of oxygen consumption at various brain temperatures are now considered to have been misleading. McCullough and associates[78] recalculated Q_{10} for the adult human brain based on direct measurements of cerebral metabolic rate for oxygen ($CMRO_2$) during HCA. Q_{10} describes the temperature-dependent decrease in cerebral metabolism. The Q_{10} for $CMRO_2$ is defined as the ratio of two $CMRO_2$ measurements differing by 10°C. These data predict that the safe period of arrest at 15°C is about 30 minutes, and that at 10°C it is 40 minutes. Beyond this limit, cerebral cellular anoxia occurs. These observations support the use of truly profound hypothermia before a period of circulatory arrest to achieve maximum cerebral metabolic suppression, particularly if arrest time will exceed 30 minutes. Intracranial temperatures should be protected from rising during HCA by packing the head in ice.[72,73,79,80]

Use of corticosteroids

High-dose methylprednisolone given at 2 and 8 hours before CPB reduces the change in cerebrovascular resistance and improves cerebral blood flow, cerebral arteriovenous oxygen difference, and oxygen metabolism following deep hypothermic circulatory arrest, and may serve as a neuroprotective agent.[81] Additionally, in 4-week-old piglets, pretreatment with corticosteroids 4 hours prior to CPB—compared to steroids in the CPB prime—reduced total body edema and cerebral vascular leakage, with improved immunohistochemical indices of neuroprotection.[82] The beneficial effect of corticosteroid pretreatment requires alterations in de novo protein synthesis at the level of the mRNA,[83] and inhibition of adhesion molecule expression in the endothelial cells, which impacts on the trafficking of leukocytes into the injured areas.[84] Other benefits of methylprednisolone given 8 hours prior to CPB and HCA were improved pulmonary compliance and alveolar-arterial gradient, and decreased pulmonary vascular resistance.[85] Consistently, benefits are more apparent when steroids are given several hours prior to the institution of CPB; this has influenced our current practice.

Clinical implementation

In patients with AA aneurysms, we no longer utilize EEG or auditory or sensory evoked potentials to guide the efficacy of cerebral cooling. Based on laboratory studies, we prefer to cool with the perfusate lowered to 10°C to an esophageal temperature of 13 to 15°C for a minimum of 30 to 40 minutes. The head is packed in ice to prevent rewarming during the period of circulatory arrest. Animal studies continue to support this practice.[72,73,79,80] We use jugular venous saturations (>95%) to indicate adequate cerebral cooling and maximal metabolic suppression, since continuing oxygen extraction is an accurate reflection of significant ongoing cerebral metabolic activity. An association between low preoperative cerebral venous saturation and poor recovery of cerebral function following circulatory arrest was noted in some of our experimental animals[69] and also has been observed clinically by others.[86]

Careful rewarming following HCA, maintaining a gradient of no more than 10°C, reduces the likelihood that oxygen demand will exceed oxygen supply during the interval of inappropriate cerebral vasoconstriction following HCA.[71,73–75,87] Avoidance of high perfusate temperatures is essential.[88] Careful hemostasis and maintenance of normal hemodynamics during the postbypass period are also important, since the vulnerable period of cerebral recovery during which increased oxygen extraction is relied upon to support adequate cerebral metabolism may extend up to 8 hours postoperatively.

Based on careful laboratory studies and clinical review, optimal cerebral protection and minimizing embolization may best be achieved by liberal use of axillary cannulation; avoiding manipulation of atherosclerotic vessels before HCA; using the above-mentioned safeguards during institution of HCA and rewarming; restricting HCA to less than 25 minutes; and, when more complex arch repairs are required, using hypothermic antegrade SCP.[89,90] Use of SCP has been demonstrated to reduce temporary neurologic dysfunction associated with prolonged periods of HCA.[91]

Selective Cerebral Perfusion

Historical and theoretical considerations

The earliest attempts to repair aneurysms of the AA were carried out by DeBakey and associates[92] using normothermic cerebral perfusion involving several pumps and cannulation of both subclavian and both carotid arteries. The problems associated with controlling pressure and flow in these separate vascular beds to ensure relatively uniform perfusion, as well as the poor outcome of the patient led to early abandonment of this technique. Interest waned, but the technique was revisited by several surgeons in the late 1980s, spurred by the realization that HCA may not be safe for the long durations required for repair of more complex and extensive aneurysms. It was recognized that combining selective cerebral perfusion with hypothermia allowed use of much lower flow rates, and that hypothermic SCP afforded better cerebral protection from global ischemia than HCA alone or HCA and retrograde cerebral perfusion.[93–95]

The resurgence of interest in selective hypothermic cerebral perfusion was pioneered by several surgeons. Bachet's group fashioned the term "cold cerebroplegia" to describe perfusion of the innominate and left carotid arteries with blood between 6 and 12°C (flow 250 to 350 mL/min) in 54 patients with arch aneurysms. Mortality was 3%, and only one episode of severe neurologic injury occurred, with a 4% incidence of transient focal lesions.[96] Matsuda and colleagues[97] operated on 34 patients with AA aneurysms using SCP at 16 to 20°C, with a mortality of 9%, a 3% incidence of stroke, and a TND incidence of 5%. His technique

required cannulation of the brachiocephalic and left carotid arteries with a two-pump system, and bilateral temporal artery and continuous internal jugular venous saturation monitoring. The authors pointed out that hypothermic cardiopulmonary bypass may not carry a higher risk of coagulopathy. Kazui and coworkers[98,99] have since championed this technique, first describing its use in 1986. Between 1990 and 1999, 220 patients underwent total arch replacement with SCP and open distal anastomosis, with an in-hospital mortality of 12.7% and permanent neurologic dysfunction of 3.3%. Multivariate analysis showed in-hospital mortality was determined by renal failure, long CPB time, and shock, and permanent neurologic deficit was associated with old cerebrovascular accident and long CPB duration. Kazui and colleagues, perfusing two arteries with flows of 10 mL/kg/min at 22°C—considered 50% of physiologic levels based on experimental studies—found that selective cerebral perfusion time had no significant impact on outcome.[100] In a multicenter study Di Eusanio and colleagues definitively demonstrated the efficacy of selective antegrade cerebral perfusion (with 15F retrograde coronary sinus perfusion cannulas) in reducing temporary and permanent neurologic dysfunction. In 588 patients undergoing both partial and full AA replacement, the risk of permanent and temporary neurological injury was 3.8 and 5.6%, respectively. Overall mortality was 8.7%.[101]

The presence of clot or atheroma in the aorta is a determinant of stroke during operation for aneurysm of the AA. Atherosclerotic lesions often develop at the origin of the brachiocephalic vessels. Complete resection and branch grafting should reduce the rate of neurologic injury. In Dr. Kazui's latest 50 patients with atherosclerotic AA aneurysms,[102] the mortality was 2%, permanent neurologic injury 4%, and TND occurred in 4% (adverse outcome 6%), with a history of cerebrovascular disease a risk factor for permanent neurologic dysfunction. The Kazui technique (Fig. 53-1) and sequence of reconstruction are as follows: systemic cooling of the patient to 22°C is followed by circulatory arrest and SCP to 22°C via two malleable cannulas (Fuji System, Tokyo, Japan), one in the innominate and one in the left common carotid artery. The left subclavian artery is clamped, distal anastomosis to the

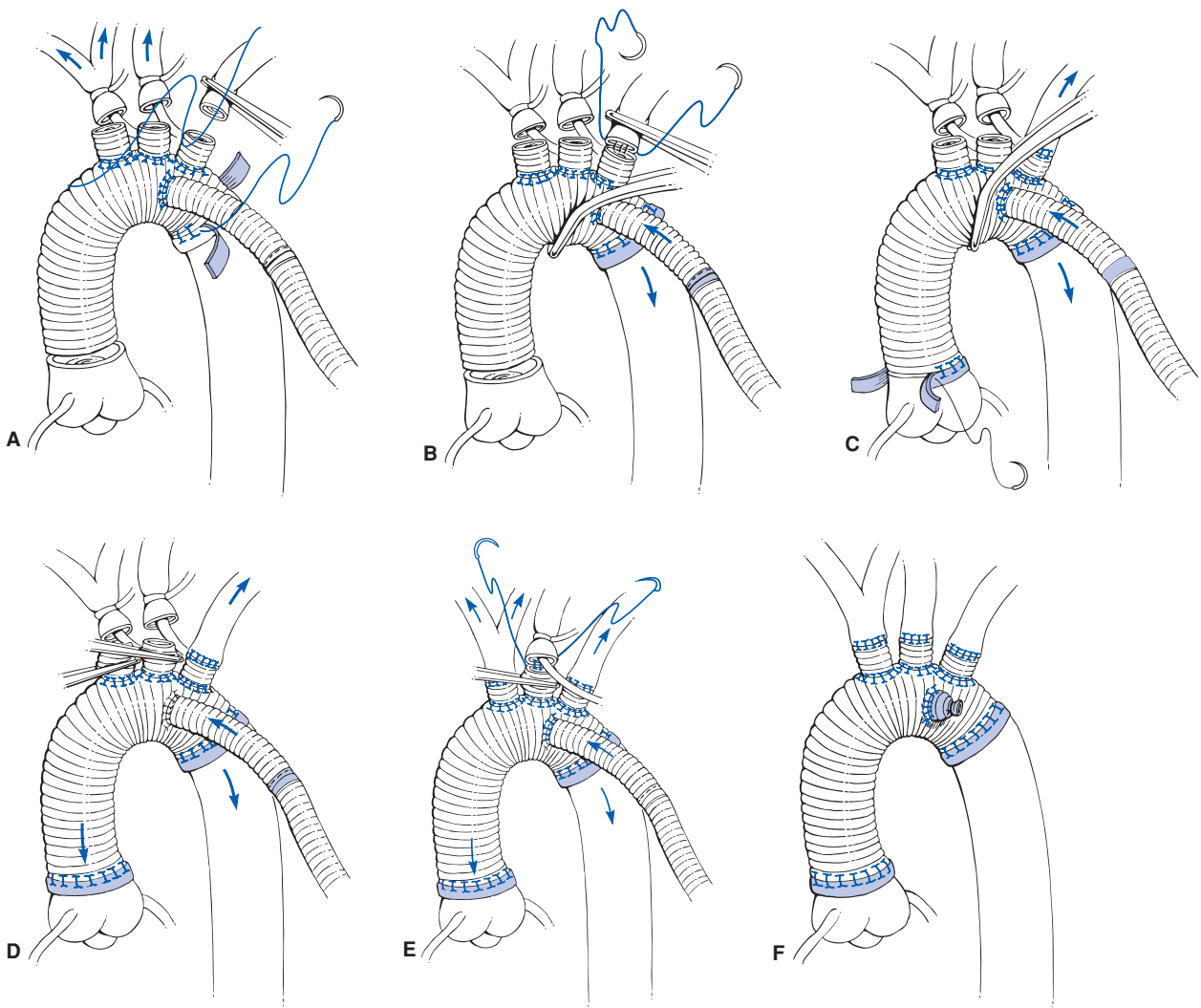

Figure 53-1. (A through F) Dr. Kazui's technique for total arch replacement with a four-branch graft.

descending aorta is performed, and lower body perfusion is achieved via the fourth side arm of the four-branch graft. Left subclavian anastomosis is followed by perfusion, measurement, and construction of the proximal anastomosis, and then the innominate artery and left common carotid artery anastomoses, with full perfusion restored. Permanent neurologic injury is again an independent risk factor for in-hospital mortality. This technique allows one to perform the transsection of the brachiocephalic vessels distal to their origins and free of macroscopic atherosclerotic disease to avoid dislodgment and embolization of debris. Newly designed malleable cannulas allow superior visibility and simultaneous pressure monitoring (personal communication).

Jacobs and associates[103] performed 50 arch replacements with selective antegrade cerebral perfusion and moderate hypothermia to 28 to 30°C. EEG monitoring guided reconstruction techniques, pump flows, and perfusion pressures. Overall adverse outcome was 6%, TND rate 4%, and pulmonary complications occurred in 25%. Antegrade cerebral perfusion time ranged from 75 to 235 minutes, with a mean of 165 minutes. No correlation between long SCP duration and neurologic injury was noted.

In patients with extensive aneurysmal disease involving the ascending aorta, arch, and varying amounts of the descending thoracic aorta, a single-stage reconstruction can be performed with the "arch first" technique via bilateral anterior thoracotomies as described by Rokkas and Kouchoukos.[26] This technique employs an interval of HCA followed by SCP of the upper body while the aortic reconstruction is completed. The use of brachiocephalic artery perfusion allows unhurried completion of AA repairs. In the recent series of 46 patients, the hospital mortality was 6.5% but no patient sustained a permanent neurologic event. Transient neurologic dysfunction occurred in 13% of patients.[28] Currently, the interval of deep HCA is shortened further with unilateral cerebral perfusion from the right axillary artery and individual branch grafting of the brachiocephalic vessels. The mean circulatory arrest time was 8.8 minutes in the initial 12 patients.[29]

Using right brachial cannulation for unilateral SCP, Kucuker and associates[104] reported a permanent stroke rate of 2.2% for 181 patients undergoing ascending and hemiarch replacement (90 patients) or total arch replacement (91 patients). No mention of temporary neurologic dysfunction was made. The patients were cooled to 26°C, and when flow was decreased to 500 to 600 mL/min (8 to 10 mL/kg/min) the innominate, left common carotid, and occasionally the left subclavian artery were clamped. Arch replacement was performed under continued low-flow perfusion. Mean SCP time was 36 ± 27 minutes (range 17 to 80 minutes). Hospital mortality occurred in 12 patients (6.6%) with five deaths in acute dissections. To ensure contralateral cerebral flow, transcranial Doppler allowed continuous noninvasive monitoring of the middle cerebral artery. In the rare case of inadequate left hemispheric perfusion an additional catheter can be placed into the left common carotid artery.[16,18] This was unnecessary in this series of patients. A separate cohort of patients undergoing neurocognitive testing revealed no postoperative deficits.[105] Still, a certain level of caution related to left hemispheric ischemia is prudent based on anatomic studies. Merkkola and colleagues found 14% of autopsy specimens with insufficient collateral circulation of at least 0.5 mm in the circle of Willis[105a]. These findings confirm the continued necessity for hypothermic perfusion. The preceding paragraphs have indicated that there is no consensus regarding the optimal temperature to implement selective cerebral perfusion. Our laboratory studies suggest that SCP at 10 to 15°C after deep HCA provides better global cerebral protection and thus we use SCP at about 15°C.[106]

Clinical implementation

In our current era of AA reconstruction, cerebral injury is most often related to the risk of embolization.[107–109] With liberal use of direct axillary artery cannulation,[110] HCA, and grafting to individual brachiocephalic vessels,[29,102,111,112] followed by SCP, lengthy periods of circulatory arrest are no longer necessary. Laboratory studies have shown that a short period of deep HCA to reduce the risk of embolization will not compromise the superior cerebral protection provided by SCP.[113] Diseased origins of the brachiocephalic vessels in the arch are avoided, and the arch repair can proceed in an unhurried fashion.

Our approach is as follows: After cooling, and during a brief period of HCA, the individual brachiocephalic arteries are dissected free and anastomosed to a ready-made trifurcated graft (Hemashield, Boston Scientific, Natick, MA), beginning either with the left subclavian or the innominate artery. The trifurcated graft is clamped, and perfusion selectively restored to the upper body. Occasionally, when the left subclavian artery is displaced lateral and cephalad, a preoperative left subclavian to left carotid bypass is performed. A bifurcated graft is sewn to the left common carotid and innominate arteries (Fig. 53-2). Typically, flows between 600 and 1000 mL/min are required to maintain a mean pressure of 40 to 60 mm Hg, while allowing the perfusate temperature to drift upward. At the end of the arch reconstruction, the branch graft is sewn to the ascending aortic graft without interrupting flow.

Retrograde Cerebral Perfusion

The limitations of HCA, the success of retrograde cardioplegia, and isolated encouraging reports of the possible efficacy of retrograde cerebral perfusion (RCP) in mitigating the effects of massive air embolism[114] contributed to widespread interest in and enthusiasm for RCP in the early 1990s.[115] The mechanisms whereby RCP may accomplish neuroprotection include: (1) flushing embolic material from the cerebral circulation,[116] (2) providing cerebral flow sufficient to support cerebral metabolism,[117] and (3) maintaining cerebral hypothermia.[118] There is, however, evidence that RCP may worsen neurologic outcome by inducing cerebral edema.

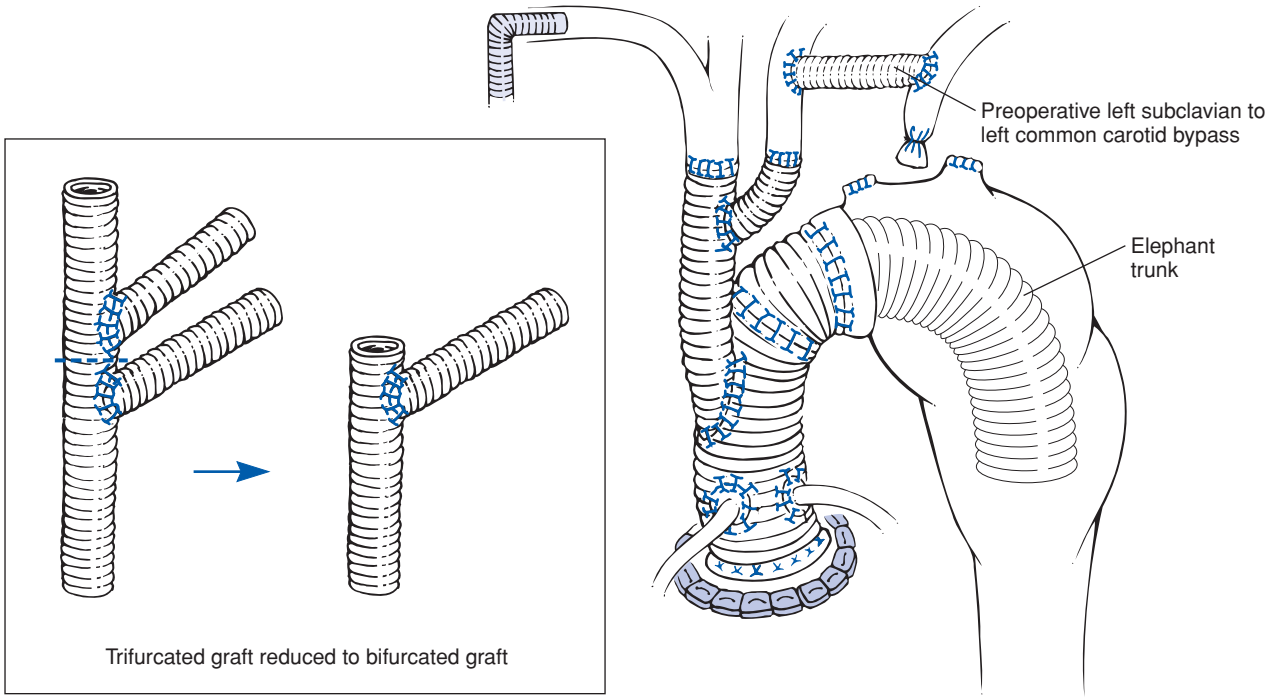

Figure 53-2. A preoperative left subclavian artery to left common carotid artery bypass is done when the left subclavian artery is markedly displaced laterally and cephalad.

Initial laboratory results and clinical reports regarding RCP were encouraging. However, upon closer examination, many of the studies that reported improved outcomes with RCP used historical controls and short durations of RCP that are well within the limits defined as safe for HCA alone. There were also some disturbing studies, using various techniques in several different animal species, reporting that no flow to the brain during RCP could be demonstrated.[119,120] In other experimental studies, the most effective conditions for retrograde flow were under circumstances—including clamping of the inferior vena cava and use of high perfusion pressures—that resulted in disturbingly high rates of fluid sequestration, significant cerebral edema, and mild cerebral histopathology; these sequelae were seen even after relatively short intervals of RCP.[116] Studies in our laboratory in which cerebral blood flow was quantitated not only by collecting AA return, but also by counting the number of microspheres trapped in the brain, have demonstrated conclusively that too little capillary flow occurs during RCP (even with occlusion of the inferior vena cava) to confer any meaningful metabolic benefit, even during deep hypothermia.[121] Other laboratory studies using intravital microscopy to directly visualize the cerebral capillary blood flow concluded that RCP does not provide adequate cerebral capillary blood flow to prevent ischemia, but may induce brain edema.[122] A recent animal study showed that intermittent pressure augmentation during moderate hypothermic RCP efficiently dilated the cerebral vessels, allowing an adequate blood supply without injury to the brain, providing similar neuroprotection as antegrade SCP.[123]

The relationship between the use of RCP and mortality rates is unclear. In some studies, RCP duration was not found to be a predictor of death,[124–126] whereas in others it was.[115,127] Clinical outcome studies comparing RCP and HCA have also yielded mixed results, with some having mortality rates comparable to those with use of other cerebral protection methods,[115,128,129] and others reporting reduced mortality rates with RCP.[130–132] In three studies that included SCP patients, RCP patients had similar mortality rates.[133–135]

The literature examining the relationship between RCP and neurologic morbidity is also mixed. In some series, RCP duration was not found to be a predictor of neurologic morbidity,[125,126] whereas in others it was.[115,127] RCP has been found to be associated with neurologic morbidity rates that are either similar to those associated with HCA,[129,136] or lower.[128,130–132,137] When patients with SCP were included, RCP patients had similar outcomes in three studies[133–135] and worse outcome in one.[137]

In our own earlier[138] and more recent[139] clinical studies, we have been unable to demonstrate any benefit of RCP in our patients. Experimental data from our laboratory suggest that RCP, especially at high pressures, although successful in removing some emboli, may aggravate cerebral injury.[116] In our recent clinical study,[139] we were unable to demonstrate a decrease in the incidence of stroke with RCP. This may be explained by a greater prevalence of patients

with clot or atheroma in the RCP group, but it nevertheless is also possible that RCP may not be effective in preventing stroke. Mortality was higher in the RCP group, and temporary neurologic dysfunction was higher with RCP than with SCP. Furthermore, RCP resulted in no reduction of transient neurologic dysfunction compared with HCA alone,[139] reinforcing the notion that RCP probably has no nutritive value for brain tissue. The induction of cerebral edema documented in our animal studies of RCP[116] cannot easily be demonstrated in the clinical situation, but may be another reason for our repeated observation of delayed neurologic recovery postoperatively in patients treated with RCP. Recently, we studied neuropsychologic dysfunction after RCP; we found that RCP was of no benefit, and probably had a negative impact on cognitive outcome.[140] Other investigators believe that neurocognitive outcome depends on the duration of RCP, and if RCP is less than 60 minutes, it is comparable with outcomes of patients undergoing CABG, whereas prolonged RCP >60 minutes is associated with neurocognitive impairment.[141]

We believe that the major benefit of RCP is in providing continued cerebral cooling by venoarterial and venovenous anastomoses during arrest of antegrade circulation, which helps to protect the brain, especially in those patients in whom systemic cooling is not as thorough and prolonged as it should be. We continue to believe that a major benefit of RCP in the studies of others—usually with a historical control group and with a duration of RCP short enough that good results would be anticipated with use of HCA alone—can be explained largely by the enhanced cooling brought about by continuous bathing of the brain with cold blood during RCP. The effective cooling achieved during RCP may make a difference, especially if the initial cooling interval is short and the head is not packed in ice. Several experimental studies reinforce this view.[118] We no longer routinely use RCP. We believe that an upward drift in temperature during HCA can more safely be prevented by thorough initial cooling and packing the head in ice.

Clinical implementation

Although we do not routinely use RCP for cerebral protection, many surgeons do occasionally use a short period of retrograde perfusion in patients who have a high risk of embolization because of clot or atheroma in the aorta, recognized either preoperatively or intraoperatively. Clinicians apply RCP very briefly at the end of a period of HCA solely for the purpose of flushing out potentially embolic debris.

Retrograde perfusion is always employed in conjunction with profound systemic hypothermia. To initiate retrograde perfusion, blood is infused into either one or both venae cavae at a flow rate to maintain the superior vena cava pressure between 15 and 20 mm Hg. Given the rich network of collaterals between the superior vena cava and inferior vena cava, it probably makes no difference whether inflow is into the superior vena cava, into the inferior vena cava, or into both venae cavae. Cardiac distention is avoided by choking both venae cavae. When whole-body retrograde perfusion is carried out in this fashion, the initial flow rate is usually 800 to 1000 mL/min, but once the venous capacitance vessels have been filled, a flow of 100 to 500 mL/min is usually sufficient to maintain superior vena cava pressure at 15 to 20 mm Hg.

REPRESENTATIVE PROCEDURES

Aortic arch reconstruction requires different approaches, techniques, and operative strategies, depending on the arch pathology and the involvement of the aorta proximal and distal to the arch. Thus, we describe seven different situations and our approach to reconstruction of the arch in each of these.

Case 1: Bentall Procedure and Hemiarch Replacement

The patient has Marfan syndrome and an aortic root aneurysm associated with severe aortic regurgitation and a dilated ascending aorta and proximal arch (Fig. 53-3).

A median sternotomy is performed. Cardiopulmonary bypass is initiated via the right axillary artery and a two-stage right atrial cannula. Cooling is begun, and when the heart fibrillates, a ventricular vent is placed via the right superior pulmonary veins. The ascending aorta is cross-clamped and opened. Cardioplegia is infused into both coronary ostia, and this is supplemented with topical cooling and retrograde blood cardioplegia. Perfusate temperature is maintained at 10°C until the esophageal temperature reaches 20°C, and is maintained at that level while the Bentall procedure is being performed. After aortic valve removal, a composite prosthesis is sutured to the aortic annulus utilizing interrupted pledgeted sutures. Coronary buttons 1 to 1.5 cm in diameter are fashioned. The remainder of the aorta proximal to the clamp is excised. The coronary buttons are mobilized. A corresponding opening is made in the posterior aspect of the graft with ophthalmic electrocautery and the left coronary button is anastomosed to the graft with 4-0 polypropylene. A thin strip of Teflon felt buttressing is used to reinforce the button. As the coronary button anastomosis is being carried out, jugular venous samples are drawn every 5 minutes and the perfusate temperature is lowered to 10°C.

When the jugular oxygen saturation is above 95% and the esophageal temperature is between 13 and 15°C, the head is placed downward after being packed in ice, perfusion is discontinued, and the cross-clamp is removed. The distal ascending aorta and proximal arch are mobilized and excised, leaving a beveled aortic cuff extending from the base of the innominate artery on the right to 1 cm proximal to the ligamentum arteriosum and the recurrent laryngeal nerve on the left. The composite Dacron graft is beveled and anastomosed to the aorta with a continuous 3-0 polypropylene suture (Fig. 53-3B). Care is taken to place a 1 cm cuff of Teflon felt outside the aorta and to invaginate the graft

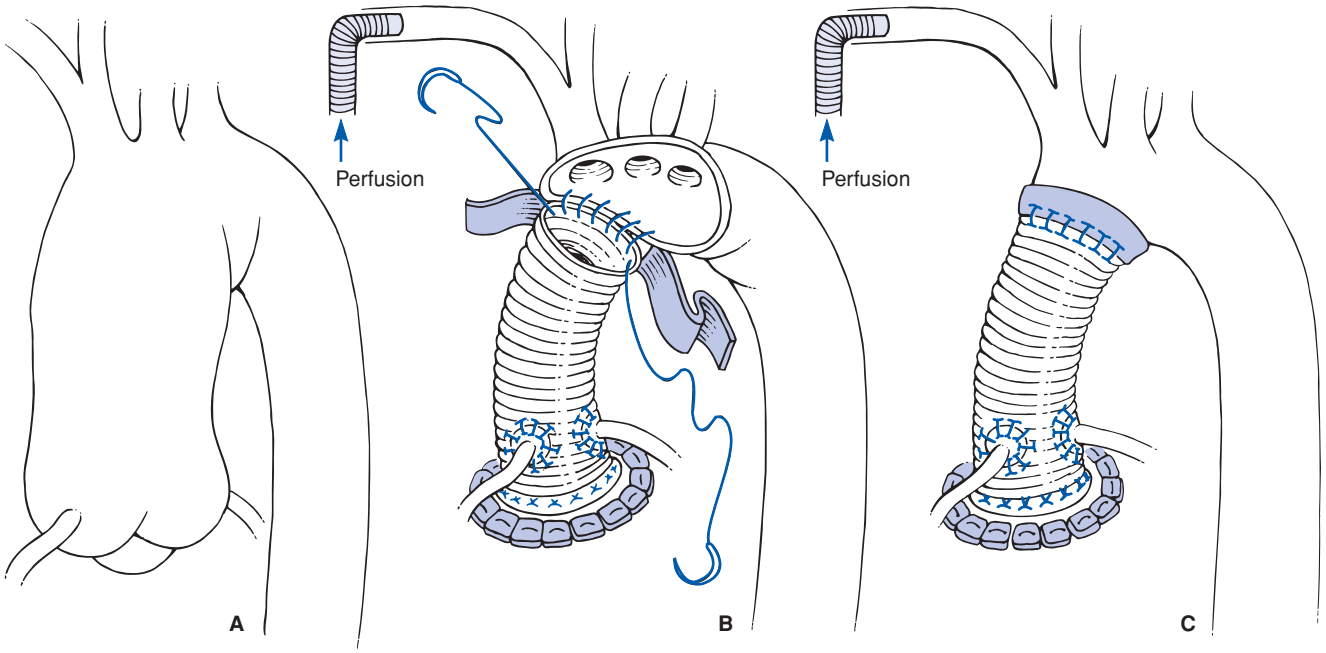

Figure 53-3. (A) Ascending aortic aneurysm extending into the underside of the aortic arch. (B) Bentall reconstruction of the aortic root with open resection of the hemiarch. Perfusion is via the right axillary artery. (C) Completed repair and full systemic perfusion.

within the aorta. The last few loops of the suture line are left loose; the head is placed in steep Trendelenburg position, and perfusion through the axillary artery cannula is restarted at a rate of 500 mL/min to flush all air from the aorta. Once all the air is evacuated, the suture line is tied and cold perfusion is commenced for several minutes, followed by rewarming (Fig. 53-3C). The location for implantation of the right coronary button is marked. The distal ascending aortic graft is cross-clamped and a separate opening is made in the anterior aspect of the graft. The right coronary artery button is reimplanted with running 5-0 polypropylene reinforced with a thin strip of Teflon felt. Prior to tightening the suture line the heart is de-aired. The cross-clamp is removed. A gradient of 10°C or less between the perfusate temperature and esophageal temperature is maintained at all times. Circulatory arrest time is usually less than 20 minutes. Approximately 50 to 60 minutes of warming is necessary to raise the esophageal temperature to 35°C and the bladder temperature to 30 to 32°C; at this time, the patient is weaned from cardiopulmonary bypass.

Case 2: Total Arch Replacement for Nonatherosclerotic Pathology

The patient is a young male with an acute type A aortic dissection referred for emergency surgery. In the past, the operation we describe here has been our standard operation for total arch replacement.[142,143] We now use this technique in rare cases in which the arch is free of atherosclerotic debris, and where an unexpected finding such as an arch tear in aortic dissection requires total arch replacement.

Intraoperative TEE confirms a type A dissection involving the ascending aorta, arch, and descending aorta (Fig. 53-4). However, the location of the intimal tear is not clearly visualized. Flow is present in both the true and false lumens, and there is minimal aortic regurgitation (AR) and no pericardial blood or tamponade.

The right axillary artery is prepared for cannulation. A median sternotomy is performed. Cannulation is carried out via the right axillary artery and the right atrium. Cardiopulmonary bypass with cooling is commenced. When the heart fibrillates, a left ventricular vent is placed via the right superior pulmonary vein. The aorta is cross-clamped and the proximal aorta is opened. Cardioplegia is infused into both coronary ostia and this is supplemented with topical cooling. Careful inspection of the ascending aorta reveals no intimal tear. Perfusate temperature is maintained at 10°C until the esophageal temperature reaches 20°C, and this temperature is maintained while the proximal aortic reconstruction is performed.

The minimal AR is dealt with by resuspending each commissure with pledgeted horizontal mattress sutures. The root is reconstructed by using a 4-0 polypropylene weave to suture a Teflon strip on the outside and a pericardial strip on the inside of the dissected aortic layer. A Dacron graft is anastomosed with 3-0 polypropylene to invaginate the graft within the aortic sandwich. During aortic reconstruction, cooling is continued, and when the esophageal temperature reaches 13 to 15°C, and the jugular venous oxygen saturation is above 95%, the head is placed downward after being packed in ice, perfusion is discontinued, and the cross-clamp is removed. The aorta is opened

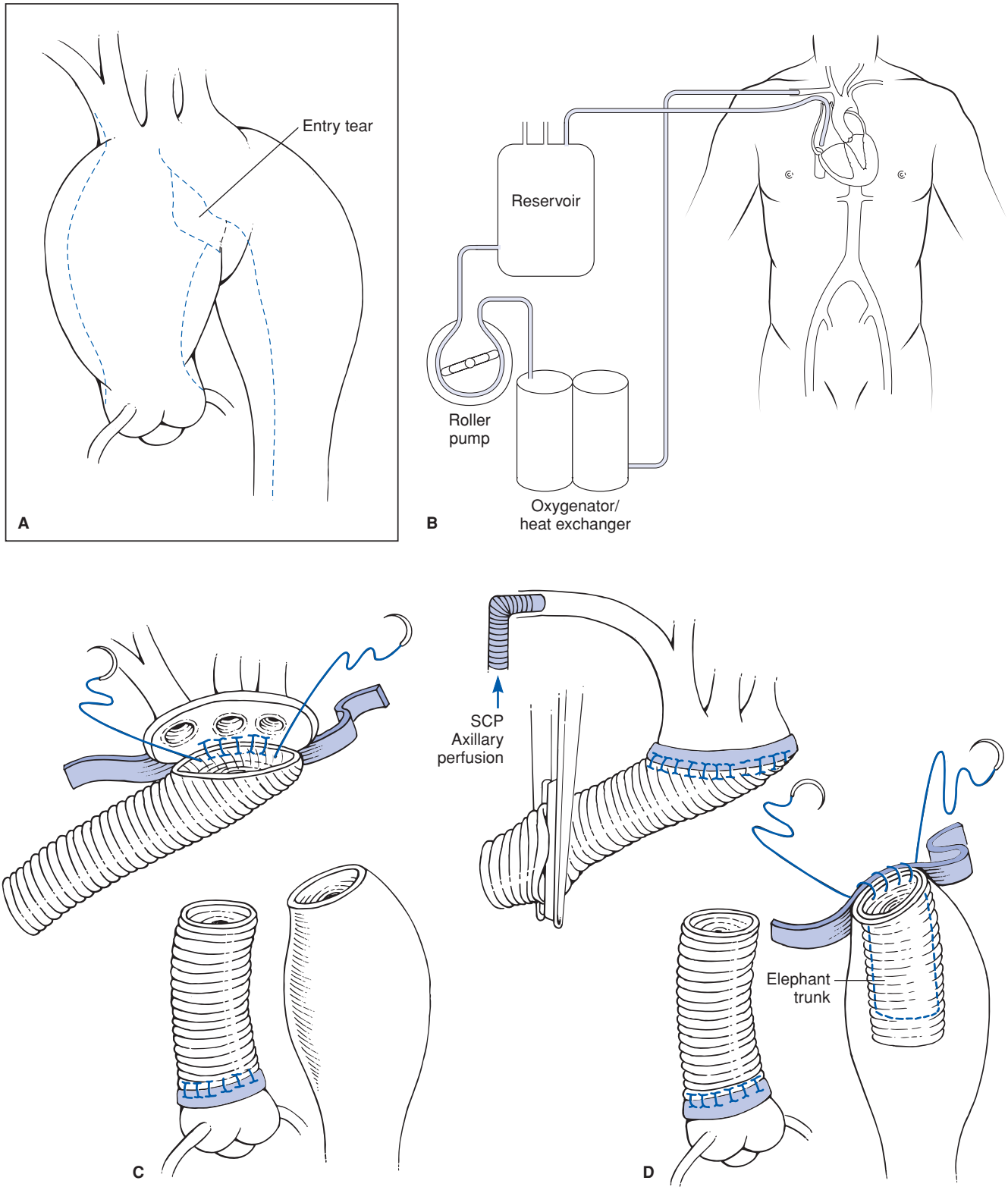

Figure 53-4. (A) Acute type A aortic dissection with the entry point located in the aortic arch. (B) Cardiopulmonary bypass via the right axillary artery. (C) Separate graft anastomosis to the brachiocephalic vessels. (D) Selective cerebral perfusion (SCP) and elephant trunk construction.

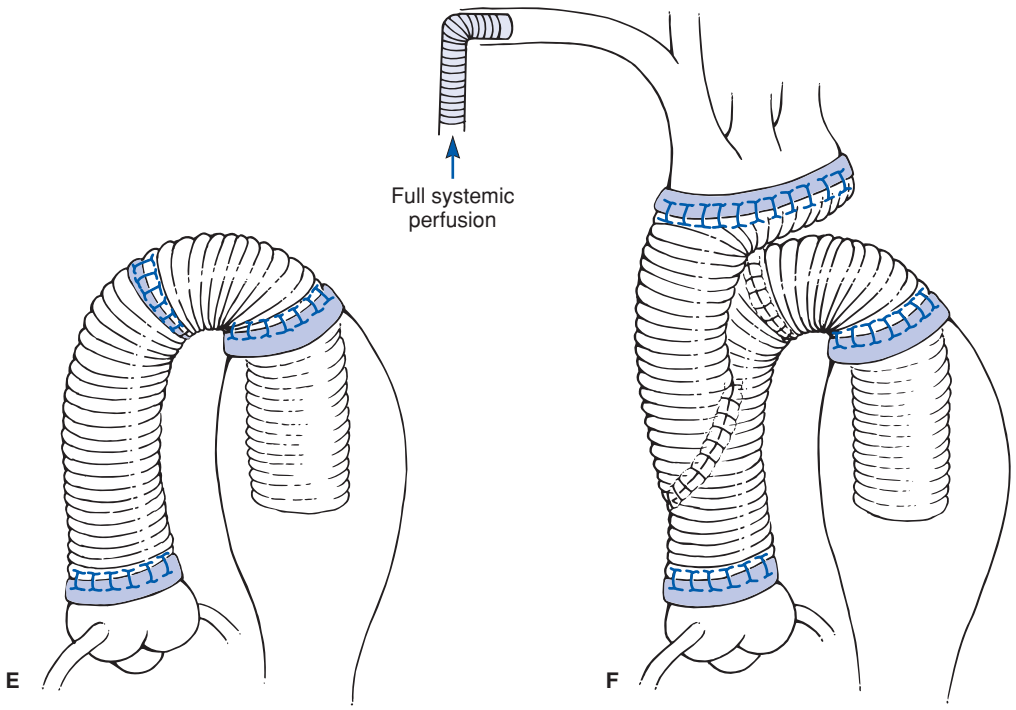

Figure 53-4. (*Continued*) (E) Arch reconstruction with graft-to-graft anastomosis. (F) Completed repair.

into the arch to search for the intimal tear, which is found in the arch opposite the arch vessels. The arch is mobilized and excised, leaving an island of aortic tissue containing the three head vessels. A 16 mm Hemashield (Boston Scientific, Natick, MA) graft is then beveled and sutured to the island of aortic tissue with Teflon reinforcement on the outside, once again invaginating the graft within the aorta, so that the dissected layers are sandwiched between the Teflon on the outside and the graft on the inside. The period of circulatory arrest is usually less than 30 minutes. Antegrade perfusion is then slowly restarted via the right axillary artery, and after careful de-airing, the beveled graft is clamped so that antegrade cerebral perfusion can be instituted at flows between 600 and 1000 mL/min to maintain a proximal perfusion pressure of 40 to 60 mm Hg (Fig. 53-4D).

Attention is now directed to the descending aorta just distal to the left subclavian artery. The aorta is incised circumferentially, Teflon felt is placed outside the aorta, and to facilitate the distal anastomosis, a small elephant trunk is constructed by invaginating the main arch portion of the graft. On completion of the suture line, the graft is everted, trimmed, and anastomosed to the ascending aortic graft with 3-0 polypropylene. The 16 mm arch graft is then beveled, and a longitudinal opening is made in the ascending aortic portion of the graft. The two grafts are anastomosed to each other with 3-0 polypropylene.

The heart is de-aired, the clamp on the beveled graft is removed, and perfusion to the heart and lower body is resumed. After rewarming, the patient is weaned from cardiopulmonary bypass in the standard fashion.

Case 3: Total Aortic Arch Replacement for Atherosclerotic and Calcified Aneurysms

Our technique for total arch replacement in elderly patients or in patients with atherosclerotic and calcified aneurysms has evolved to our current "no-touch" technique (Fig. 53-5). A trifurcated graft is anastomosed to the arch vessels during hypothermic circulatory arrest in order to reduce the risk of embolization; cerebral ischemia is minimized by permitting antegrade cerebral perfusion as arch reconstruction is completed.[144,145]

A median sternotomy is performed with extension of the incision superiorly along the medial border of the left sternocleidomastoid muscle. The recurrent laryngeal nerve is preserved as the AA and its branches are exposed. A no-touch technique of dissection is utilized: the patient is dissected away from the aneurysm.

Cardiopulmonary bypass is initiated using the right axillary artery and the right atrium, with a perfusate temperature lowered to 10°C. Examination of the AA with transesophageal echo confirms retrograde flow in the arch, and monitors for dissection or malperfusion. Cardioplegia is given after cross-clamp application, and is supplemented with topical hypothermia. If the ascending aorta is calcified or severely atherosclerotic, no attempt at cross-clamping is made. The patient is cooled and the heart vented. Just prior to circulatory arrest, 60 mEq of potassium chloride is added to the pump prime over 2 minutes to produce diastolic cardiac arrest. Alternatively, the heart is protected with retrograde blood cardioplegia.

Even in patients with severe atherosclerotic disease of the AA, the arch vessels just beyond their origins are

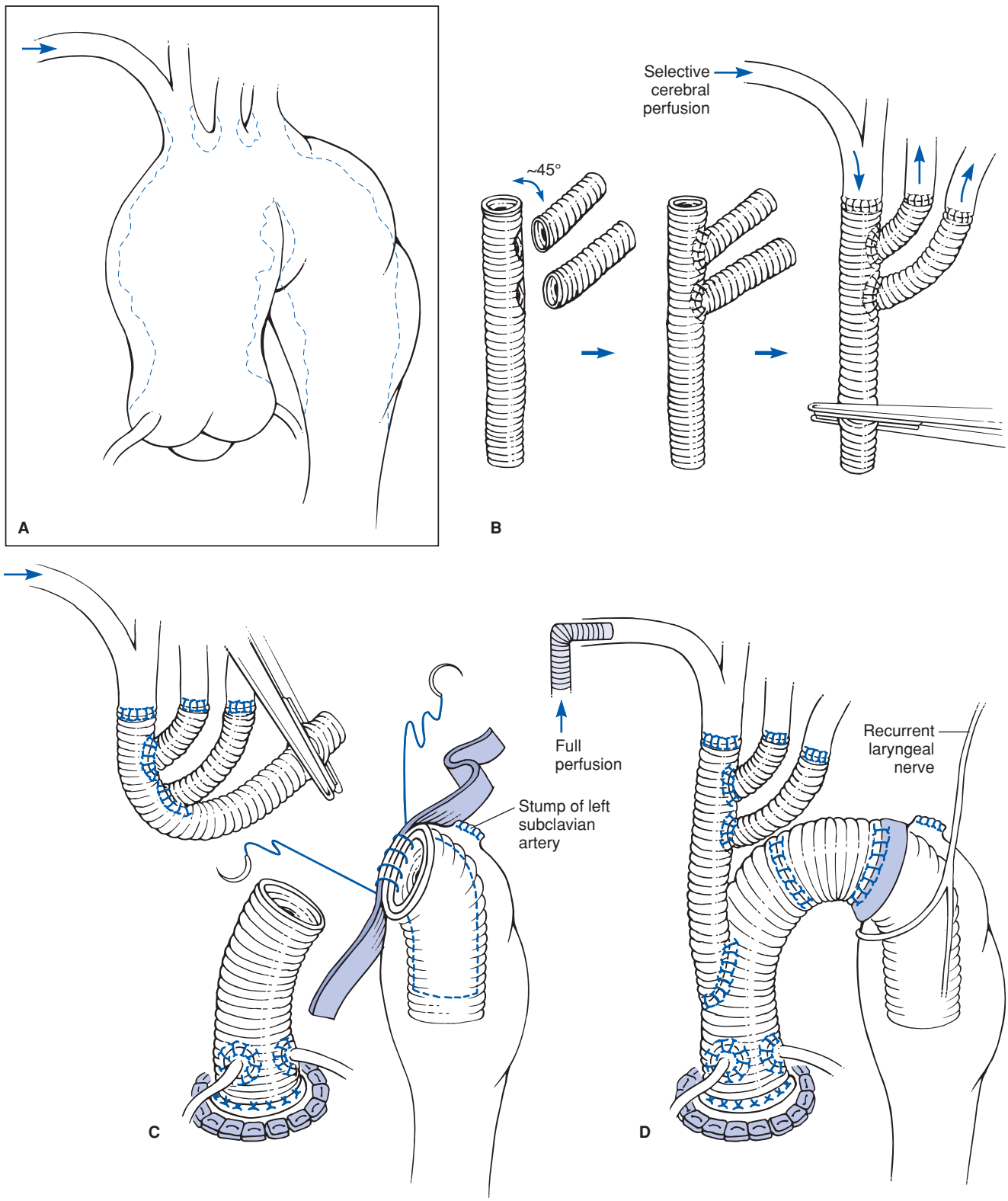

Figure 53-5. (A) Atherosclerotic ascending and arch aneurysm. (B) Fabrication of the trifurcated graft. (C) Selective cerebral perfusion and construction of the elephant trunk. (D) Completed repair.

usually spared. This location is ideal for subsequent anastomoses. After carefully sizing the innominate, left carotid, and left subclavian arteries, a trifurcated graft is constructed as illustrated (see Fig. 53-5B). Completion of this phase usually coincides with adequate core cooling. The head is packed in ice to prevent rewarming during the ischemic period. When the esophageal temperature reaches 13 to 15°C, and jugular bulb oxygen saturation is above 95%, maximum cerebral metabolic suppression is achieved. The patient is placed in the Trendelenburg position to prevent air trapping during the period of circulatory arrest. The arterial line is clamped during deep HCA.

At the beginning of circulatory arrest, the innominate artery is transsected just distal to its origin or at the level where atherosclerosis is minimal. The large limb of the trifurcated graft is trimmed and anastomosis is carried out with 5-0 polypropylene suture. The common carotid and the left subclavian artery anastomoses are constructed in a similar fashion. Each anastomosis takes 6 to 10 minutes, depending on the exposure. Reversing the order of the anastomoses may provide better access to the left subclavian artery in some patients. The trifurcation graft is carefully de-aired, and the proximal portion is clamped, restoring perfusion to the head and upper extremities. Perfusion pressures are maintained at 40 to 60 mm Hg, requiring flows between 600 and 1000 mL/min. Perfusate blood temperature is allowed to drift upward. No active rewarming is done. The AA is reconstructed in a variety of ways depending on the pathology.

For ascending and arch disease with aortic valve involvement, a Bentall or valve-sparing procedure precedes arch reconstruction. If the aortic valve is spared, arch repair begins at the proximal descending thoracic aorta with a suitable cuff of aortic tissue preserving the recurrent laryngeal nerve. If aneurysmal disease involves distal aortic segments, an elephant trunk[30,111,146] may be constructed in either the distal or the more proximal aortic arch, or in the distal ascending aorta where the aortic caliber permits. This maneuver, as described by Kuki,[146] avoids potential nerve injury. The anastomosis is constructed with running 3-0 polypropylene, reinforced with a strip of Teflon felt, taking great care to place the Dacron graft within the native aorta and the felt on the outside. The everted graft is then stretched and measured to the appropriate length and sutured to the sinotubular junction or to the graft previously used for aortic root reconstruction. Graft-to-graft anastomoses are constructed with 3-0 polypropylene. At this point, the Dacron graft is distended with cardioplegic solution to facilitate choosing the ideal site for anastomosing the trifurcated graft to the ascending portion of the aortic graft. An elliptical opening is made and the trifurcation graft is beveled and trimmed. Cerebral and upper extremity perfusion are not interrupted. On completion of this anastomosis, the patient is placed in the Trendelenburg position, and the cross-clamp is removed, restoring full myocardial and systemic perfusion. The patient is now rewarmed. With a blood temperature of approximately 30°C, the ascending aortic graft is vented, and the heart is defibrillated. Cardiopulmonary bypass is discontinued once the patient's esophageal temperature is 35°C.

Case 4: Total Arch Replacement with an Aberrant Left Vertebral Artery

On occasion the left vertebral artery (LVA) will exit the AA directly (Fig. 53-6). This poses a small challenge during arch reconstruction with branch grafts.[147] This anomaly is recognized on CT angiography and prompts a duplex ultrasound evaluation of the right vertebral artery (RVA) to ensure patency and antegrade flow. With a patent normal sized RVA, the LVA can be temporarily occluded during selective cerebral perfusion and reimplanted during patient rewarming. Three options have been used: direct reimplantation of the LVA into the left common carotid artery, attachment of a portion of reverse saphenous vein to the vertebral artery, and anastomosis to the arch graft or the left subclavian limb of the trifurcated graft. This last technique is essential if any question of the integrity of the RVA exists. A very small LVA (<2 mm) with a patent RVA may be ligated. Follow-up imaging studies have confirmed continued patency.

Case 5: Thoracosternotomy for Arch Reconstruction

For patients with prior ascending aortic replacement presenting with arch and proximal descending aortic pathology (Fig. 53-7), or patients with arch and proximal descending aortic disease alone, an alternative approach can facilitate a one-stage repair.[27,28] A bilateral anterior thoracotomy can be used. Both internal mammary arteries are ligated. Exposure of the transverse AA and proximal descending thoracic aorta is outstanding. For brachiocephalic artery reconstruction, either a large Carrell patch to a separate graft or a trifurcated graft or a four-branch graft to the individual vessels can be used, depending on the degree of atherosclerotic disease and/or scarring from previous surgery. Patients tolerate the incision, and adequate exposure of the phrenic and recurrent laryngeal nerves allows careful preservation. The only drawback involves sternal union, and therefore secure stabilization of the sternal tables at the end of the procedure is imperative. Arterial perfusion is the same, through the right axillary artery. Venting of the left ventricle during systemic cooling and cardiac fibrillation can be carried out either via the right superior pulmonary vein or via a small separate thoracotomy overlying the left ventricular apex.

Case 6: Arch Replacement Following a Previous Bentall Procedure for Extensive Thoracic Aortic Aneurysmal Disease

Replacement of the AA following a previous surgical procedure involving the ascending aorta can be challenging.

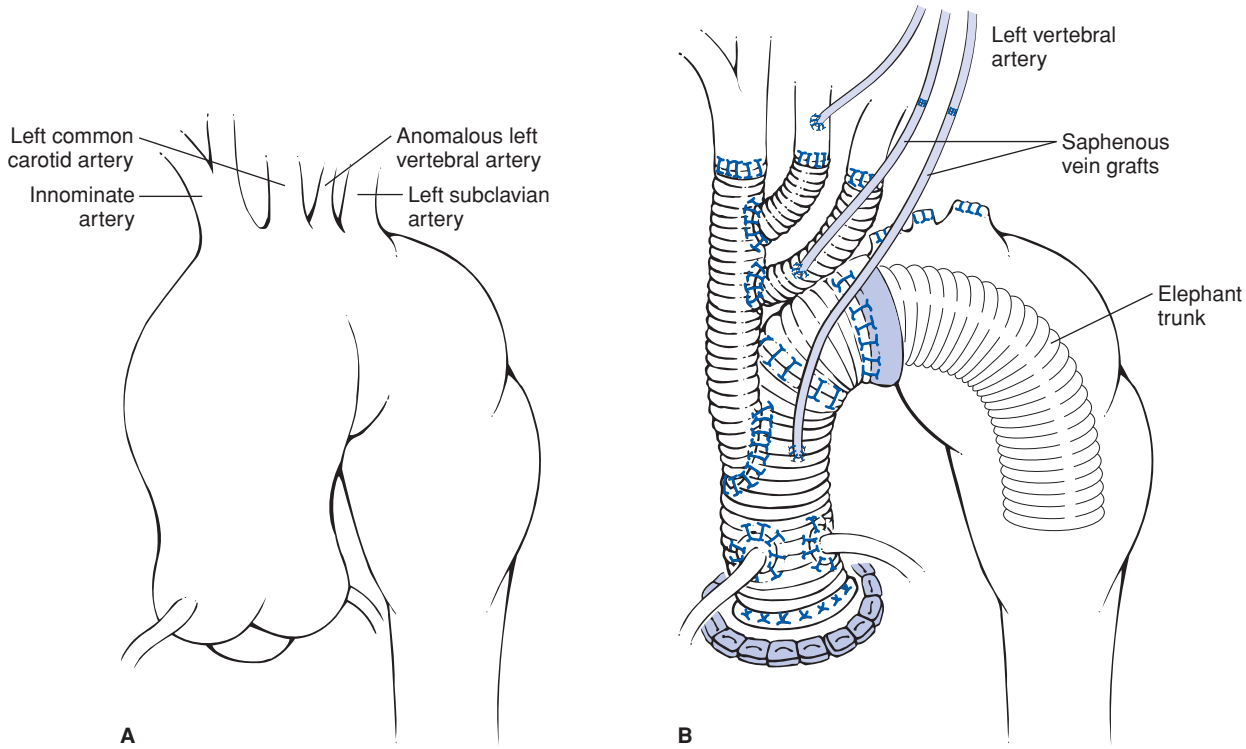

Figure 53-6. (A) Anomalous left vertebral artery exiting the aortic arch directly. (B) Three techniques for reconstruction.

A simple approach will facilitate repair and avoid many of the pitfalls of other techniques (Fig. 53-8). The arch is exposed through the previous sternotomy and the brachiocephalic vessels are dissected free, mobilizing the innominate vein. Extensive dissection of the previous graft risks injury to the pulmonary artery. The right atrium and right superior pulmonary vein are exposed. Cannulation is via the right axillary artery and right atrium. A coronary sinus retrograde catheter is an important adjunct for myocardial protection. Cardiopulmonary bypass is begun and the patient is cooled. The left ventricle is vented. After adequate cooling and circulatory arrest a trifurcated graft is placed to the brachiocephalic vessels as previously described, followed by SCP. To facilitate the procedure all of the arch vessel stumps are oversewn with 3-0 polypropylene. The elephant trunk is constructed proximal to the origin of the innominate artery and left long to traverse the arch into the proximal descending aorta. If the reason for re-operation is residual chronic aortic dissection, a small caveat can avoid disaster. The elephant trunk should not be longer than the distal fenestration allowing equal perfusion of the true and false lumens. On occasion the false lumen is partially filled with thrombus. In this situation the elephant trunk should be directed into the true lumen to avoid embolization from the false lumen. Part of the graft is everted back into the mediastinum and trimmed as short as possible, leaving perhaps two or three rings. This is anastomosed to the previous Bentall graft with 2-0 or 3-0 polypropylene. The trifurcated graft is then attached to the old Bentall graft through an elliptical opening in the right lateral side. The surgical procedure continues to conclusion. The arch remains pressurized until the second stage repair, with either an open surgical technique or thoracic endograft. Using this technique we have reduced our morbidity and mortality comparable to first-time arch replacement.

Case 7: Descending Thoracic Aortic Aneurysm Involving the Distal Arch

Descending thoracic aortic aneurysms often involve the distal AA, or are associated with a distal arch that is calcified and severely atherosclerotic, making cross-clamping dangerous (Fig. 53-9). If the arch appears severely diseased, one might consider a two-stage reconstruction to isolate the cerebral circulation and reduce the risk of embolic stroke. For lesser degrees of intraluminal disease we use the following technique.

Operation is carried out through a left thoracotomy in the fourth or fifth intercostal space with the incision extended inferiorly across the costochondral plate to improve exposure if necessary. The internal mammary artery is usually preserved. The left femoral artery and vein are dissected out in preparation for cannulation. The descending aorta is gradually mobilized. Intercostal arteries are serially clamped and then sacrificed when no changes in the SSEPs and MEPs develop. Care is taken not to manipulate the distal arch adjacent to the left subclavian artery. Cannulation for CPB is carried out with a long perfusion catheter inserted via

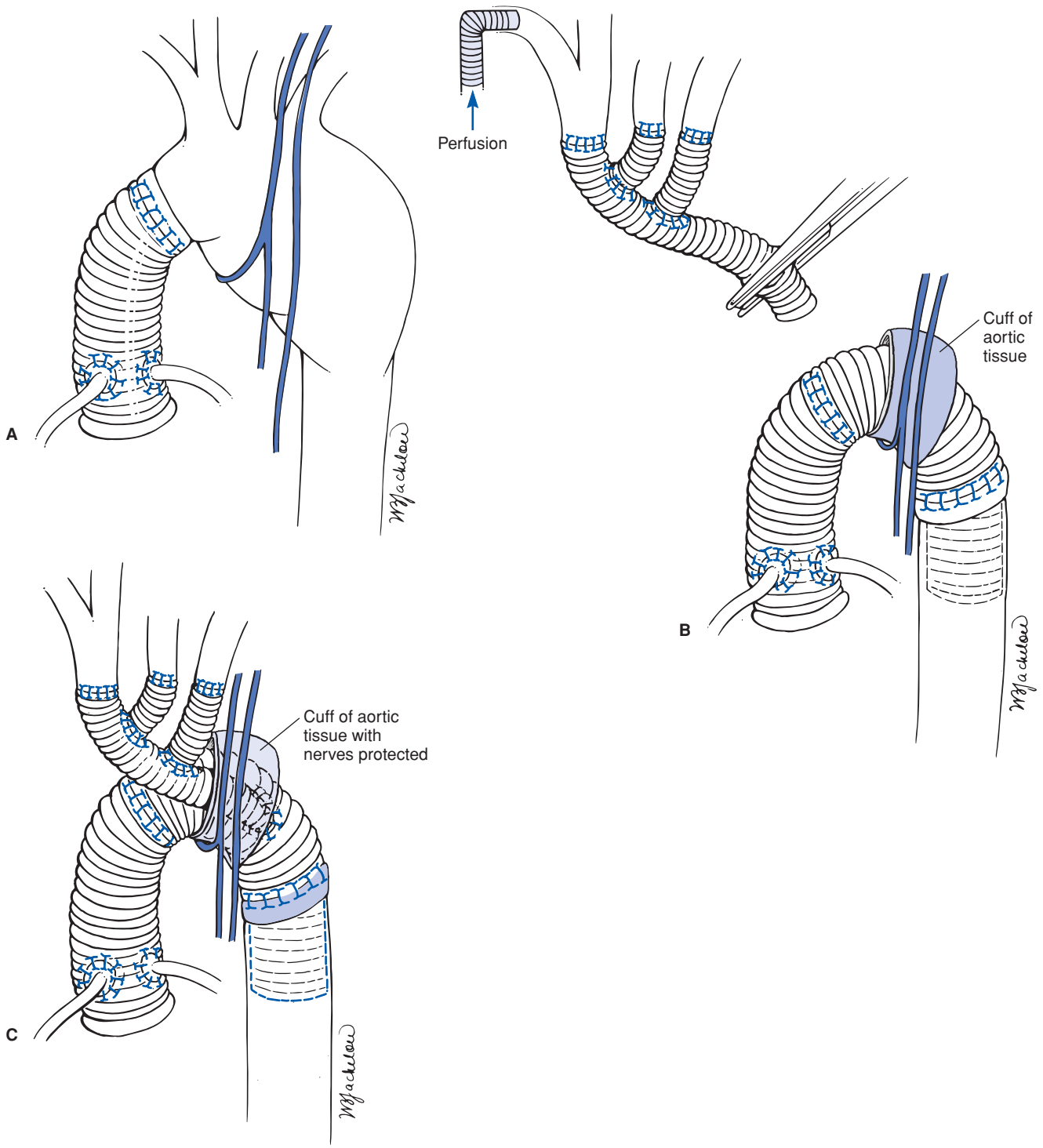

Figure 53-7. (A) Recurrent arch proximal descending aneurysm approached via a thoracosternotomy. (B) Selective cerebral perfusion and arch reconstruction. (C) Completed repair.

the left common femoral vein, and positioned in the right atrium with the aid of a guidewire and TEE monitoring. Occasionally the main pulmonary artery is used for venous inflow. The left common femoral artery is cannulated. Perfusion is begun gradually to avoid a rapid shift in the perfusion patterns in the aorta that might dislodge atheromatous debris. Once perfusion is established, care is exercised to avoid manipulating the descending thoracic aorta, inasmuch as dislodged debris would be carried retrograde toward the arch vessels and the coronary arteries. During cooling and once ventricular fibrillation has occurred, left ventricular distention is closely monitored with TEE and pulmonary

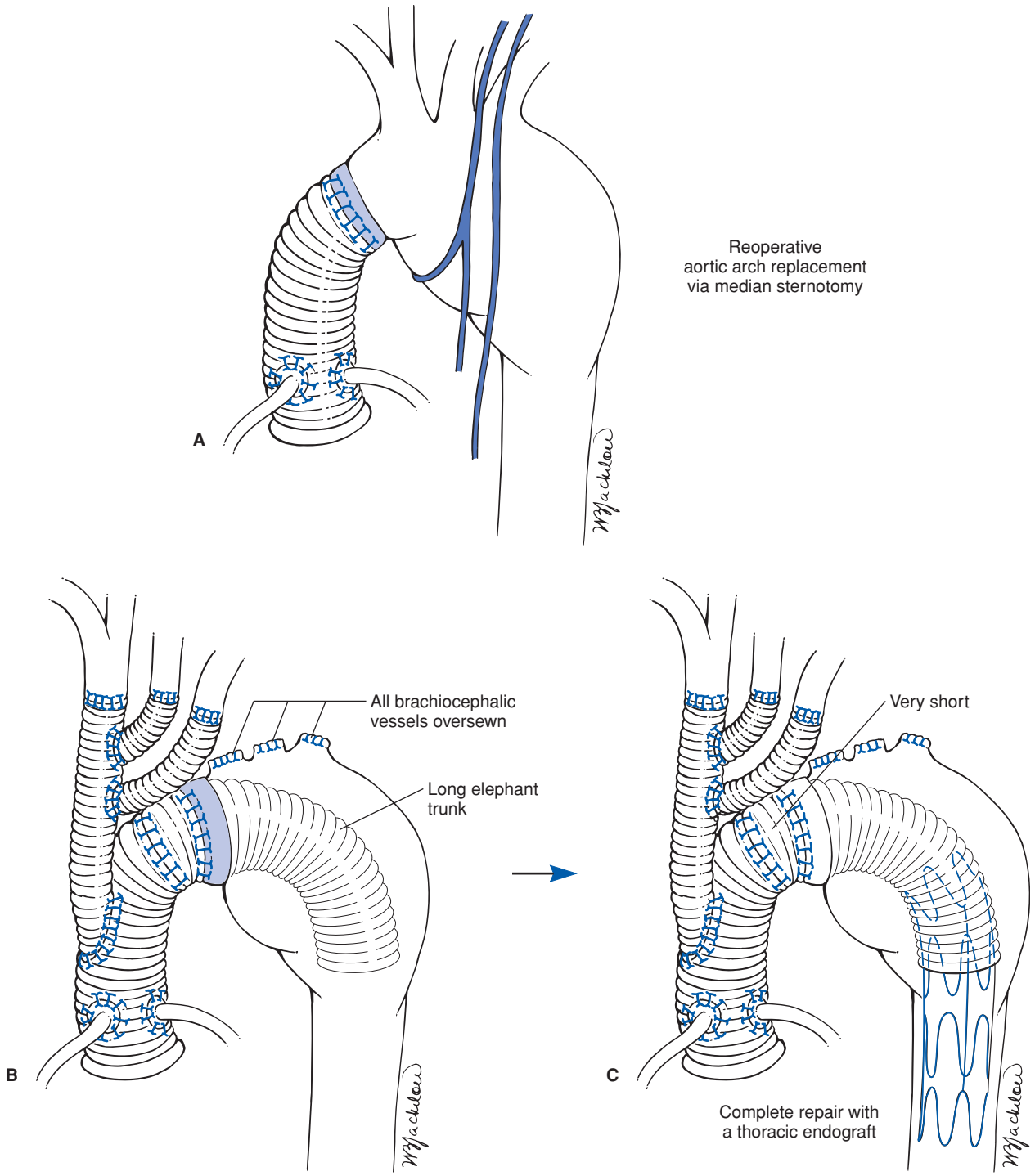

Figure 53-8. (A) Reoperative aortic arch aneurysm approached via median sternotomy. (B) Elephant trunk reconstruction proximal to the innominate artery. (C) Completed repair with a thoracic endograft placed retrograde.

artery pressures. If there is any sign of left ventricular dilatation, a vent is introduced into the left ventricular apex or via the left atrium. After about 30 to 40 minutes of cooling, the esophageal temperature has usually decreased to 13 to 15°C, and the jugular venous saturation exceeds 95%. Cardiopulmonary bypass is discontinued.

The left ventricular vent is clamped, and the descending thoracic aorta is opened. A cuff of the underside of the AA, extending inferiorly to the distal ascending aorta and superiorly to the margin of the left carotid artery, is fashioned. An attempt is made to preserve the recurrent laryngeal nerve. A single side-arm graft is anastomosed to the

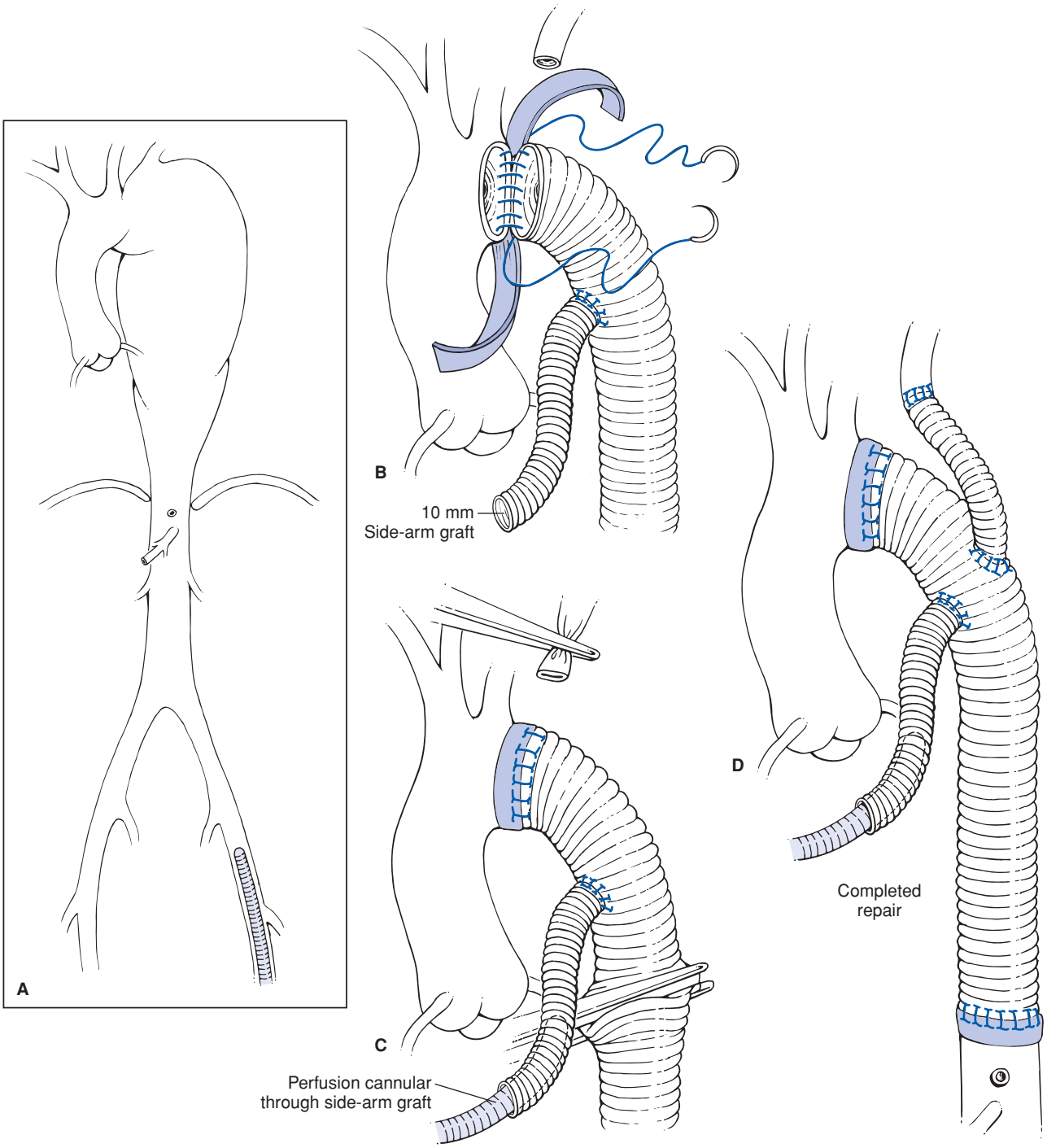

Figure 53-9. (A) Distal arch descending thoracic aortic aneurysm with femoral artery perfusion. (B) Hypothermic circulatory arrest and anastomosis to the distal arch. (C) Selective cerebral perfusion via a side-arm graft. (D) Reattachment of the left subclavian artery and completed repair.

native aorta with a running suture of 3-0 polypropylene. Teflon felt is used, and the graft is invaginated within the aorta. The brachiocephalic vessels are carefully aspirated. To facilitate the de-airing and removal of debris, the left ventricular vent is attached to the cardioplegia line and cold blood is infused at approximately 400 mL/min into the left ventricle out the ascending aorta and arch. This continues for several minutes until the blood returning through the graft is free of air and particulate matter. A perfusion cannula is then placed into the side-arm graft, and antegrade perfusion is begun to the brachiocephalic and coronary arteries. The graft and subclavian artery are clamped. The left ventricular vent is returned to low suction.

Attention is now turned to the distal descending aorta. Perfusion via the femoral artery catheter is used briefly to wash any loose debris in the descending aorta out into the

field. A distal cuff is fashioned, and the graft is anastomosed to it with a running 3-0 polypropylene suture. Teflon felt is utilized. The clamp on the graft is removed, and the flow to the entire body is provided through the perfusion catheter placed in the side-arm graft. Rewarming, defibrillation, and weaning from CPB are carried out in standard fashion. During rewarming, a separate 8 or 10 mm graft is sewn to the left subclavian artery, trimmed to the appropriate length, and anastomosed to the descending graft with a side-biting clamp.

SSEP and MEP monitoring is continued to the conclusion of the operation, and arterial pressures are maintained in the high normal range. The evoked potentials gradually return, but below baseline secondary to systemic hypothermia. An intrathecal catheter is placed preoperatively and is used to drain cerebrospinal fluid in order to keep the cerebrospinal fluid pressure below 12 mm Hg for the first 24 to 48 hours, depending on the extent of resection.

RESULTS

The contemporary experience suggests that HCA/SCP is superior to HCA alone for preventing cerebral injury during aortic arch reconstruction and that SCP/trifurcated graft with axillary artery cannulation may be the optimal technique for reducing adverse outcome.[112,148]

Recently reported series of total AA replacement compare favorably with our results. Safi and associates[31] reported a 30-day mortality of 5.1% in 117 patients undergoing stage I elephant trunk reconstruction, with an adverse outcome rate of 6.8%. Interestingly, 43 (37%) of patients did not return for second-stage repair, and 30.2% died from distal aneurysm rupture in short-term follow-up. Schepens and colleagues[149] reviewed 100 consecutive stage I elephant trunk reconstructions from 1984 to 2001, with an 8% mortality, 12% adverse outcome, and 2% TND. The majority of patients received isolated unilateral or bilateral antegrade cerebral perfusion for cerebral protection.

Ueda[150] described 207 consecutive patients with AA repairs from 1988 to 2000, 50% with atherosclerotic aneurysm, and a 12% mortality. The author re-emphasized the poor long-term outcome of patients with postoperative neurologic injury. Recently, the use of the anterolateral approach to complicated arch repair avoided cerebral dysfunction;[151] this is a technique we have employed with contained ruptures and redo arch replacements. Hilgenberg and Logan[152] reported adverse outcome in 6% of 67 patients, with 16% experiencing TND with acute dissection, which was the only independent risk factor for neurologic dysfunction. Hirotani and colleagues,[153] using a pharmacologic mixture to improve cerebral protection with HCA, performed total arch replacement in 43 patients with a mortality of 10.7% and an adverse outcome rate of 14.7%. The duration of circulatory arrest did not correlate with mortality or postoperative stroke, again illustrating the embolic nature of focal neurologic injury.

Coselli and coworkers,[154] in a series of 227 patients with AA surgery, experienced a 6% early and a 9% late mortality, with a 3% incidence of stroke. The reduction in neurologic injury was attributed to a >50% use of retrograde cerebral perfusion during HCA. Finally, Kazui and associates[102] in their contemporary collection of 50 patients and use of a refined technique of total arch replacement in atherosclerotic aneurysms, achieved outstanding results: 2% mortality, 6% rate of adverse outcome, and 4% incidence of TND. Duration of CPB was the only univariate risk factor for TND, and a history of cerebrovascular accident was correlated with permanent neurologic dysfunction. Di Eusanio and colleagues,[101] in a multicenter study using antegrade cerebral perfusion for total arch replacement in 352 patients, experienced an 8.7% rate of in-hospital mortality, permanent stroke rate of 3.8% (adverse outcome rate of 12.5%), and rate of TND of 5.6%. Independent predictors of adverse outcomes included urgent operation, recent stroke, tamponade, unplanned coronary revascularization, and pump time. Postoperative complications were a 12.1% return for bleeding, myocardial infarction in 2.9%, prolonged ventilation (>5 days) in 17.7%, and renal failure requiring temporary hemodialysis in 4.6%. Numata and coworkers,[17] using right axillary perfusion and a separate cannula in the left common carotid artery for 120 arch replacements, achieved impressive results: 5.8% mortality and 0.8% permanent stroke rate, with 5.8% (7 patients) experiencing TND.

From our prospectively compiled database of patients undergoing aortic surgical procedures, we identified 150 consecutive patients (91 male, 59 female) who underwent nonemergent resection of aneurysms of the transverse arch between September 1999 and December 2005, utilizing hypothermic antegrade cerebral perfusion after an interval of deep hypothermic circulatory arrest provided by direct axillary artery cannulation and a trifurcated graft.

The mean age was 63 ± 14 years (range 20 to 87 years). The most frequent etiology of the aneurysm was chronic dissection, which was present in 56 patients (37.3%). Atherosclerosis occurred in 48 patients (32.0%), and the aneurysms were classified as degenerative in 29 (19.3%). Sixty-eight patients (45.3%) had undergone previous cardiac surgery.

Among the known risk factors for adverse outcome after surgery, chronic obstructive pulmonary disease was present in 23 patients (15.3%), insulin-dependent diabetes in 8 (5.3%), and dialysis-dependent renal failure in 6 patients (4.0%). Among potential risk factors for postoperative neurologic injury, a history of transient ischemic attack was present in 5 patients (3.3%), and 13 patients (8.6%) had experienced a preoperative stroke.

The mean maximal diameter of the aorta was 6.1 cm (range 4.0 to 12 cm). The extent of aortic replacement varied, and a number of patients had concomitant procedures. Lone arch replacement was undertaken in 38 patients

(25.5%). In addition, 74 patients (49.6%) had ascending aortic replacement, 21 (14.1%) had ascending and root replacement, and 4 (2.7%) had resection of the descending aorta. An elephant trunk was placed in 144 patients (96.6%), distal to the left subclavian artery in 87 (58.0%), distal to the left common carotid in 34 (22.7%), between the brachiocephalic and left carotid arteries in 9 (6.0%), and proximal to all arch branches in 18 (12.0%). Coronary artery bypass grafting was performed in 36 patients (24.0%). All arch reconstructions were completed using a single period of HCA followed by SCP utilizing the trifurcated graft technique. Mean duration of HCA was 31.1 ± 6.5 minutes (range 17 to 48 minutes). Mean duration of SCP was 66.6 ± 21.0 minutes (range 21 to 125 minutes). Mean temperature of SCP was 15.8 ± 2.1°C (range 12.0 to 22.1°C). The duration of CPB was 239 ± 53.1 minutes (range 157 to 390 minutes).

Adverse outcomes were seen in 13 patients (8.7%). There were 7 hospital deaths (4.7%) and 6 permanent strokes (4.1%).

The most frequent complication was prolonged intubation (>48 hours), which was necessary in 24 patients (16.0%). TND developed in seven patients (4.7%). No correlation between preoperative neurologic risk factors and postoperative events was found. Return to the operating room for bleeding was required in seven patients (4.7%). Temporary renal support was needed in nine patients (6.0%), but none required permanent dialysis. Median intensive care unit stay was 3 days (range 1 to 108 days) and hospital stay was 10 days (range 4 to 108 days).

Techniques of AA replacement must be an integral part of the neurologic protection scheme. The two facets of neurologic protection, prevention of cerebral injury during global ischemia and avoidance of particulate athero-emboli, are not mutually exclusive. In the current era, with a combination of deep hypothermia and SCP, the prevention of cerebral embolization plays an even greater role in further reducing the risks of arch replacement in an aging population. To this end, two surgical strategies have emerged to balance the neurologic risks: the four-branched graft AA replacement championed by Dr. Kazui and others,[99,101,155] and more recently, the trifurcated graft technique.[112] The benefits are illustrated by shorter durations of deep HCA and the utilization of SCP to restore and maintain cerebral oxygenation while isolating the brachiocephalic vessels during subsequent arch repair. Selective cerebral perfusion can be performed in several different ways: right axillary artery cannulation and a single balloon catheter in the left common carotid artery,[104] direct balloon tip catheter perfusion of the innominate artery and left common carotid arteries,[99,101,155] unilateral brain perfusion from the right axillary artery[29] or the right brachial artery,[104] and even direct bilateral cannulation of the carotid arteries outside the thorax.[156] Our technique avoids instrumentation of the brachiocephalic vessels and ensures bilateral cerebral perfusion, albeit at the expense of lower core brain temperatures and longer deep HCA intervals but well within the accepted safe limits. Recently, a slight modification of the trifurcation graft method has shortened the deep HCA times further (Fig. 53-10). Using the same perfusion technique following a single period of deep HCA, the left subclavian artery is anastomosed to the first limb of the trifurcated graft followed by the innominate artery. Partial SCP at 400 to 500 mL/min is begun with the left common carotid open to back-flush via collaterals. The left common carotid is then gently occluded with a soft clamp, restoring cerebral circulation. Next, under partial SCP the left carotid artery is attached and de-aired. Flows are increased to 10 mL/kg/min. The remaining reconstruction proceeds as usual. The deep HCA time is shortened to ~20 minutes without the need to instrument the vessels. This may become important when residual atherosclerotic disease is present in the individual brachiocephalic vessels or in the event of acute or chronic dissection, when cannulation may be difficult and risk malperfusion. It is possible that perfusion cannulas can become dislodged or displaced during SCP.[15] Lastly, the perfusion cannulas in the limited space of the mediastinum may obscure the operative field during subsequent arch replacement.

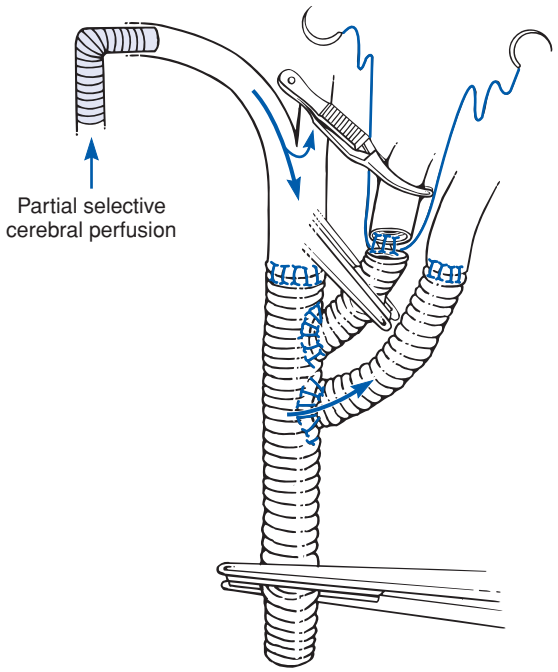

Figure 53-10. Partial selective cerebral perfusion.

LONG-TERM FOLLOW-UP

Aortic arch aneurysms may represent a localized manifestation of an often multilevel disease process of the aorta. Therefore, long-term follow-up of the unresected aorta in postoperative patients is mandatory. All patients with aortic aneurysms are entered into our database (n = 2308) and follow-up program. Patients with small aneurysms require ongoing radiographic imaging at either 6- or 12-month intervals, depending on the location, rate of progression, and

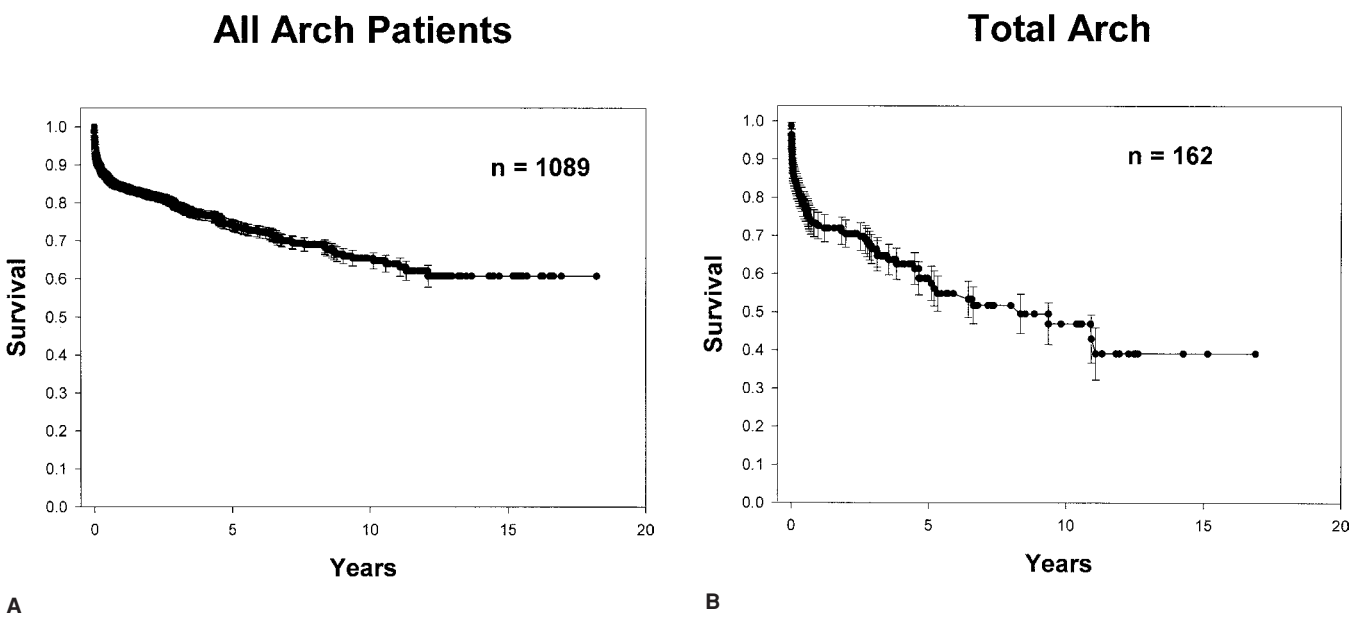

Figure 53-11. Life table analysis of long-term survival following total aortic arch replacement with the trifurcated graft technique.

etiology. Baseline CT scan, MRI, or angiograms obtained in the postoperative period document the integrity of the repair and provide a baseline for later comparison. In those patients with no portion of the unresected aorta dilated to a diameter exceeding 4 cm, the first re-evaluation is scheduled in 1 year. Patients with significant residual dissection or aneurysmal dilatation are followed more closely at 6-month intervals. Medical therapy includes control of hypertension, β-blocker therapy in patients with aortic dissection and Marfan syndrome, and encouragement of cessation of cigarette smoking.

When examining patients undergoing total arch replacement with a trifurcated graft—reflecting more extensive aneurysmal disease—survival at 1 year is 75%; it is 73% at 3 years, and 61% at 5 years (Fig. 53-11). Reduced 1-year survival results from rupture prior to a staged repair, mortality from the second stage surgery, and failure to return for stage two. Long-term results reported in the literature confirm the importance of continued surveillance of patients following total arch replacement. Crawford and colleagues[157] found that 70% of patients with operations involving the AA had significant disease elsewhere in the aorta. Coselli and associates documented that 15% of 227 patients with AA repairs required additional surgery within a mean interval of 17 months.[154] Heinemann and coworkers[158] reoperated on 24% of 82 patients with type A dissection over a 10-year period. Detter and colleagues,[158,159] examining the long-term prognosis of aortic aneurysm in patients with and without Marfan syndrome, found a reoperation rate of 10.7 and 66.7%, respectively, reinforcing the necessity of continued radiographic follow-up, particularly in patients with Marfan syndrome, residual dissection, and AA aneurysms. Late death occurred in 25% of Marfan patients and 14% of nonMarfan patients, with 18% caused by redissection and recurrent aneurysm in the Marfan group. In our series of 162 patients following type A aortic dissection, 17% required reoperations: 23 distal and 4 proximal.[160]

Elective replacement of other aortic segments can be carried out with an acceptable morbidity and mortality, in contrast with the low salvage rate seen in patients presenting with contained ruptures and untreated comorbid disease.

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CHAPTER 54

Descending and Thoracoabdominal Aortic Aneurysms

Joseph S. Coselli • Scott A. LeMaire

An aortic aneurysm is a permanent localized dilatation whose diameter is at least 1.5 times larger than the expected normal diameter of that portion of the aorta.[1] Aneurysms of the descending thoracic aorta can involve any portion of the aorta between the left subclavian artery and the diaphragm. Thoracoabdominal aortic aneurysms (TAAAs) are characterized by dilatation of the aorta at the diaphragmatic hiatus—the boundary that separates the descending thoracic and abdominal aortic segments—with varying degrees of extension into the chest and abdomen (Fig. 54-1). Because of the extent of this type of aortic disease and the formidable operative procedures required to treat it, this entity continues to represent a significant clinical challenge to the cardiovascular surgeon. As our population ages and the availability of new diagnostic modalities increases, so do both the number of identified descending thoracic aortic aneurysms (DTAAs) and TAAAs and the number of patients in need of surgical intervention.

PATHOGENESIS

Causes of DTAAs and TAAAs include nonspecific medial degeneration, dissection, connective tissue disorders, aortitis (e.g., Takayasu's arteritis), aortic coarctation, and infection. Traditionally, many thoracic aortic aneurysms were labeled atherosclerotic aneurysms; however, although atherosclerosis and aortic aneurysms share common risk factors and frequently coexist, thoracic aortic aneurysms are primarily the result of age-related medial degeneration, which is characterized by changes in elastin and collagen that reduce aortic integrity and strength. Subsequent aortic enlargement and aneurysm formation provide fertile ground for superimposed intimal atherosclerosis and further degeneration of the aortic wall. The usual histologic changes in the aging aorta include elastin fragmentation, fibrosis with increased collagen, and medial degeneration.[2] As with most aneurysmogenic processes, medial degeneration usually causes diffuse, fusiform aortic dilatation. In some cases, however, medial degeneration produces saccular aneurysms along the descending thoracic aorta. These saccular aneurysms may be superimposed on or coexist with more generalized, fusiform aneurysmal disease of the thoracoabdominal aorta.

Aortic dissection is the progressive separation of the aortic wall layers that usually occurs after a tear forms in the intima and inner media. Propagation of the separation within the layers of the media creates a new channel—the false lumen—that is separated from the original, true lumen by the dissecting membrane. The weakened outer aortic wall is prone to progressive aneurysmal dilatation (Fig. 54-2). Penetrating aortic ulcers and intramural hematomas are two variants of aortic dissection that can occur in the descending and abdominal aortic segments. Penetrating aortic ulcers are disrupted atherosclerotic plaques that can penetrate the aortic wall, leading to formal dissection or rupture. Intramural hematomas are collections of blood within the aortic wall without an intimal tear; accumulation of the hematoma can result in formal dissection.

Connective tissue disorders are genetic diseases characterized by defective components of the extracellular matrix, such as fibrillin in Marfan syndrome and collagen in Ehlers-Danlos syndrome. When the defect occurs in the aortic wall, the resulting weakness often leads to aneurysm formation. In the Marfan aortic wall, fragmentation of elastic fibers and the deposition of extensive amounts of mucopolysaccharides produces abnormal elastic properties that predispose the aorta to dilatation.[3,4] The aorta in Marfan patients is particularly prone to dissection, which is the most common cause of DTAAs and TAAAs in these patients.[5]

Both chronic, nonspecific aortitis and systemic autoimmune disorders, such as Takayasu's arteritis, giant cell arteritis (temporal arteritis), and rheumatoid aortitis, can cause destruction of the aortic media and progressive aneurysm formation. Although Takayasu's arteritis usually causes

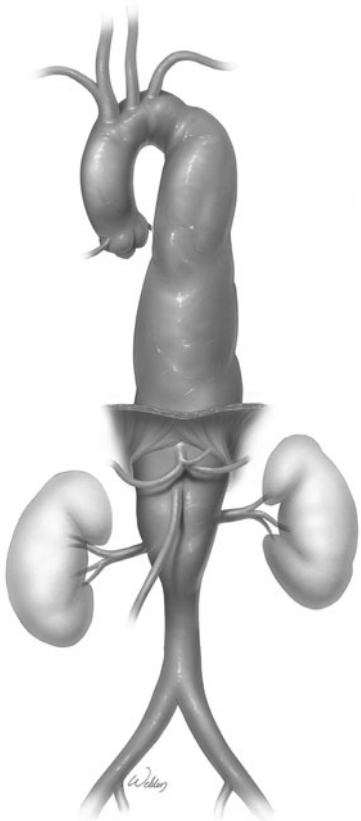

Figure 54-1. Drawing depicting a thoracoabdominal aortic aneurysm.

obstructive lesions related to severe intimal thickening, the associated medial destruction can result in aneurysmal dilatation.

Aneurysms involving the upper descending thoracic aorta can develop in patients with congenital aortic coarctation. These aneurysms occur in the setting of unrepaired coarctation as well as after coarctation repair.[6] The post-repair aneurysms appear to be most common in patients who have had patch graft aortoplasty operations.[7,8] Histologic examination of the aneurysmal tissue has revealed medial degeneration, smooth muscle cell necrosis, and loss and fragmentation of elastic fibers.[9]

Infection can produce a saccular "mycotic" aneurysm in a localized area of the aortic wall that has been damaged by the infectious process. For unknown reasons, such mycotic aneurysms tend to occur along the lesser curvature of the transverse aortic arch or in the upper abdominal aorta adjacent to the origins of the visceral branches. In such cases, only a portion of the aortic circumference is affected; consequently, localized weakening causes a diverticular or saccular outpouching.

Each of the disease processes described above cause aneurysms through progressive degeneration and dilatation of the aortic wall. In contrast, pseudoaneurysms of the thoracic aorta form as the result of chronic leaks through discrete defects in the aortic wall. These leaks are initially contained by surrounding tissue; the accumulation of organized thrombus and the associated fibrosis forms the wall of the

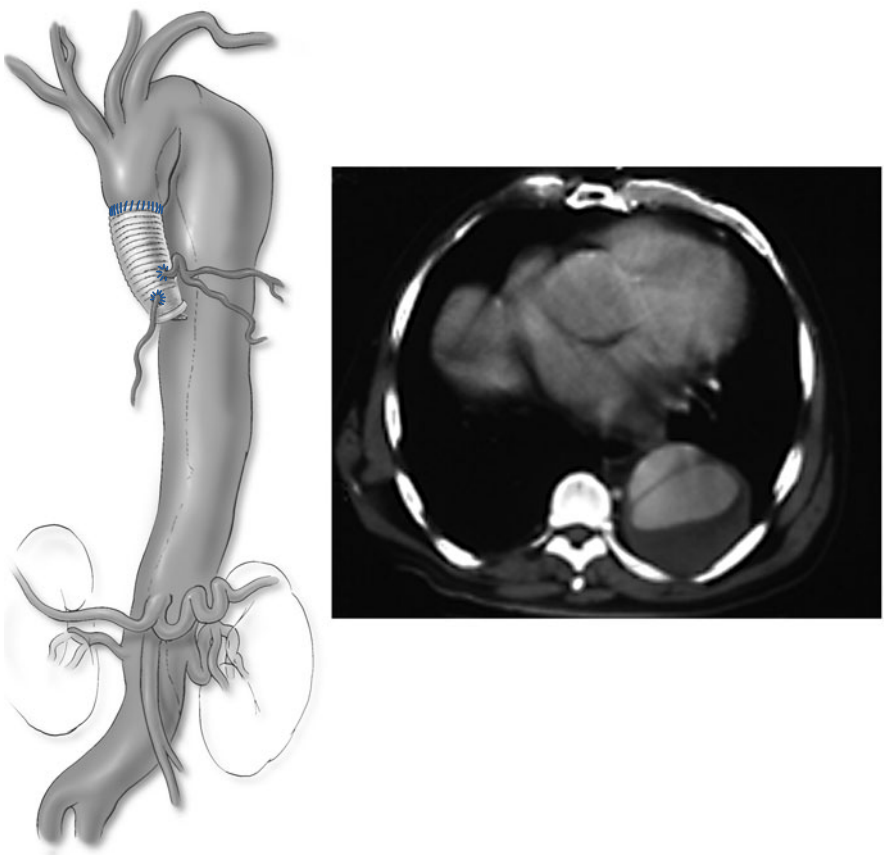

Figure 54-2. Drawing and computed tomography image of a thoracoabdominal aortic aneurysm caused by dilatation of the false lumen in a patient with chronic aortic dissection.

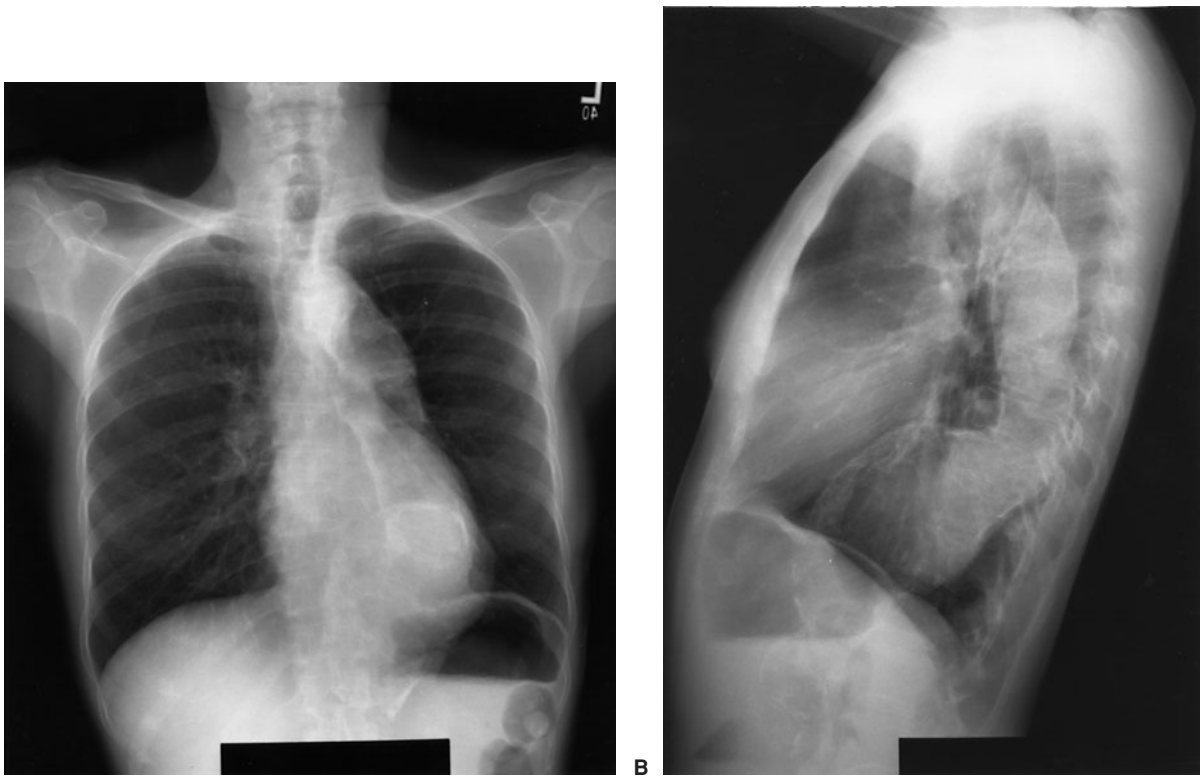

Figure 54-3. Chest radiographs in (A) posteroanterior and (B) lateral projections showing the calcified wall of a thoracoabdominal aortic aneurysm.

pseudoaneurysm. Pseudoaneurysms can develop after surgical or percutaneous interventions performed to repair aortic coarctation, dissection, or aneurysm.[10] Unrepaired blunt and penetrating injuries are the other common cause of aortic pseudoaneurysms. Chronic traumatic pseudoaneurysms typically develop in the proximal descending thoracic aorta after blunt aortic injuries;[9,11] the management of these lesions is covered in detail in a subsequent chapter.

Although the underlying pathologic processes may differ among various types of aortic aneurysms, the ultimate disease process is the same for all: progressive aortic dilatation and eventual rupture. The relationship among pressure gradients, vessel diameter, and vessel wall tension described by the Laplace law—which states that increasing luminal diameter leads to greater wall tension—contributes to the cycle of progressive dilatation.

CLINICAL PRESENTATION AND DIAGNOSIS

At the time of diagnosis, patients with DTAAs and TAAAs are commonly asymptomatic. For example, Panneton and Hollier[12] reported that degenerative TAAAs are asymptomatic in roughly 43% of patients. In asymptomatic patients, DTAAs and TAAAs are often discovered when imaging studies are performed to evaluate unrelated problems. For example, chest radiographs may show widening of the descending thoracic aortic shadow, which may be highlighted by a rim of calcification outlining the dilated aneurysmal aortic wall (Fig. 54-3). Aneurysmal calcium may also be seen in the upper abdomen on standard radiographs.

Although DTAAs and TAAAs remain asymptomatic for long periods of time, most ultimately produce a variety of symptoms before they rupture. Degenerative TAAAs produce symptoms in approximately 57% of patients; 9% of patients present with rupture.[12] The most frequent symptom is back pain between the scapulae. When the aneurysm is large in the region of the aortic hiatus, pressure on adjacent structures may cause mid-back and epigastric pain. Other potential signs and symptoms related to compression or erosion of adjacent organs include stridor, wheezing, cough, hemoptysis, dysphagia, and gastrointestinal obstruction or bleeding.[13] Hoarseness results from traction on the vagus nerve as the distal aortic arch expands and causes recurrent laryngeal nerve paralysis. Thoracic or lumbar vertebral body erosion (Fig. 54-4) causes back pain, spinal instability, and neurologic deficits from spinal cord compression; mycotic aneurysms have a peculiar propensity to destroy vertebral bodies. Additionally, neurologic symptoms, including paraplegia, paraparesis, or both, may result from thrombosis of intercostal and spinal arteries. This is most frequently seen with acute aortic dissection, which may occur primarily or be superimposed on medial degenerative fusiform aneurysmal disease. Thoracic aortic aneurysms, like aneurysms in other locations, may produce distal emboli of clot or atheromatous debris that gradually obliterates and thromboses visceral, renal, or lower extremity branches.

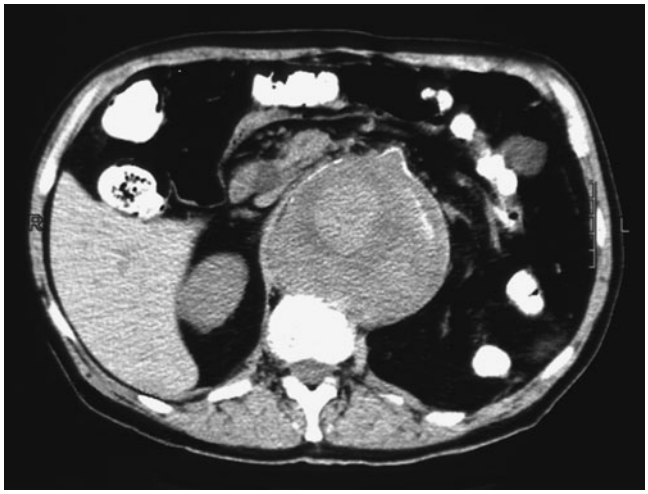

Figure 54-4. Computed tomography image of a large thoracoabdominal aortic aneurysm that has caused erosion of the adjacent vertebral body.

DETERMINING APPROPRIATE TREATMENT

Once an aneurysm involving the descending or thoracoabdominal aorta has been discovered, precise determination of the extent and severity of disease is the critical next step toward clarifying the specific diagnosis, determining the appropriate treatment, and when repair is indicated, planning the appropriate intervention.

Determining Extent and Severity of Disease

Aneurysm diameter and changes in diameter are major considerations in treatment planning. Because aneurysms are defined as permanent localized dilatations of an artery to at least 150% of the artery's expected normal diameter, the diagnosis of an aneurysm in the thoracic aorta requires knowledge of its normal diameter.[1] At the level of the mid-descending thoracic aorta, the average aortic diameter is 28 mm for men and 26 mm for women; at the level of the celiac axis, it is 23 mm for men and 20 mm for women; and at the infrarenal aorta, it is 19.5 mm for men and 15.5 mm for women.[14] Normal aortic diameters, however, vary with a person's age, gender, and body surface area. Aortic enlargement with advancing age has been reported in a number of studies.[15–18] Even when adjusted for age and body surface area, mean aortic size is significantly smaller in women than in men; on average, aortic diameter is 2 to 3 mm greater in men than in women. Body surface area is a better predictor of aortic size than is height or weight, particularly in patients less than 50 years of age.[15,19]

In addition to aneurysm diameter, the precise location of the aneurysm needs to be determined to enable the selection of appropriate treatment options. Descending thoracic aortic aneurysms can involve any portion of the aorta between the left subclavian artery and the diaphragm. Thoracoabdominal aneurysms may involve the entire thoracoabdominal aorta from the origin of the left subclavian artery to the aortic bifurcation, or they may involve only portions of the thoracic and abdominal segments. The Crawford classification of TAAAs (Fig. 54-5)

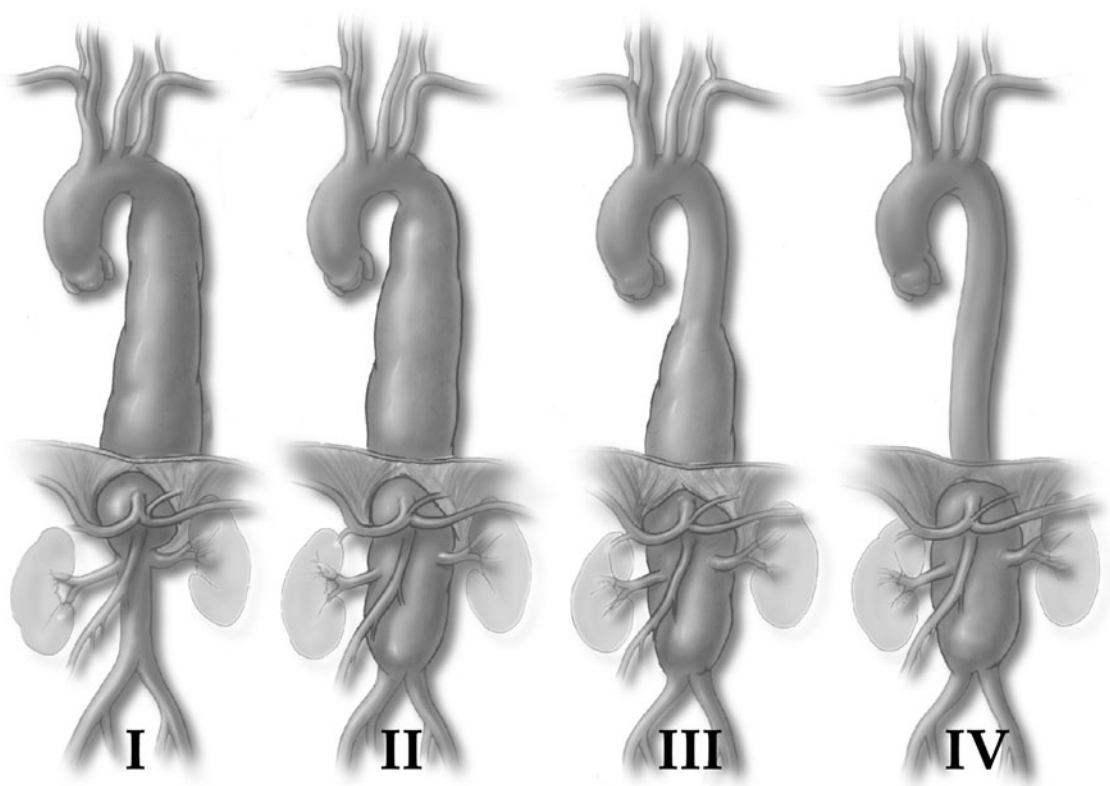

Figure 54-5. The Crawford classification of thoracoabdominal aortic aneurysms.

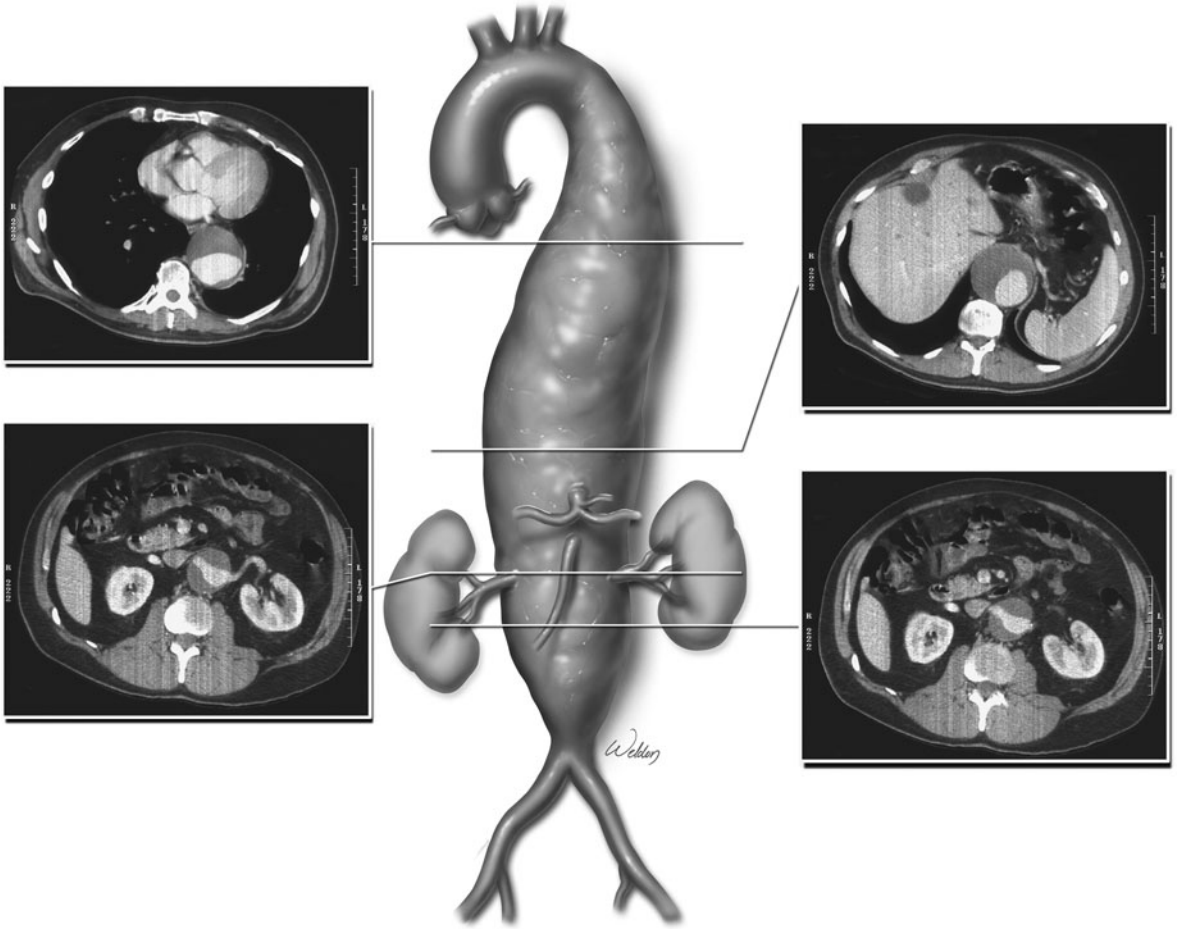

Figure 54-6. Drawing and contrast enhanced computed tomography images of a degenerative extent II thoracoabdominal aortic aneurysm with extensive intraluminal thrombus.

permits standardized reporting of the extent of aortic involvement, thereby allowing appropriate risk stratification, choice of specific treatment modalities based on the extent of the aneurysm, and a type-specific determination of the risks for neurologic deficits and other morbidity and mortality associated with TAAA repair. Extent I aneurysms involve most or all of the descending thoracic aorta and the upper abdominal aorta. Extent II aneurysms involve most or all of the descending thoracic aorta and extend into the infrarenal abdominal aorta. Extent III aneurysms involve the distal half or less of the descending thoracic aorta and varying portions of the abdominal aorta. Extent IV aneurysms involve most or all of the abdominal aorta.

Cross-sectional imaging techniques are the primary means of visualizing the thoracic and abdominal aorta and determining aneurysmal diameter and extent. Computed tomography (CT) scanning and magnetic resonance angiography (MRA) enable clinicians to obtain excellent images without the potential morbidity or cost associated with angiography.[20] CT scanning is widely available and can image the entire thoracic and abdominal aorta, major branch vessels, and virtually all adjacent organs.[21] Computer programs can construct sagittal, coronal, and oblique images, as well as three-dimensional reconstructions, from CT data.[22–24] Contrast-enhanced CT scanning also provides information about the aortic lumen, intraluminal thrombus (Fig. 54-6), presence of aortic dissection (see Fig. 54-2), intramural hematoma, mediastinal or retroperitoneal hematoma, aortic rupture, and periaortic fibrosis associated with inflammatory aneurysms.[25] CT angiography with multiplanar reconstruction is especially useful for planning endovascular procedures. Advantages of CT include being less expensive and somewhat quicker to perform than MRA, and at present, the wider availability of CT expertise. Also, CT can be used with patients who have implanted ferromagnetic prostheses or other devices, which can cause image artifacts or injury in patients undergoing MRA.[26] Advantages of MRA include its use of nontoxic gadolinium instead of a nephrotoxic contrast agent, the fact that it does not expose the patient to ionizing radiation, and its ability to reveal pathology within the aortic wall, including intramural hemorrhage.

Ongoing improvements in noninvasive imaging modalities have substantially reduced the role of catheter aortography in assessing thoracic aortic aneurysms. However, catheter aortography remains useful in situations where noninvasive

methods are not feasible—for example, when artifact or heavy calcification obscures the area of interest.[27] Anterior, posterior, oblique, and lateral views provide detailed information about branch vessels. The risks of aortography include renal toxicity from the large volumes of contrast material required to adequately fill large aneurysms. There is also a risk of embolization from laminated thrombus secondary to manipulation of intraluminal catheters. Angiography can be helpful in patients with suspected renal or visceral ischemia, aortoiliac occlusive disease, horseshoe kidney, or peripheral aneurysms.

Indications for Operation

In asymptomatic patients, the decision to consider surgical repair is based primarily on the diameter of the aneurysm. To prevent fatal rupture, elective operation is recommended when diameter exceeds 5 to 6 cm or when the rate of dilatation exceeds 1 cm per year. In patients with connective tissue disorders, such as Marfan syndrome and related disorders, the threshold for operation is lower for both absolute size and rate of growth.[5] Nonoperative management—which consists of strict blood pressure control, cessation of smoking, and at least yearly surveillance with imaging studies—is appropriate for asymptomatic patients who have small aneurysms. Symptomatic patients, however, are at increased risk of rupture and warrant expeditious evaluation and urgent aneurysm repair, even when the above threshold diameters have not been reached. The onset of new pain in a patient with a known aneurysm is particularly concerning and often heralds significant expansion, leakage, or impending rupture. Malperfusion caused by chronic dissection is also an indication for TAAA repair. Degenerative DTAAs and TAAAs with superimposed acute dissection are especially prone to rupture and are therefore treated with emergent operation.

Open Repair versus Endovascular Repair

An evolving aspect of selecting appropriate treatment in these patients is the choice between performing an open repair, an endovascular repair, or a combined procedure. Two major factors that clinicians consider when deciding between open and endovascular aneurysm repair are the patient's physiologic reserve and vascular anatomy.[28] The open repairs described in this chapter are ideal for directly addressing complex anatomy but require considerable physiologic reserve.

Endovascular repairs—which are covered in detail in a subsequent chapter—are associated with less physiologic strain than are open surgical approaches but may not provide durable repair in patients with complex anatomy. The use of endovascular surgical options for treating DTAAs is rapidly increasing.[29–34] This less invasive approach has been used in patients with aortic dissection and traumatic, mycotic, and ruptured DTAAs.[35–37] Repairing DTAAs with stent grafts is an attractive alternative to standard open procedures in selected patients with compromised cardiac, pulmonary, or renal status, who have undergone previous complex thoracic aortic procedures, or who are very elderly. Recent data show that in general, endovascular repair of the descending thoracic aorta is associated with less early mortality and morbidity than is open repair.[29–32] Appropriate anatomy, however, is critical for successful endovascular repair. Landing zones that have inadequate length, excessive angulation, extensive intraluminal thrombus, or severe vessel calcification will not allow secure endograft fixation, precluding endovascular repair. Furthermore, the long-term durability of these repairs remains unclear, particularly in patients with complex aortic disease, such as chronic aortic dissection or connective tissue disorders. In contrast with endovascular DTAA repair, pure endovascular treatment of thoracoabdominal aortic disease—which often requires the use of fenestrated or branched endografts to maintain branch vessel perfusion while the aneurysm is being excluded—remains rare and purely experimental.[38–42]

Combining open and endovascular procedures capitalizes on the principal benefits of both by creating durable repairs in patients with complex anatomy while minimizing physiologic stress and postoperative complications. Accordingly, combined approaches—commonly called "hybrid" procedures—appear well-suited for patients with limited physiologic reserve (precluding standard open repair) and complex aneurysmal anatomy (precluding standard endovascular repair). For example, in patients with DTAAs that have an insufficient proximal landing zone, an open procedure to reroute the brachiocephalic circulation can convert the aortic arch into a satisfactory landing zone for a stent-graft.[43] Thoracoabdominal aortic aneurysms have also been repaired using hybrid approaches: open visceral bypass grafting to secure organ perfusion is followed by stent-graft coverage of the entire aneurysm, including branch vessel ostia.[44–47] Although hybrid procedures are feasible and appear to be associated with reduced postoperative morbidity and mortality, the durability of these repairs is unclear.

PREOPERATIVE EVALUATION

In each patient, the indications for operation discussed above are weighed against the risks posed by surgical intervention.[48,49] An adequate preoperative assessment of physiologic reserve is critical in evaluating operative risk. With the exception of patients who require emergency operation, patients undergo a thorough preoperative evaluation, with emphasis on cardiac, pulmonary, and renal function.[50]

Cardiac Status

Impaired myocardial contractility and reduced coronary reserve are common among elderly patients undergoing aortic reconstruction. Patients need substantial cardiac reserve in order to tolerate clamping of the thoracic aorta. Given the prevalence of preoperative cardiac disease and the physiologic strain of aortic clamping, it is not surprising that cardiac complications are a major cause of postoperative mortality. Reports indicate that cardiac disease has been responsible for 49% of early deaths and 34% of late deaths after TAAA repair, attesting to the importance of careful preoperative cardiac evaluation.[12,51]

Several imaging techniques are useful for preoperative screening for cardiac disease. Transthoracic echocardiography is noninvasive and can satisfactorily evaluate both valvular and biventricular function. Dipyridamole-thallium myocardial scanning identifies regions of myocardium that are reversibly ischemic, and it is more practical than exercise testing in this generally elderly population, whose exercise capacity is often limited by concurrent lower extremity peripheral vascular disease. In patients with evidence of reversible ischemia on noninvasive studies, and in those with a significant history of angina or an ejection fraction of 30% or less, cardiac catheterization and coronary arteriography are performed. Patients who have asymptomatic aneurysms and severe coronary artery occlusive disease (i.e., significant left main, proximal left anterior descending, or triple-vessel coronary artery stenosis) undergo myocardial revascularization before aneurysm repair. In appropriate patients, percutaneous transluminal angioplasty is carried out before surgery. If clamping proximal to the left subclavian artery is anticipated in patients in whom the left internal thoracic artery has been used as a coronary artery bypass graft, a left-common-carotid-to-subclavian bypass is necessary to prevent cardiac ischemia when the aortic clamp is applied.

Renal Status

Preoperative renal insufficiency has been a major risk factor for early mortality throughout the history of TAAA repair. It was among the predictive variables selected in Svensson and associates'[52] multivariate analysis of Crawford's complete experience with TAAA surgery in 1509 patients treated between 1960 and 1991. The reports by Acher and coworkers[53] and our group[48] confirm that preoperative renal impairment remains an important predictor of early death. Patients with preoperative renal failure who are being treated with an established hemodialysis program appear to have a level of risk similar to that of patients with normal renal function. Patients with severely impaired renal function who are not on chronic hemodialysis frequently require transient temporary hemodialysis early after operation and are clearly at increased risk for postoperative complications.

Although patients are not rejected as surgical candidates on the basis of renal function, careful assessment of renal function aids in predicting perioperative risk and adjusting treatment strategies accordingly. Renal function is assessed preoperatively by measuring serum electrolytes, blood urea nitrogen, and creatinine. Kidney size and perfusion can be evaluated using the imaging studies obtained to assess the aorta. Patients who have poor renal function secondary to severe proximal renal artery occlusive disease are revascularized at operation by either renal arterial endarterectomy, stenting, or bypass grafting, with the expectation that renal function will stabilize or improve.[51,54]

Because of the nephrotoxic effects of vascular contrast agents, surgery is delayed (if possible) for 24 hours or longer after CT scanning or aortography has been performed. This is especially important in patients with preexisting renal impairment. Strategies to reduce the risk of contrast-induced nephropathy include periprocedural administration of acetylcysteine and intravenous hydration.[55,56] If renal insufficiency occurs or is worsened after contrast administration, the surgical procedure is postponed until renal function returns to baseline or is satisfactorily stabilized.

Pulmonary Status

Pulmonary complications are the most common form of postoperative morbidity in patients undergoing DTAA and TAAA repairs. Most patients undergo pulmonary function screening with arterial blood gases and spirometry. Patients with a forced expiratory volume in 1 second >1.0 L and a partial carbon dioxide pressure <45 mm Hg are satisfactory surgical candidates. In suitable patients, borderline pulmonary function frequently is improved by smoking cessation, progressive treatment of bronchitis, weight loss, and a general exercise program that the patient follows for a period of 1 to 3 months before operation. However, surgery is not withheld from patients with symptomatic aortic aneurysms and poor pulmonary function. In such patients, preservation of the left recurrent laryngeal nerve, phrenic nerve, and diaphragmatic function is particularly important.

OPEN SURGICAL REPAIR

Intraoperative Strategies for Organ Protection

Organ ischemia is a major source of the morbidity related to DTAA and TAAA repair. We currently employ a multimodal approach (Table 54-1) in an attempt to maximize organ protection during these operations (Fig. 54-7).[57] The rationale for and details of several important strategies are discussed below.

Table 54–1.

Current Strategy for Spinal Cord and Visceral Protection During Descending and Thoracoabdominal Aortic Aneurysm Repair

All extents
- Moderate heparinization (1 mg/kg)
- Permissive mild hypothermia (32–34°C, nasopharyngeal)
- Aggressive reattachment of segmental arteries, especially between T8 and L1
- Perfusion of renal arteries with 4°C crystalloid solution when possible
- Sequential aortic clamping when possible

Extent I and II thoracoabdominal repairs
- Cerebrospinal fluid drainage
- Left heart bypass during proximal anastomosis
- Selective perfusion of celiac axis and superior mesenteric artery during intercostal and visceral anastomoses

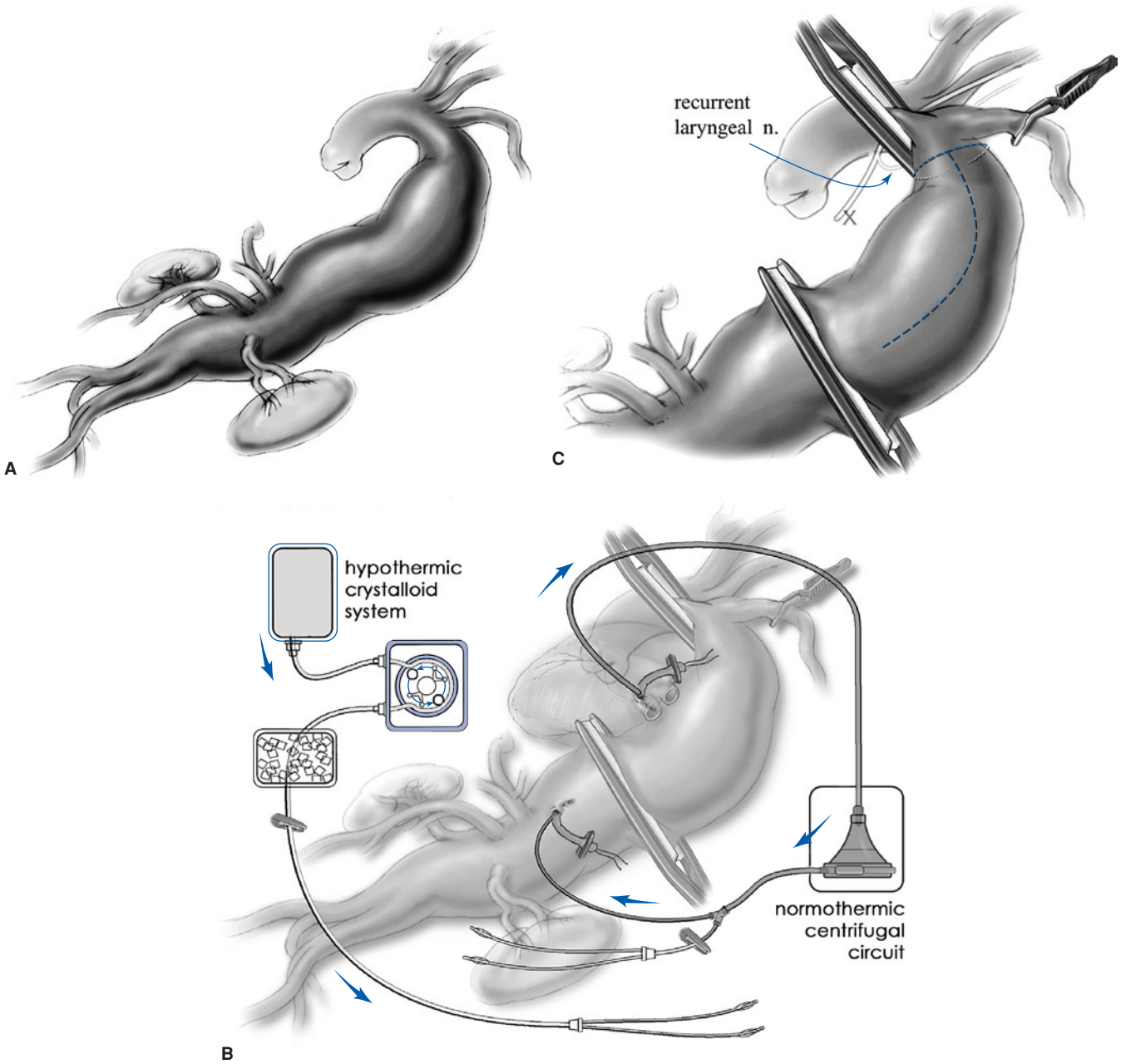

Figure 54-7. Drawings illustrating repair of an extent II thoracoabdominal aortic aneurysm (A) that extends from the left subclavian artery to the aortoiliac bifurcation. (B) The perfusion systems used during the repair are a left heart bypass circuit to provide distal aortic perfusion and a cold renal delivery system to provide selective renal hypothermia. The proximal portion of the aneurysm is isolated between clamps placed on the aortic arch (between the left common carotid and left subclavian arteries), the mid-descending thoracic aorta, and the left subclavian artery. (C) Whenever possible, the phrenic, vagus (indicated by X), and recurrent laryngeal nerves are preserved during the repair. The isolated segment of aorta is opened longitudinally and divided circumferentially a few centimeters beyond the proximal clamp.

Heparin

Heparin (1 mg/kg) is administered intravenously before aortic clamping or the start of left heart bypass (LHB). Potential benefits of heparinization include preserving the microcirculation and preventing embolization. After this small heparin dose is administered, the activated clotting time generally ranges from 220 to 270 seconds. By inhibiting the clotting cascade, the use of heparin may help to reduce the incidence of disseminated intravascular coagulation.

Hypothermia

The benefits of hypothermia during ischemia are well accepted.[58,59] Hypothermia's protective effects are largely

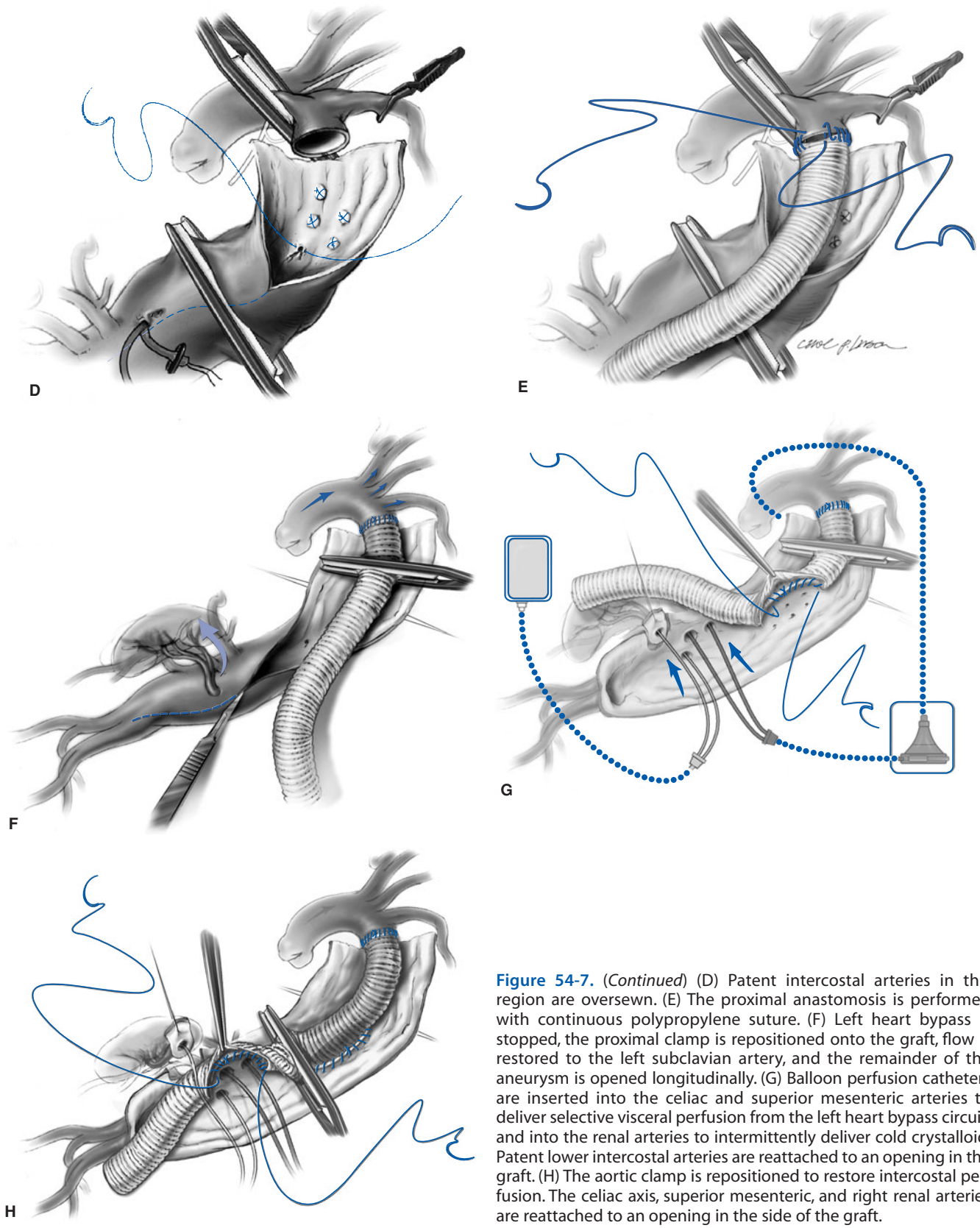

Figure 54-7. (*Continued*) (D) Patent intercostal arteries in this region are oversewn. (E) The proximal anastomosis is performed with continuous polypropylene suture. (F) Left heart bypass is stopped, the proximal clamp is repositioned onto the graft, flow is restored to the left subclavian artery, and the remainder of the aneurysm is opened longitudinally. (G) Balloon perfusion catheters are inserted into the celiac and superior mesenteric arteries to deliver selective visceral perfusion from the left heart bypass circuit, and into the renal arteries to intermittently deliver cold crystalloid. Patent lower intercostal arteries are reattached to an opening in the graft. (H) The aortic clamp is repositioned to restore intercostal perfusion. The celiac axis, superior mesenteric, and right renal arteries are reattached to an opening in the side of the graft.

presumed to be secondary to decreased tissue metabolism and a generalized reduction in energy-requiring processes in the cell. However, the mechanisms may be more complex and involve, for example, membrane stabilization and reduced release of excitatory neurotransmitters.[60,61]

We routinely use mild passive systemic hypothermia during DTAA and TAAA repairs. The patient's temperature is allowed to drift down to a nasopharyngeal temperature of 32 to 33°C. Warm water is used to irrigate the operative field after the aortic repair is completed, thereby reversing the

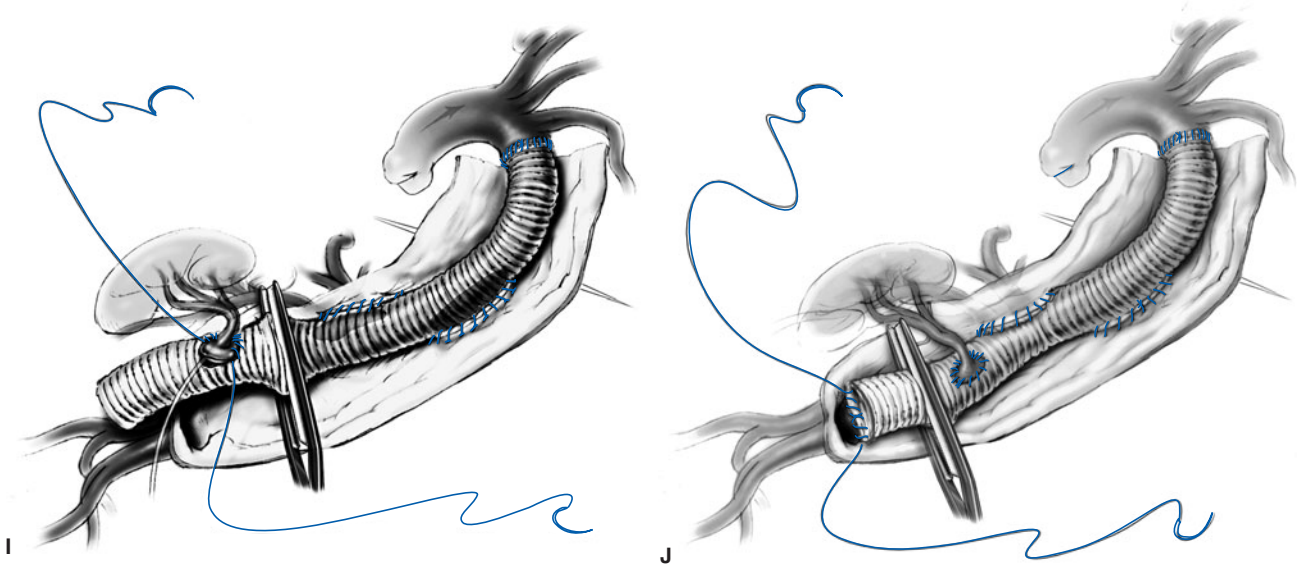

Figure 54-7. (*Continued*) (I) The aortic clamp is repositioned to restore visceral and right renal perfusion. The mobilized left renal artery is reattached. (J) The aortic clamp is repositioned to restore left renal perfusion. The distal anastomosis at the aortoiliac bifurcation completes the repair.

cooling process and initiating slow rewarming of the patient. In patients in whom LHB is used, an in-line heat exchanger in the bypass circuit may be used to rewarm patients and reduce the risk of arrhythmia or coagulopathy, but in our experience this has generally not been necessary.

In addition, whenever possible during TAAA repairs, renal protection is achieved by perfusing the kidneys with cold (4°C) crystalloid (see Fig. 54-7G). We reported on a group of patients who underwent Crawford extent II TAAA repair with LHB and who were randomized either to renal artery perfusion of cold lactated Ringer solution for renal cooling or to normothermic blood perfusion from the LHB circuit.[62] Multivariate analysis confirmed that the use of cold crystalloid perfusion was independently protective against acute renal dysfunction.

Profound systemic hypothermia and regional spinal hypothermia are two alternative methods of employing the protective effects of hypothermia. Kouchoukos and colleagues[63–66] have published several reports showing that hypothermic cardiopulmonary bypass with circulatory arrest can provide safe and substantial protection against paralysis and renal, cardiac, and visceral organ system failure during operations on the thoracic and thoracoabdominal aorta. Despite these protective effects, many clinicians avoid using this approach, principally because of the associated risks of coagulopathy, pulmonary dysfunction, and massive fluid shift.

With regard to regional spinal cord hypothermia, two methods are described in the literature: direct infusion of cold perfusate into the epidural or intrathecal space, and intravascular cold perfusion into isolated thoracic aortic segments (with the expectation that the intercostal vessels will deliver the cold perfusate to the spinal cord). Epidural cooling for regional spinal cord hypothermia is effective in preventing paraplegia after aortic cross-clamping in canine and leporine models.[67–71] Additionally, a series of 337 TAAA repairs reported by Cambria and colleagues[72] showed that, in patients with extent I, II, or III TAAAs, the incidence of spinal cord ischemic injury was reduced from 19.8% to 10.6% after the introduction of epidural cooling at their institution in 1993. A similar technique, cold perfusion into isolated aortic segments, has been tested in animal models to show that cord temperature, and thereby the extent of ischemic spinal cord injury, can be rapidly and effectively reduced by this method.[73,74]

Cerebrospinal fluid drainage

The body of evidence supports using cerebrospinal fluid (CSF) drainage to reduce the risk of ischemic spinal cord injury in TAAA patients, although the mechanisms remain controversial.[75–80] In our study of 145 patients undergoing extent I or II TAAA repair, patients were randomized to CSF drainage or no CSF drainage. Postoperatively, 9 patients (13%) in the control group developed paraplegia or paraparesis, whereas only 2 patients (2.6%) in the CSF drainage group developed such deficits ($p = 0.03$).[81] Additionally, a meta-analysis of eight studies (three randomized controlled trials and five cohort studies) of CSF drainage in TAAA repair found that CSF drainage substantially reduced the incidence of postoperative neurologic impairment ($p < 0.0001$).[82]

Cerebrospinal fluid drainage does carry risks, including intracranial bleeding, perispinal hematoma, and meningitis. Therefore, although we routinely use CSF drainage in patients undergoing Crawford extent I or II TAAA repairs, we do not routinely use CSF drainage during less extensive

repairs, such as DTAA or extent III or IV TAAA repairs, because the risks may outweigh the benefits in these cases.

After induction, an 18-gauge intrathecal catheter is placed through the second or third lumbar space. The catheter permits CSF pressure monitoring and aspiration of fluid throughout the operation and for 2 to 3 days postoperatively. Cerebrospinal fluid is allowed to drain passively from the catheter and is aspirated with a closed collection system as needed to keep the CSF pressure between 8 and 10 mm Hg during the operation, between 10 and 12 mm Hg during the early postoperative period, and between 12 and 15 mm Hg after patients have confirmed that they are able to move their legs.

Segmental artery reattachment

Because of the often tenuous nature of the blood supply to the spinal cord, we take an aggressive approach to reattaching patent segmental arteries. Intimal atherosclerosis, particularly in medial degenerative fusiform aneurysms, obliterates many intercostal and lumbar arteries and complicates matters anatomically. Patent segmental arteries from T7 to L2 are selectively reattached to one or more openings made in the graft (see Fig. 54-7G). Large arteries with little or no back-bleeding are considered particularly important. After intercostal arteries are reattached, the proximal clamp is often moved down the graft to restore intercostal perfusion. When none of these arteries is patent, endarterectomy of the aortic wall and removal of calcified intimal disease can be considered as a means of identifying arteries suitable for reattachment.

Left heart bypass

Disruption of blood flow to the spinal cord and abdominal viscera contributes significantly to the development of ischemic complications. Conversely, maintaining flow through spinal and visceral arteries during all or part of the anatomic repair should reduce the duration of organ ischemia and prevent associated morbidity.[83,84] Borst and associates[85] found that using LHB for distal perfusion during DTAA and TAAA repair effectively unloads the proximal circulation during aortic occlusion and maintains adequate perfusion of distal vital organs, thereby reducing early mortality and renal failure. Furthermore, combined distal perfusion and aggressive reattachment of distal intercostal arteries decreased the risk of spinal cord damage.

Like CSF drainage, LHB appears to provide the greatest benefit to patients undergoing the more extensive repairs. Our own retrospective review of 1250 consecutive repairs of extent I or extent II TAAAs found that LHB (used in 666 cases) reduced the incidence of spinal cord deficits only in patients with extent II repairs,[86] replicating the findings of our previous study of LHB in TAAA repair procedures.[87] In patients undergoing extent I repairs, the incidence of paraplegia was similar in the LHB and no-LHB groups, despite the fact that the LHB group had significantly longer aortic clamp times. This suggests that by providing spinal cord protection, LHB enables the surgeon to spend more time creating secure anastomoses. A propensity score analysis of 387 of our patients who underwent DTAA repair with (n = 46) or without (n = 341) LHB during the construction of the proximal anastomosis found no effect of LHB on postoperative paraplegia and paraparesis rates.[88] Data from series in which LHB and CSF drainage were used together suggest that combining these adjuncts may further reduce rates of spinal cord injury.[89–91]

Because patients with extensive TAAAs (extents I and II) are at greatest risk of developing postoperative paraplegia or paraparesis, we use LHB to provide distal aortic perfusion during the proximal portion of the aortic repair. This is achieved by using temporary bypass from the left atrium to either the femoral artery (most commonly the left) or the distal descending thoracic aorta with a closed-circuit in-line centrifugal pump (see Fig. 54-7B). The left atrial cannula is placed via an opening in the inferior pulmonary vein. Initially, cannulation of the distal descending thoracic aorta (usually at the level of the diaphragm) was used solely as an alternative to femoral artery cannulation in patients with femoral or iliac artery occlusive disease. Because this technique causes few complications and eliminates the need for femoral artery exposure and repair, distal aortic cannulation has become our preferred approach. Careful examination of CT or magnetic resonance images assists selection of an appropriate site for direct aortic cannulation. Areas with intraluminal thrombus are avoided because cannulation could lead to distal embolization. Bypass flows are adjusted to maintain normal proximal arterial and venous filling pressures. Flows between 1500 and 2500 mL/min are generally required. Left heart bypass facilitates rapid adjustment of proximal arterial pressure and cardiac preload, thereby reducing the need for pharmacologic intervention. Because LHB effectively unloads the left ventricle, it is useful in patients with suboptimal cardiac reserve.

Selective visceral perfusion

Distal aortic perfusion can only provide flow to the mesenteric and renal branches during the initial portion of a TAAA repair. However, after the aorta is opened adjacent to the visceral branches, selective visceral perfusion can be delivered through separate balloon perfusion catheters that are placed within the origins of the celiac, superior mesenteric, and renal arteries; these catheters are attached to the LHB circuit using a Y-line off the arterial perfusion line (see Fig. 54-7B). This provides oxygenated blood to the abdominal viscera while the intercostal and visceral branches are reattached to the graft (see Figs. 54-7G and H). With this technique, the total mesenteric and renal ischemic times can be reduced to just a few minutes during even the most complex aortic reconstructions. Reducing hepatic ischemia in this fashion may decrease the risk of postoperative coagulopathy, and reducing bowel ischemia may decrease the risk of bacterial translocation.

Although we continue to use selective perfusion of the celiac and superior mesenteric arteries, we no longer selectively perfuse the renal arteries with blood from the LHB

circuit. Instead, as discussed above, we intermittently infuse cold crystalloid into the renal arteries.[62] Other groups, however, still selectively perfuse the renal arteries. Jacobs and colleagues[92] recently reported the use of distal aortic and selective renal perfusion in 295 patients undergoing TAAA repair. After surgery, only 6% of patients had substantially elevated levels of serum creatinine, which was temporary in all cases. Additionally, only 1% of patients required dialysis, which was also temporary in each case.

Spinal cord monitoring

Motor evoked potential (MEP) monitoring can potentially estimate spinal cord motor neuron function, and thereby motor tract blood supply, during the aortic repair. This monitoring technique involves stimulating the motor cortex or motor neurons and recording the amplitude of the resulting motor response, usually from a peripheral muscle. Monitoring of MEPs, which was approved by the U.S. Food and Drug Administration in 2003 for use in the intraoperative monitoring of spinal cord function in TAAA patients, has generally been found to be more sensitive to spinal cord ischemia and more predictive of adverse neurologic events than is somatosensory evoked potential monitoring.[93–95] The method requires special anesthetic techniques, because complete neuromuscular blockade does not allow the degree of motor activity necessary for myogenic MEP monitoring. This technique is generally used in conjunction with LHB.

The results of several studies suggest that monitoring MEPs to guide the use of spinal perfusion-enhancing measures (e.g., reattaching more segmental arteries, increasing distal and proximal perfusion pressures, and enhancing CSF drainage) improves the outcome of TAAA and DTAA repair. For example, Jacobs and colleagues[96] published excellent results in a series of 184 patients undergoing TAAA repair with a protocol that included LHB, CSF drainage, and MEP monitoring. The authors found that MEP was a sensitive technique for assessing spinal cord ischemia and identifying the segmental arteries that critically contribute to spinal cord perfusion. With this protocol, the incidence of neurologic deficits after TAAA repair was 2.7%. Other series of TAAA and DTAA repairs have found similarly low rates of postoperative paraplegia and paraparesis when MEP is used in this fashion.[95,97]

Incisions and Aortic Exposure

A fundamental principle of surgical DTAA and TAAA repair is the importance of adequate exposure.[98] Exposure is optimized when the patient is placed in a modified right lateral decubitus position with the shoulders placed at 60 to 80° and the hips flexed to 30 to 40° from horizontal. The patient is stabilized in this position with a beanbag. Selective ventilation of the right lung and deflation of the left lung are ideally achieved by using a double-lumen endobronchial tube. Deflating the left lung reduces retraction trauma to the lung, improves exposure, and alleviates the risk of cardiac compression.

Aneurysms limited to the descending thoracic aorta are approached through a full posterolateral thoracotomy (Fig. 54-8A). In most cases, the left pleural space is entered through the sixth intercostal space. When the aneurysm predominantly involves the upper portion of the descending thoracic aorta, using the fifth intercostal space improves access to the distal aortic arch. Exposure of the distal descending thoracic aorta is enhanced by dividing the costal margin.

The thoracoabdominal incision varies in length and level, depending on the anticipated extent of aortic replacement. When the aneurysm extends into the superior aspect of the thorax (as in extents I and II), the upper portion of the thoracoabdominal incision is made through the sixth intercostal space; the upper or lower ribs may be divided posteriorly to achieve additional proximal or distal exposure, respectively, as needed. The posterior portion of the incision is made between the scapula and the spinal processes. With extent III aneurysms, an incision through the seventh or eighth intercostal space is made according to the desired level of exposure. In each of these approaches, the incision is gently curved as it crosses the costal margin to reduce the risk of tissue necrosis at the apex of the lower portion of the musculoskeletal tissue flap (Fig. 54-9A). In contrast, extent IV aneurysms are approached via a straight oblique incision through the ninth or tenth interspace (Fig. 54-9B). The distal extent of the incision is at the level of the umbilicus. The incision is extended toward the pubis if iliac aneurysms also require repair.

Fixed metal retractors attached to the operating table provide consistent static exposure. For TAAA repairs, the diaphragm is divided in a circular fashion to protect the phrenic nerve and to preserve as much diaphragm as possible. A 3- to 4-cm rim of diaphragmatic tissue is left laterally and posteriorly to facilitate closure when the operation is complete. The abdominal aortic segment is exposed via a transperitoneal approach; the retroperitoneum is entered lateral to the left colon. A dissection plane is developed in the retroperitoneum anterior to the psoas muscle and posterior to the left kidney. Dissection within this plane extends directly to the left posterolateral aspect of the abdominal aorta. The left colon, the spleen, the left kidney, and the ureter are retracted anteriorly and to the right. An open abdominal approach permits direct inspection of the bowel, abdominal viscera, and visceral blood supply after aortic reconstruction is completed. An entirely retroperitoneal approach can be used in patients with a "hostile abdomen" (i.e., patients with multiple prior abdominal operations or a history of extensive adhesions, peritonitis, or both).

The crus of the diaphragm is divided, and the left renal artery is identified but not circumferentially dissected or encircled with a tape. Commonly, a large lumbar branch of the left renal vein courses posteriorly around the aorta. This branch may be ligated and divided as needed. If a retroaortic left renal vein is encountered and the aortic repair must extend below the vein, portions of the vessel are isolated with

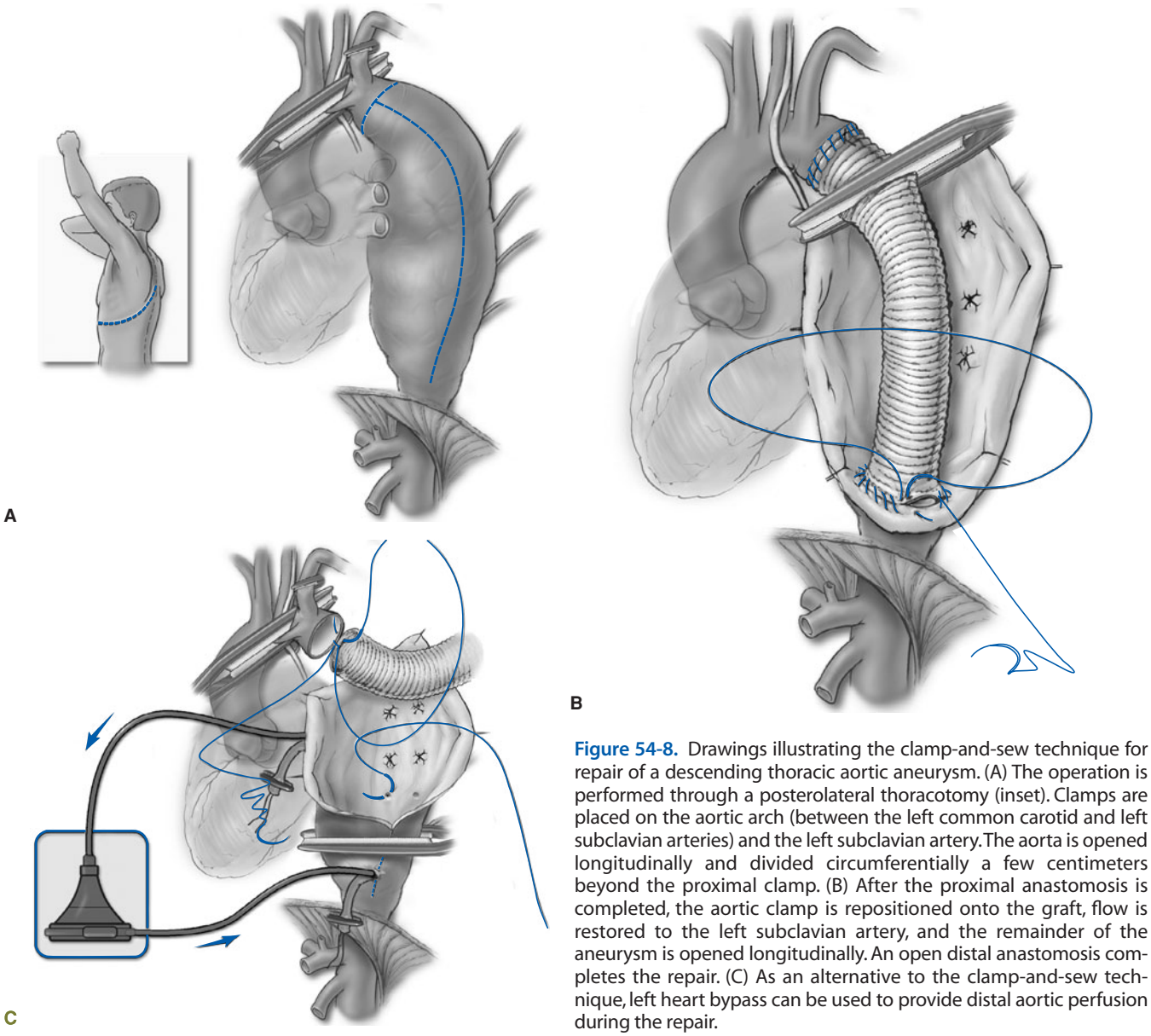

Figure 54-8. Drawings illustrating the clamp-and-sew technique for repair of a descending thoracic aortic aneurysm. (A) The operation is performed through a posterolateral thoracotomy (inset). Clamps are placed on the aortic arch (between the left common carotid and left subclavian arteries) and the left subclavian artery. The aorta is opened longitudinally and divided circumferentially a few centimeters beyond the proximal clamp. (B) After the proximal anastomosis is completed, the aortic clamp is repositioned onto the graft, flow is restored to the left subclavian artery, and the remainder of the aneurysm is opened longitudinally. An open distal anastomosis completes the repair. (C) As an alternative to the clamp-and-sew technique, left heart bypass can be used to provide distal aortic perfusion during the repair.

vascular clamps. Direct reanastomosis or interposition grafting of this retroaortic renal vein is necessary if the left kidney appears congested and has distended collaterals.

Management of the Descending Thoracic Aortic Segment

When the aneurysm encroaches on the left subclavian artery, the distal aortic arch is mobilized gently by dividing the remnant of the ductus arteriosus. The vagus and recurrent laryngeal nerves are identified (see Fig. 54-7C). The vagus nerve may be divided below the recurrent nerve to provide additional mobility, thereby protecting the recurrent nerve from injury. Preserving the recurrent laryngeal nerve is particularly important in patients with chronic obstructive pulmonary disease and reduced pulmonary function. If clamping proximal to the left subclavian artery is anticipated, the left subclavian artery is separately and circumferentially mobilized to enable placement of a bulldog clamp.

After heparin is administered, a clamp is applied to the proximal descending thoracic aorta or the distal transverse aortic arch (between the left common carotid and left subclavian arteries) (see Figs. 54-7B and 54-8A). When LHB is being used, a distal aortic clamp is placed between T4 and T7 (see Fig. 54-7C). After the aorta is opened, patent upper intercostal arteries are oversewn (see Fig. 54-7D). In the setting of chronic dissection, the partition between the true and false lumens is completely removed. The aorta is transected 2 to 3 cm beyond the proximal clamp and separated from the esophagus to allow the surgeon to place full-thickness sutures in the aortic wall without injuring the esophagus. A

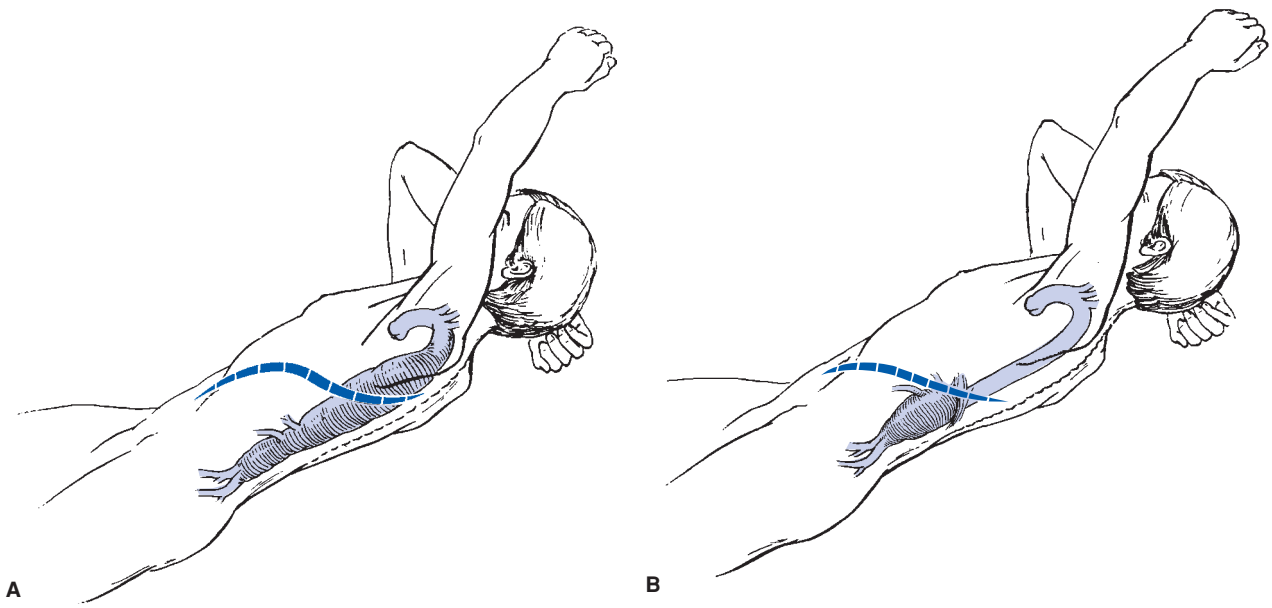

Figure 54-9. Drawings of the typical incisions used in thoracoabdominal aortic aneurysm repairs. (A) A curvilinear incision is used to approach extent I, II, and III thoracoabdominal aneurysms. (B) A straighter, oblique incision is used to approach extent IV thoracoabdominal aortic aneurysms.

22- or 24-mm gelatin-impregnated woven Dacron graft (Vascutek USA, Inc., Ann Arbor, Mich) is used in most patients. The proximal anastomosis is performed with continuous polypropylene suture (see Fig. 54-7E). Most anastomoses are made with 3-0 polypropylene suture; however, in patients with particularly fragile aortic tissues, such as those found in patients with acute aortic dissection or Marfan syndrome, 4-0 polypropylene sutures are commonly used. Felt strips are generally not used; instead, intermittent polypropylene mattress sutures with felt pledgets are used to reinforce selected portions of the anastomoses. The use of surgical adhesives is avoided in these operations.

After the proximal anastomosis is completed, the entire remaining aneurysm is opened longitudinally (see Fig. 54-7F). For repairs that extend to the diaphragm or beyond, patent lower intercostal arteries are selected and reattached to an opening cut in the side of the graft (see Fig. 54-7G). In DTAA repairs, the distal anastomosis is then performed (see Fig. 54-8B). A distal clamp is not used, allowing an "open" anastomosis.

Elephant trunk repairs

A staged operative procedure is preferred in patients presenting with extensive aneurysmal disease involving the ascending aorta, aortic arch, and descending thoracic or thoracoabdominal aorta. When the DTAA or TAAA is not causing symptoms and is not substantially larger than the ascending aorta, the proximal aortic repair is performed first. This allows treatment of valvular and coronary artery occlusive disease during the first operation.

In these patients, the elephant trunk technique described by Borst and colleagues[85] is employed (Fig. 54-10). In this technique, the ascending and transverse aortic arch are replaced first, leaving a segment of graft suspended within the proximal descending thoracic aorta to be used in the second procedure.[99] This technique permits access to the distal graft during the second operation without the need to dissect in and around the distal transverse aortic arch. This reduces the risk of injury to the left recurrent laryngeal nerve, esophagus, and pulmonary artery.

Reversed elephant trunk repairs

Conversely, in patients with similarly extensive aneurysmal disease who present with a DTAA or TAAA that has ruptured, causes symptoms (e.g., back pain), or is considerably larger than the ascending aorta, the DTAA or TAAA is treated during the initial operation, and the ascending aorta and transverse aortic arch are repaired in a second procedure. During this "reversed" elephant-trunk repair (Fig. 54-11), a portion of the proximal end of the aortic graft is inverted down into the lumen during the first operation and is later used to facilitate second-stage repair of the ascending and transverse aortic arch.[100,101]

Repairs requiring hypothermic circulatory arrest

In some cases, the upper descending thoracic aorta cannot be safely clamped because it is too large, or because the aneurysm has ruptured. Hypothermic circulatory arrest is used in these situations.[63–66] Cardiac bypass is usually established using the femoral vessels. A cannula connected to a Y-limb from the venous line is placed in the left atrium via a pulmonary vein; this enhances venous drainage and prevents cardiac distention. After the patient has been cooled to electrocerebral silence, circulatory arrest is initiated, the

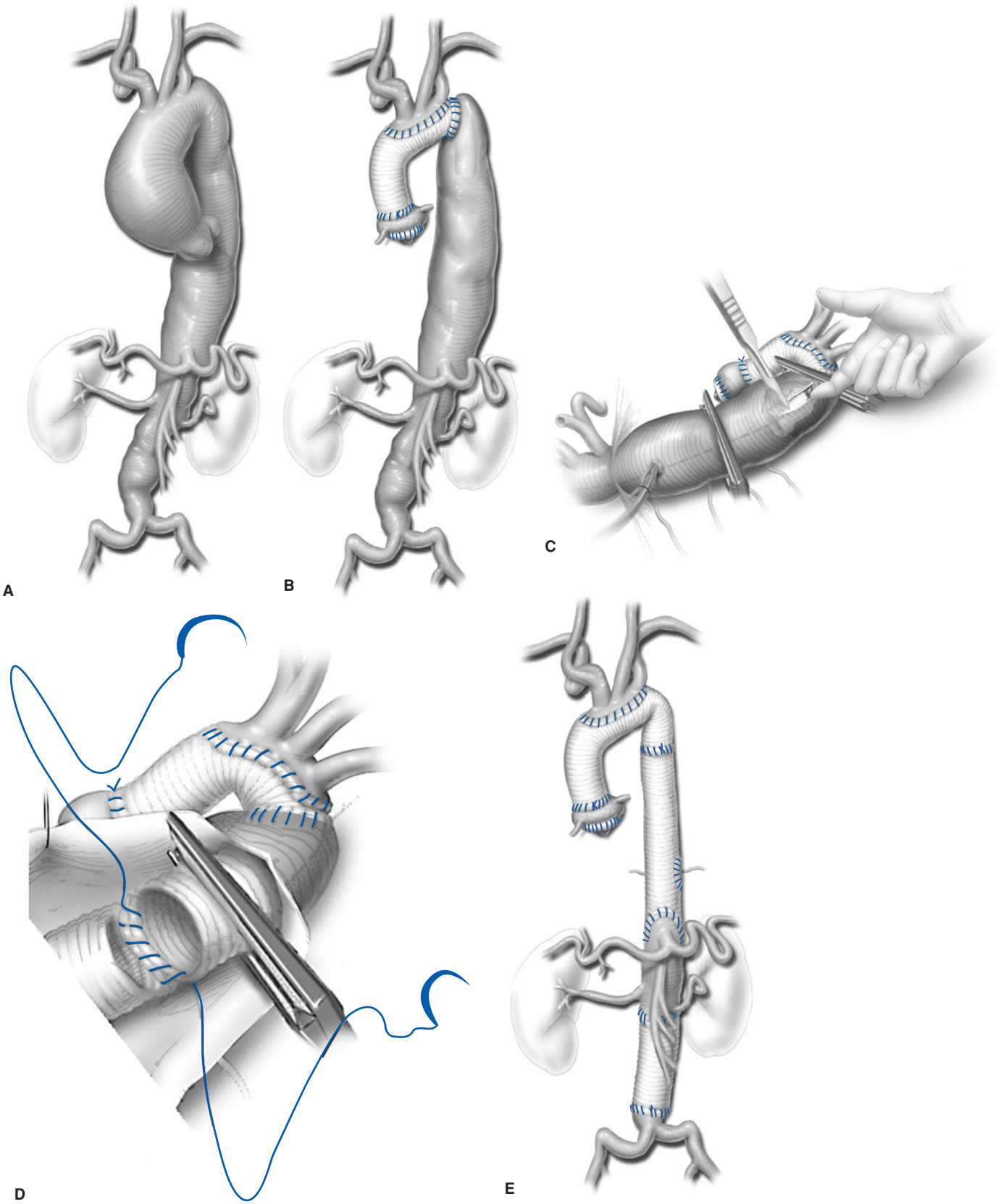

Figure 54-10. Drawings illustrating the two-stage elephant trunk repair of an extensive aneurysm (A) involving the ascending, transverse arch, and entire thoracoabdominal aorta. (B) The first stage includes graft replacement of the ascending aorta and transverse aortic arch. A segment of the graft (the trunk) is left suspended within the aneurysmal descending thoracic aorta. (C) During the second stage, the graft trunk is retrieved and (D) used for the proximal anastomosis. (E) The completed repair includes reattachment patches for a pair of intercostal arteries and the visceral arteries.

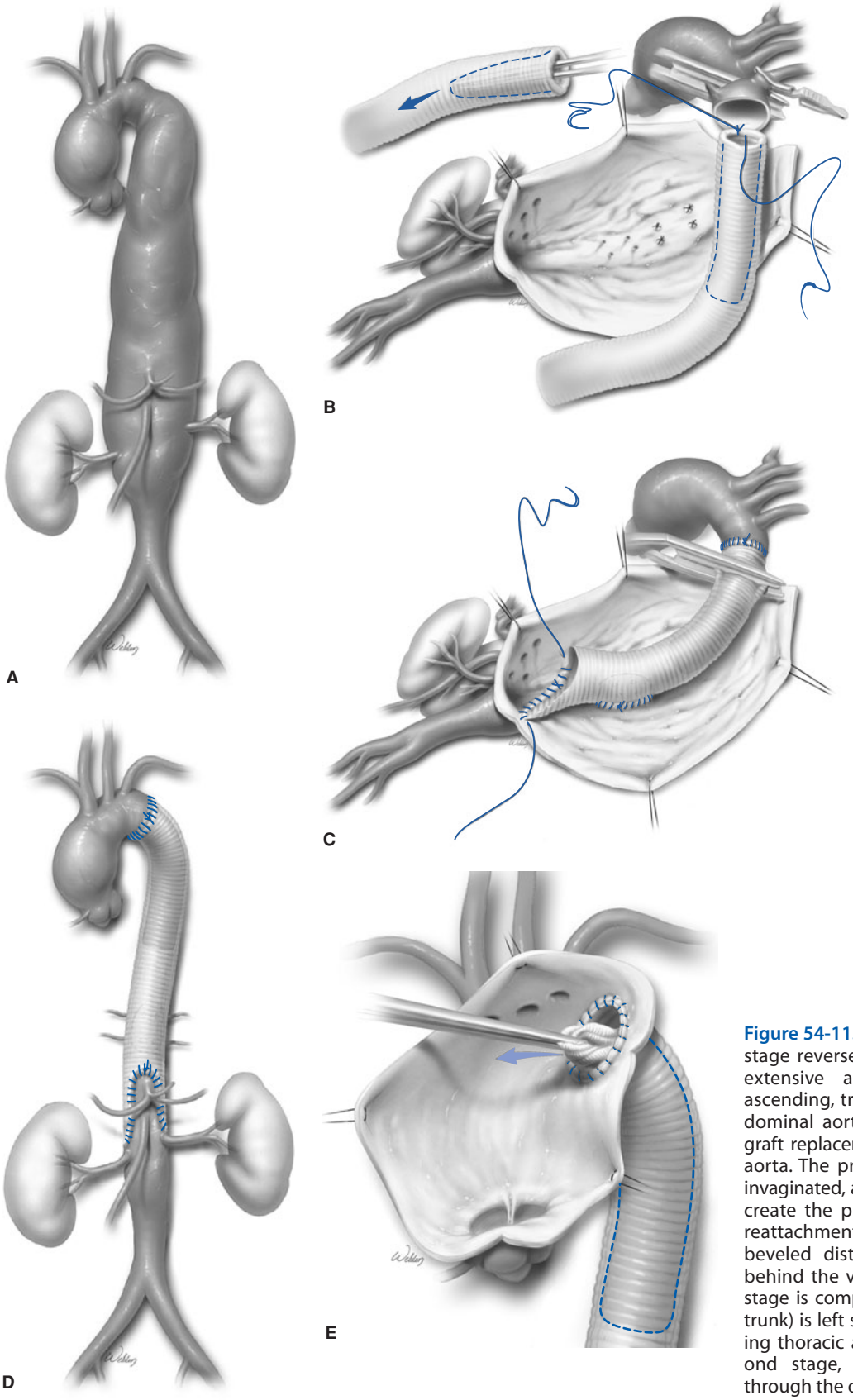

Figure 54-11. Drawings illustrating the two-stage reversed elephant trunk repair of an extensive aneurysm (A) involving the ascending, transverse arch, and thoracoabdominal aorta. (B) The first stage involves graft replacement of the thoracoabdominal aorta. The proximal portion of the graft is invaginated, and the folded edge is used to create the proximal anastomosis. (C) After reattachment of intercostal arteries, a beveled distal anastomosis is performed behind the visceral ostia. (D) After the first stage is completed, a segment of graft (the trunk) is left suspended within the descending thoracic aortic graft. (E) During the second stage, the graft trunk is retrieved through the open aortic arch and

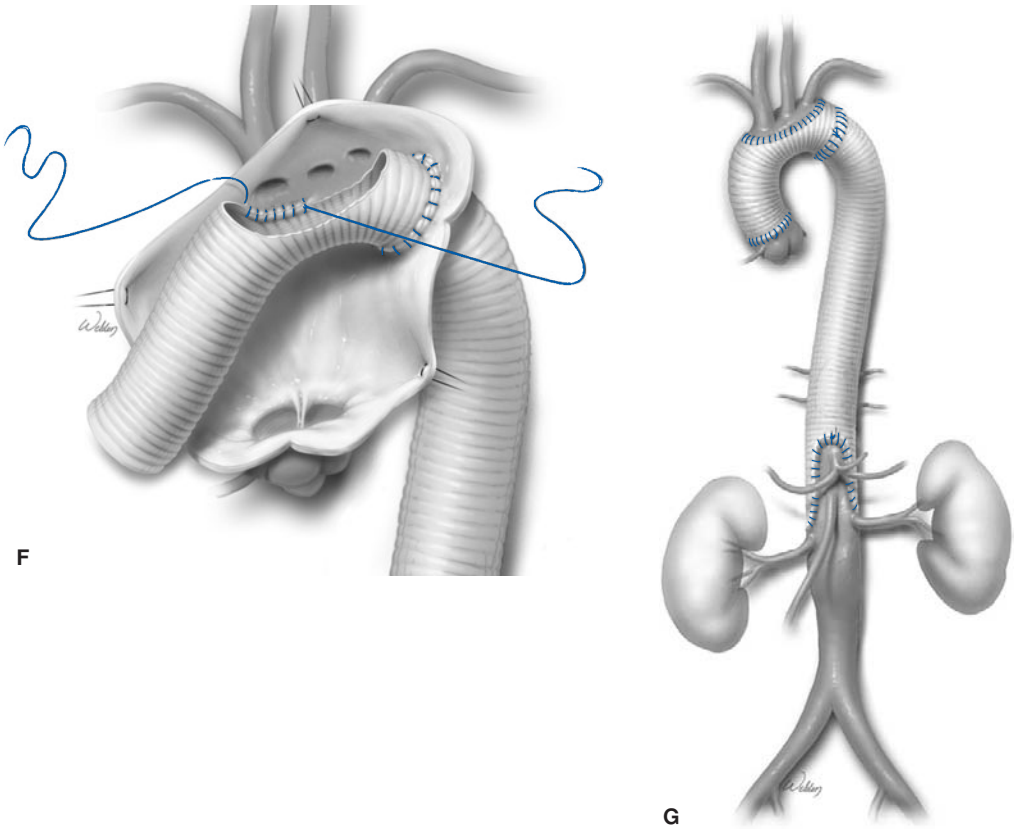

Figure 54-11. (*Continued*) (F) used to replace the arch and ascending aorta, (G) which completes the repair.

aneurysm is opened, and the proximal anastomosis is performed. After completing this anastomosis, a Y-limb from the arterial line is connected to a side branch of the graft. The graft is de-aired and clamped, pump flow to the upper body is resumed, and the remainder of the aortic repair is performed.

Management of the Abdominal Aortic Segment

In patients with TAAAs, after completing the descending thoracic aortic repair, the remainder of the aneurysm is opened longitudinally (see Fig. 54-7F). This incision runs posterior to the left renal artery and continues to the distal extent of the aneurysm. When present, the remaining dissecting membrane is excised. The origins of the visceral and renal branches are identified. Cold saline is intermittently delivered to the renal arteries via balloon catheters (see Fig. 54-7G). In patients receiving LHB, balloon cannulas are also placed in the celiac and superior mesenteric arteries so that selective visceral perfusion can be delivered from the pump circuit. Patent lower intercostal arteries are reattached to an opening in the graft. Subsequently, the celiac, superior mesenteric, and renal arteries are reattached. In extent I repairs, the reattachment of the visceral arteries is often incorporated into a beveled distal anastomosis (see Fig. 54-11C), but in extent II and III repairs, the visceral artery origins are reattached to one or more oval openings in the graft (see Fig. 54-7H). The left renal artery requires attachment to a separate opening in the graft in 30 to 40% of cases (see Fig. 54-7I). Patients with Marfan syndrome are prone to developing aneurysms involving their visceral reattachment patch; a multi-branched graft enables separate bypasses to each of the vessels, thereby minimizing the amount of remaining aortic tissue and reducing the risk of recurrent aneurysms. Multi-branched grafts are also useful in patients with large aneurysms that have caused wide displacement of the celiac, superior mesenteric, and renal arterial ostia (Fig. 54-12). Visceral artery stenosis is encountered in at least 25% of cases and requires endarterectomy (if anatomically suitable), stenting, or interposition bypass grafting.[52,54,102] As the aorta is replaced from the proximal to the distal portion of the aneurysm, the aortic clamp is moved sequentially to lower positions along the graft to restore proximal blood flow. Sequential clamping is occasionally precluded by anatomic facters. When the TAAA extends below the renal arteries, a distal anastomosis is performed near the aortoiliac bifurcation (see Fig. 54-7J).

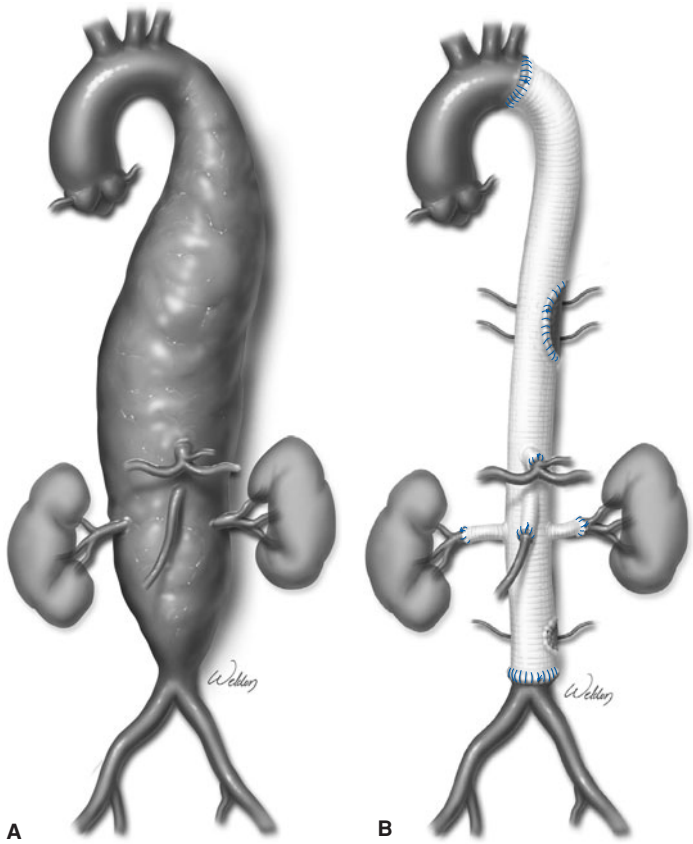

Figure 54-12. Drawings showing (A) a thoracoabdominal aortic aneurysm with wide displacement of the celiac, superior mesenteric, and both renal arterial ostia. (B) The aorta was replaced with a multi-branched graft that facilitated separate reattachment of each of the visceral arteries.

In patients with iliac artery aneurysms, a bifurcation graft is sewn onto the end of the straight graft; the graft's limbs are then anastomosed to the common iliac, external iliac, or common femoral arteries, depending on the extent of disease. Care is taken to preserve circulation to at least one of the internal iliac arteries.

Closure

After aortic unclamping, protamine sulfate is administered to reverse the effects of heparin. It is imperative that adequate hemostasis be achieved and secured at all suture lines. The renal, visceral, and peripheral circulations are assessed. The aneurysm wall is then loosely wrapped around the aortic graft. Two posteriorly located thoracic drainage tubes and a closed-suction retroperitoneal drain are placed before closure. The diaphragm is closed with continuous polypropylene suture; postoperative disruption of the diaphragmatic repair is exceedingly rare.

PERIOPERATIVE COMPLICATIONS

Since 1986, we have performed open surgical repair of 2755 DTAAs or TAAAs. Overall operative mortality was 6.3% (n = 173), which included the 4.7% of patients (n = 130) who died within 30 days of surgery. Complications that are commonly associated with an increased risk of death include paraplegia, renal failure, respiratory failure, cardiac events, and bleeding. The incidence of paraplegia or paraparesis in our series was 3.6% (n = 99), and the incidence of renal failure requiring hemodialysis was 5.1% (n = 140). Return to the operating room for postoperative bleeding was required in 2.5% of patients (n = 69). Early results stratified by the extent of repair are listed in Table 54-2.

Because aortic anastomoses are often extremely fragile during the early postoperative period, even brief episodes of hypertension may disrupt suture lines and cause severe bleeding or pseudoaneurysm formation. Therefore, to protect the integrity of the anastomosis, meticulous blood pressure control is maintained during the first 24 to 48 hours. In most cases, we use nitroprusside and intravenous beta-antagonists to maintain the mean arterial blood pressure between 80 and 90 mm Hg. In patients with severely friable aortic tissue, such as those with Marfan syndrome, we use a target range of 70 to 80 mm Hg. Hypotensive episodes must also be avoided because they can precipitate ischemic complications, including paraplegia and renal failure.

Patients who develop paraplegia or paraparesis are treated aggressively in an attempt to reverse the deficit. Treatment includes inserting a CSF drain (if not already present), administering steroids and osmotic diuretics, optimizing hemodynamics (including liberalizing blood pressure), correcting anemia, and preventing fever.

Table 54–2.

Results of 2755 Open Descending Thoracic or Thoracoabdominal Aortic Aneurysm Repairs

Extent of repair	No. of patients	30-Day deaths	Paraplegia/paraparesis	Renal failure
DTAA	469	15 (3.2%)	12 (2.6%)	11 (2.3%)
TAAA I	706	35 (5.0%)	23 (3.3%)	19 (2.7%)
TAAA II	762	46 (6.0%)	48 (6.3%)	63 (8.3%)
TAAA III	391	21 (5.4%)	10 (2.6%)	24 (6.1%)
TAAA IV	427	13 (3.0%)	6 (1.4%)	23 (5.4%)
Total	2755	130 (4.7%)	99 (3.6%)	140 (5.1%)

DTAA = descending thoracic aortic aneurysm; TAAA = thoracoabdominal aortic aneurysm.

Vocal cord paralysis can exacerbate respiratory complications and should be suspected in patients with postoperative hoarseness and confirmed by direct examination. Effective treatment can be provided by direct cord medialization (i.e., type 1 thyroplasty) or in higher-risk patients, by polytetrafluoroethylene injection.[103]

Infection of a DTAA or TAAA graft is often fatal. In an effort to minimize this risk, intravenous antibiotics are administered throughout the postoperative course until all drains, chest tubes, and central venous lines have been removed.

SURVEILLANCE FOR ADDITIONAL AORTIC DISEASE

Patients who have undergone DTAA or TAAA repair remain at risk for developing new aneurysms in other aortic segments or in reattachment patches. Progressive weakening of aortic tissue at suture lines can lead to pseudoaneurysm formation. To detect new aortic pathology before life-threatening complications occur, we recommend that all patients undergo annual CT or MRI of the chest and abdomen. This strategy of lifelong surveillance is especially important in patients with connective tissue disorders.[5] Subsequent aortic repairs can be performed with surprisingly low mortality and morbidity, particularly when done in an elective setting.[104]

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CHAPTER 55

Endovascular Therapy for the Treatment of Thoracic Aortic Disease

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Patients with thoracic aortic disease are a difficult population to treat, as they frequently consist of an aged population with multiple comorbidities. The modern surgical treatment of thoracic aortic diseases began in the 1950s when successful treatment using segmental resection and graft replacement was reported by Swan, Lam, DeBakey, and Etheredge.[1–3] Thereafter, DeBakey and Cooley reported the first successful repair of an ascending aortic aneurysm using cardiopulmonary bypass.[4] Our understanding of the pathophysiology and natural history of thoracic aortic disease has evolved, which has expanded our treatment choices.[5,6] In addition, improvements in diagnostic capabilities, surgical techniques, and perioperative care have resulted in improved outcomes, even as the risk profile has increased. Nonetheless, operative intervention in this patient population frequently results in substantial mortality and long-term morbidity.[7,8] The concept of using an endovascular stent-graft in patients with thoracic aortic disease emerged a decade ago, propelled by the desire to avoid surgical risk as well as to induce reconstructive modeling of the diseased aorta by initiating a natural healing process through exclusion and depressurization of the aneurysmal sac.[9] In an effort to improve outcomes in the treatment of patients with thoracic aortic disease, endovascular stent-graft technology has rapidly followed applications on the abdominal aorta.[10,11] Originally devised for high-risk patients with multiple comorbidities, thoracic stent-graft applications are being expanded to young and old patients with a variety of pathologies, including thoracic aortic aneurysms, aortic dissections, intramural hematomas, penetrating atherosclerotic ulcers, and thoracic aortic trauma.[12–19] Initial reports using these endovascular stent-grafts have been encouraging, but long-term outcomes are unknown, and the necessity for long-term follow-up, with its attendant expense, has raised serious concern.[20–22]

HISTORY

Endovascular stent-graft technology was initially envisioned for use in abdominal aortic aneurysms.[23] Introduced by Parodi, balloon expandable stents attached to the ends of a vascular tube graft were utilized to exclude the aneurysm sac. There were several attractive features of this concept, including the introduction of the device from a peripheral site, eliminating the necessity for an invasive laparotomy, the avoidance of aortic cross-clamping and its requisite physiologic perturbations, and minimizing respiratory complications. Lastly, hospital stay and recovery time could be potentially shortened.

At Stanford University Medical Center, a collaborative effort between interventional radiologists and cardiovascular surgeons proved highly synergistic, and resulted in the manufacture and clinical use of thoracic stent-grafts. Work had commenced years earlier with the use of uncovered stents for the repair of aortic dissections in an animal model. The stent-grafts were manufactured using self-expanding Gianturco Z stents (Cook Co., Bloomington, Ind), which were fastened together and then covered with a woven Dacron graft (Meadox-Boston Scientific, Natick, Mass; Fig. 55-1). Institutional review board (IRB) approval was initially obtained for a high-risk study using endovascular stent-grafts for the treatment of thoracic aortic aneurysms in patients who were deemed not to be surgical candidates.[24] A total of 13 patients underwent transluminal endovascular grafting of thoracic aortic aneurysms with a mean diameter of 6.1 cm. The stent-grafts, custom-designed for each patient, were constructed of self-expanding stainless steel stents covered with woven Dacron grafts. Placement of these stents was successful in all patients with thrombosis of the aneurysm surrounding the stent occurring in 12 of the 13 patients. As reported, at 1 year there were no deaths, paraplegia, stroke, distal embolization, or infection.[24] It was therefore

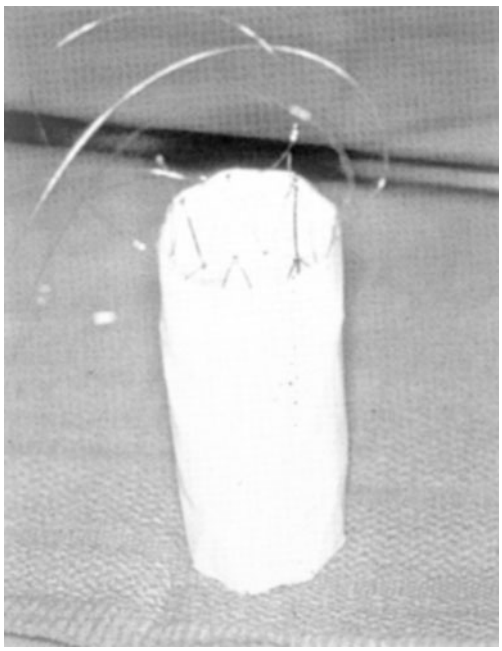

Figure 55-1. First-generation stent-graft assembled from articulated Z stents and covered with a woven Dacron tube graft.

concluded that these preliminary results demonstrated that endovascular stent-graft repair was safe in highly selected patients.

This feasibility trial led to the extension of the IRB approval for the treatment of 103 patients with thoracic aortic aneurysms.[25] Of these 103 patients, 60% were unsuitable candidates for conventional open surgical repair and therefore deemed inoperable. Again, these patients underwent repair of a descending thoracic aortic aneurysm using "home-made" or first-generation stent-grafts fabricated from self-expanding Z stents covered with woven Dacron tube graft. Complete aneurysm thrombosis was achieved in 83% of patients. Early mortality was 9% and was significantly associated with preoperative cerebrovascular accidents and myocardial infarctions. Major perioperative morbidity included paraplegia in 3 patients, cerebrovascular accidents in 7 patients, and respiratory insufficiency in 12 patients. Treatment failure occurred in 38 of the 103 patients, and 5 patients required late operative therapy for endoleaks associated with aneurysm enlargement. Actuarial survival was 81% at 1 year and 73% at 2 years. Given the high-risk nature of this patient population, these first-generation results were deemed satisfactory. It was, however, recognized that mortality and morbidity occurred frequently and that long-term follow-up was necessary to fully define the efficacy of an endovascular approach in thoracic aortic aneurysm therapy. Subsequently, in 2004, midterm results were reported for these 103 patients treated with the first-generation stent-grafts.[26] Overall actuarial survival was dismal; 82%, 49%, and 27% at 1, 5, and 8 years, respectively. However, the survival of the potentially operable candidates was 93% and 78% at 1 and 5 years, respectively, as compared to 74% and 31% at 1 and 5 years, respectively, in those patients designated as inoperable. In patients judged not to be surgical candidates, life expectancy, despite endovascular therapy, was therefore quite bleak, and has raised concerns whether any surgical therapy is appropriate for these patients. Further results revealed that 11 of the 103 patients suffered late aortic rupture at the site of endovascular treatment. This was a very sobering finding considering that open surgical graft replacement has been associated with durable long-term results with only a negligible late hazard of anastomotic problems. However, it must be remembered that this study involved the use of a relatively primitive first-generation device, with a fairly steep learning curve.

Extending the use of the endovascular stent-grafts to the treatment of complicated acute aortic dissections of the descending thoracic aorta, Dake and associates reported their findings in the *New England Journal of Medicine* in 1999.[27] Again these stents were the first-generation "home-made" devices described above. Placement of the stents across the primary entry tears was technically successful in all patients, with correction of malperfusion. Complete thrombosis of the false lumen occurred in 79%. The early mortality rate was 16%, which reflected late referral, with established intestinal gangrene, and another patient with Ehlers-Danlos syndrome, perhaps a poor candidate for endovascular repair. Favorable clinical results persisted out to a mean follow-up of 13 months.

These pioneering efforts at the Stanford University Medical Center established some interesting concepts. Namely, that these were complex patients with complex aortic problems, and that endograft therapy for aneurysmal disease was effective, potentially with reduced morbidity, but with uncertain long-term durability. Improved results could likely be obtained with more sophisticated devices, and endograft repair could effectively reverse malperfusion syndromes in complicated type B aortic dissections.

NATURAL HISTORY AND SURGICAL OUTCOMES OF THORACIC AORTIC DISEASES

Thoracic Aortic Aneurysms

Approximately 50% of all thoracic aortic aneurysms are located in the descending aorta; these aneurysms commonly arise at the level of the left subclavian artery and are often atherosclerotic in nature.[28] The size-rupture correlation has been demonstrated by studying the natural history of these aneurysms as reported by Clouse and associates, using the Olmstead County database, in which thoracic aortic aneurysms have an overall 5-year rupture risk of 30%.[29] The Mount Sinai group has identified clinical variables that determine the risk for rupture, which include increasing age, presence of chronic obstructive pulmonary disease, maximal thoracic and abdominal aneurysm diameter, and the presence

of pain.[30] The Yale Aortic Diseases Group has documented rupture and dissection of ascending or arch aneurysms at a median size of 6 cm and descending or thoracoabdominal aneurysms at a median size of 7.2 cm.[6] Furthermore, the Yale group has reported that the mean rate of rupture or dissection is 2% per year for small aneurysms, 3% for aneurysms 5.0 to 5.9 cm, and 6.9% for aneurysms of 6.0 cm and larger. Using proportional hazards regression, the odds ratio for rupture is more than 25 times higher in patients with aneurysms of 6.0 cm or greater than in those with aneurysms in the range of 4.0 to 4.9 cm.[31]

Open surgical graft replacement is the traditional treatment for these patients. The presence of comorbidities in this specific population increases the surgical risks, especially in the case of emergency intervention. However, with increasing experience, very good surgical morality rates in the 5 to 10% range have been reported from experienced centers.[32–34] Similarly, paraplegia and paraparesis rates range from 3 to 16%, with predictive factors including extent of resection, emergency operation, renal dysfunction, distal circulatory support, and cerebrospinal fluid drainage.[35–37] Nevertheless, 5-year survival rates between 60 and 80% have been achieved in recent surgical series.[32–34]

Thoracic Aortic Dissections

Acute aortic dissection is the most common catastrophe affecting the thoracic aorta, with many more people dying of rupture of dissections than of aneurysms. Although poorly understood, a primary intimal tear allows a high-pressure entry of blood into the subadventitial space, which then rapidly propagates proximally and distally. With the Stanford classification system, type A connotes involvement of the ascending aorta. The high mortality rate of 50% at 48 hours usually mandates emergent surgical repair. Conversely, type B dissections involve the descending thoracic aorta, and are typically managed with anti-impulse therapy, with surgical management reserved for those patients presenting with complications, namely intractable pain, rupture or impending rupture, or visceral or limb malperfusion syndromes.[38–41]

The Stanford group has compared the actual survival of medically and surgically treated type B dissection over a 36-year period. The actuarial survival estimates for all patients were 71%, 60%, 35%, and 17% at 1, 5, 10, and 15 years, respectively, and were similar for the medical and surgical patients.[40] The hope for benefits of avoiding the late complications from false-lumen expansion following surgical repair was not demonstrated in this follow-up.

The utility of thoracic endografts in chronic dissections is even more unclear. Given the multiple septal fenestrations, and the relative immobility of the chronically dissected septum, it seems unlikely that stent-graft insertion could realistically confer any long-term benefits, with the possible exception of a very focal aneurysmal false-lumen dilation distant from septal fenestrations near the level of the diaphragm.

Penetrating Atherosclerotic Ulcers and Intramural Hematomas of the Thoracic Aorta

Penetrating atherosclerotic ulcers (PAUs) and intramural hematomas (IMHs) are distinct pathologic entities now being diagnosed with increasing frequency.[42] PAUs probably represent rupture of an atherosclerotic plaque, with penetration into the internal elastic lamina of the aorta, and may be associated with proximal and distal progression of an intramural hematoma. Conversely, IMH not associated with a penetrating ulcer may result from the spontaneous rupture of aortic vasa vasorum that may initiate hemorrhage into the aortic media, and may progress to an intimal tear and classic aortic dissection.[42]

In the ascending aorta, IMH, with or without PAU, frequently progresses to frank dissection during the acute phase, and thus warrants early ascending aortic replacement. The highest mortality rate among patients with IMH is associated with ascending aortic involvement.[43,44] Experience has therefore suggested that a more aggressive approach with early surgery is warranted in those patients who have ascending aortic involvement or in those who have a coexisting aneurysm with IMH.[44]

In the descending thoracic aorta, pure IMH in the absence of aneurysmal change is usually treated with aggressive control of hypertension. For IMH with PAU, increasing maximal depth and maximal diameter were both associated with disease progression, in addition to persistent pain and increasing pleural effusion.[45] The risk of aortic rupture is higher among patients with PAU by almost 30% than with patients with type A or B dissection.[42] However, the progression of PAU is slow and is associated with a low incidence of acute rupture or other life-threatening events. Among patients with PAU who are not treated surgically, the natural history would indicate that the majority of patients will have aortic enlargement with the formation of saccular or fusiform pseudoaneurysms and intramural thrombus.[43]

Thoracic Aortic Trauma

Trauma is the most common cause of nondegenerative disease affecting the thoracic aorta. According to autopsy series, 36 to 54% of disruptions occur at the aortic isthmus, 8 to 27% involve the ascending aorta, 8 to 18% occur in the arch, and 11 to 21% involve the distal descending aorta.[46] Blunt trauma is commonly a catastrophic injury with only approximately 20% surviving to hospital admission. Mortality following admission ranges from 39 to 73% and is frequently the result of other major injuries.[47] The other multiple injuries a patient may experience almost invariably limit operative approaches and timing. All operations involving the thoracic aorta pose some risk of ischemic injury to the spinal cord, which is a dreaded complication in a predominantly young population. In addition, the immediacy of the operation associated with traumatic injury may require inexperienced surgeons to deal with complex pathology.[46] Fortunately, in the past decade there has been increased understanding, suggesting that for some patients without

radiographic signs of impending rupture, that permissive hypotension may be an effective temporizing strategy, allowing operative intervention after a patient has recovered from serious brain or lung injury that may have compromised immediate operative management.

ENDOVASCULAR THERAPY OF THE THORACIC AORTA

Technical Development

The first stent-grafts used at Stanford were manufactured using 2.5-cm self-expanding Gianturco Z stents (Cook Co., Bloomington, Ind), which were fastened together and then covered with a woven Dacron graft (Meadox-Boston Scientific, Natick, Mass; see Fig. 55-1). These stent-grafts were oversized approximately 10 to 15% above the cross-sectional diameter ascertained by computed tomography (CT) in an effort to obtain sufficient radial force to achieve an endoseal and prevent stent-graft migration. A minimum of 2 cm of normal aorta was required for adequate fixation, otherwise referred to as the "landing zone," both proximally and distally. The covered stent was loaded into a delivery capsule which required femoral and iliac arteries greater than 8 mm to allow the introduction of a 28 F delivery sheath. This dilator contained a sheath that had been previously placed over a super-stiff guidewire and was positioned proximal to the point of deployment. Once this was achieved, the compressed stent-graft was advanced into the sheath and deployed by using a "pusher" rod. Devices were limited to a maximal diameter of 40 mm in that aortas larger than 37 mm in diameter were themselves aneurysmal and unlikely to serve as stable attachment zones. Other anatomic constraints of these early "home-made" or first-generation stent-grafts that precluded secure fixation included acute angulation at the distal arch, and severe sigmoid-like tortuosity coursing through the diaphragmatic crura, reflecting the relative inflexibility of these early delivery systems.

The advent of this new stent-graft technology required a new terminology for endoleaks that allowed blood to leak around or through the stent-graft, thus allowing the aneurysmal sac to remain pressurized. Type I endoleaks occur at the proximal or distal attachment sites, and signify a failure to achieve a hemostatic seal at these implantation sites.[14,24,25] Type II endoleaks denote a communication between a branch vessel and the excluded aneurysm sac. These usually occur from a back-bleeding inferior mesenteric artery in the abdomen, or intercostal artery in the chest. Type III endoleaks originate from the middle graft sections, and are usually caused by disruption of graft-to-graft overlaps, or by leakage through the graft itself. Type IV endoleaks are characterized by an increase in size of the aneurysm sac in the absence of an identifiable patent branch vessel, variously referred to as "endotension."

Years of experience with endovascular abdominal aorta repair and follow-up of thoracic aortic repairs has yielded important information for improved stent-graft technology.[11,48,49] Commercially produced second- and third-generation stent-grafts are more flexible and have a lower profile, and thereby allow use of a smaller introducer sheath in the femoral vessels. Experience has shown that tapered, flexible, over-the-wire delivery systems that are less than 20F in diameter rarely fail to traverse tortuous femoral or iliac arteries. Hooks at the proximal end of the stent-graft appear to provide the most secure means of attachment, but may be suboptimal for treating patients with acute dissections. It is likely that different grafts may be developed for different pathologies, with devices for dissections being devoid of hooks or uncovered metal components. For traumatic aortic lacerations, smaller device sizes are necessary, as these are usually nonatherosclerotic normal-sized aortas with small access vessels. Ideal device components have been broken down into three categories: delivery system, graft material, and metal frame.[50] The delivery system should be of low profile, flexible for maneuverability, rigid enough to resist kinking, and hemostatic during use. The graft material should also be of low profile, strong and durable, and reasonably thin. The graft metal frame should provide high column strength and ductility, be compression and kink resistant from external forces, radiopaque, and corrosion and fatigue resistant. Nitinol is now used for the stent material in the majority of grafts and the graft material is usually polytetrafluoroethylene (PTFE) or polyester.

Currently, the Gore Excluder TAG system (W. L. Gore, Sunnyvale, Calif) is the only Food and Drug Administration (FDA)-approved graft. However, the Talent and Valiant systems (Medtronic, Sunrise, Fla) and the Zenith system (Cook-Cardiovascular, Bloomington, Ind) are being used with special release consents required (Fig. 55-2). These second- and third-generation endoprostheses are more flexible

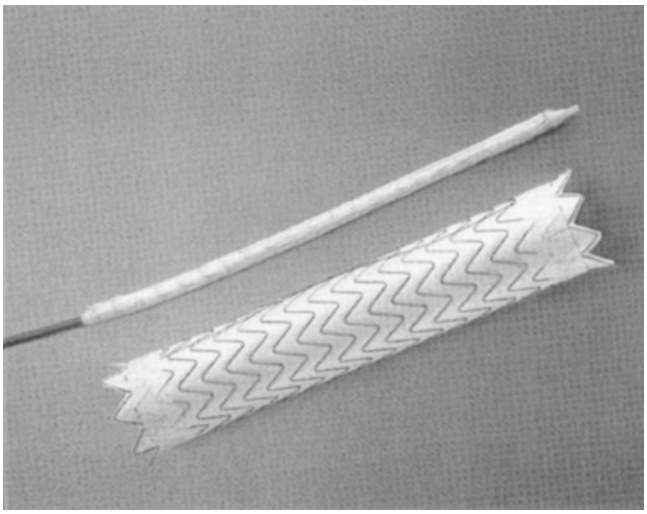

Figure 55-2. Second-generation commercially manufactured thoracic aortic stent-graft. The thoracic Excluder TAG system by W. L. Gore contains a thin-walled PTFE graft covered by a nitinol exoskeleton.

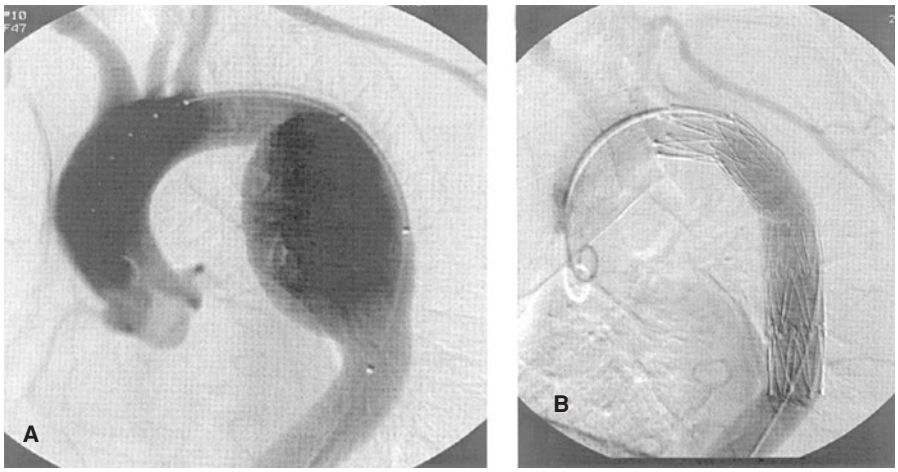

Figure 55-3. (A) Angiogram of a descending thoracic aortic aneurysm suitable for stent-graft repair. (B) Angiogram illustrating successful exclusion of the aneurysm sac with a thoracic stent graft.

and have a lower profile with smaller delivery systems that can be inserted easily to treat a number of thoracic aortic pathologies.

Clinical Results Using Endovascular Stents for Thoracic Aortic Disease

Thoracic aortic aneurysms

The Stanford group originally reported their outcomes of endovascular stent-graft placement in 13 patients back in 1994.[24] These preliminary results demonstrated that endovascular stent-graft repair was safe in highly selected patients with descending thoracic aneurysms (Fig. 55-3). This paper was followed by a report of 103 patients treated with endovascular stent-graft technology as part of a 5-year clinical trial. Using first-generation "home-made" stent-grafts, early mortality was reported as 9%, but a stroke rate of 7% and paraplegia rate of 3% were also reported. More recently, the Stanford group has reported 5- and 10-year results and has identified risk factors for adverse late outcomes.[26] Overall survival was 82%, 49%, and 27% at 1, 5, and 8 years. This included patients who were deemed both operable and inoperable. In the group of patients who were deemed operable and could have undergone open repair of their descending thoracic aneurysms, the survival was 93% and 78% at 1 and 5 years, compared with 74% and 31% in those deemed inoperable. Independent risk factors for death were older age, previous stroke, and designation as a nonoperative candidate. Freedom from aortic reintervention and treatment failure at 8 years was only 70% and 39%, respectively. Ultimately these findings suggested that by using the first-generation stent-grafts, good operative candidates had satisfactory outcomes. Conversely, those deemed inoperable had bleak outcomes, perhaps no better than if they had not been treated at all. Therefore the question of intervening at all in this cohort of patients comes into question, with many questions concerning resources and quality of life being asked. This study also revealed that late aortic complications were detected in nearly 30% of patients, which re-emphasizes the importance of follow-up serial imaging surveillance.

In January 2005 the phase II multicenter trial of the Gore Excluder TAG thoracic endoprosthesis results were reported.[51] This multicenter prospective nonrandomized trial was conducted at 17 sites and compared results of stent-graft repair of descending thoracic aortic aneurysms in 140 patients with results of open repair in 94 patients. Strict inclusion and exclusion criteria attempted to ensure comparability of both groups. Follow-up CT scans were obtained at 1, 6, 12, and 24 months. For stent-graft patients, operative blood loss, renal failure, paraplegia, and mortality rates were all significantly less than for the open repair group. Interestingly, stroke rates were about equal in both groups. ICU stay and total hospital stay, and time to return to normal activity were 50% shorter for the stent-graft group than for those with open repair. Although stent-graft patients maintained an advantage from aneurysm-related mortality out to 2 years (97 versus 90%), interestingly, all-cause mortality was similar between groups at 2 years, which is similar to results of recent randomized trials in abdominal aortic aneurysm stent-graft trials.[52]

Ricco and colleagues have most recently reported on an independent nationwide study in France using a variety of endovascular devices to treat descending thoracic aortic aneurysms in the majority of cases.[53] The Gore Excluder TAG (Gore) and Talent (Medtronic) devices were used in 84% of patients and an operative mortality of 10% was reported. A complication rate of 21% was reported, which included endoleaks in 16% of patients that were fatal in three patients. The 6-month survival rate was 86% and freedom from other complications (other than endoleak) was only 63% at 6 months. This study, involving 166 stent-graft repairs, performed in 29 centers and using 6 different types of endoprostheses, demonstrated that stent-graft repair of thoracic aortic disease could be performed with acceptable morbidity and mortality, at short-term follow-up. They do, however, qualify their conclusions by stating that endograft

treatment of thoracic aortic aneurysms should continue to be used in an investigative setting.

Thoracic aortic dissection

For dissections originating distal to the origin of the left subclavian artery, referred to as Stanford type B dissections, aggressive antihypertensive therapy has been the mainstay of treatment.[40] For complicated dissections, however, including rupture, impending rupture, intractable pain, rapid expansion, or malperfusion syndromes, surgical intervention is indicated. In these instances, however, surgical mortality has been reported to be as high as 50 to 60%. Endograft coverage of the primary intimal tear, redirecting flow into the true lumen, would appear to be an ideal application of this endograft technology. The Stanford group, with their colleagues in Mie University in Japan, reported the use of the first-generation stent-grafts in 19 patients with complicated type B aortic dissections. Placement was successful in all patients, and revascularization of ischemic branch vessels occurred in 76% of cases. There were three hospital deaths, two of which resulted from late referral, and one in a patient with Ehlers-Danlos syndrome who was perhaps untreatable by any modality. Although the follow-up was short, there were no incidences of aortic rupture or aneurysm formation, and a single-lumen aorta to the level of the stent-graft was achieved in the majority of patients[27] (Fig. 55-4).

More recently, Kato and associates reported their use of endovascular stent-grafts for the treatment of aortic dissections, both acute and chronic.[54] Significant findings were that although 2 of the 38 treated patients died early, there were no late deaths during a mean follow-up of 27 months. Furthermore, early and late complication rates were 33% and 36%, respectively, in patients with acute dissections, whereas rates were 4% and 0%, respectively, in patients with chronic dissections. These complications included endoleak and aneurysmal degeneration of the aorta in 25% of patients. Only one case of paraplegia was reported. This group therefore concluded that acute dissections could be treated with endovascular stent-grafts but that stent-graft repair should be delayed for acute Stanford type B dissections without complications.

Currently, a randomized trial is underway to compare the 2-year outcome of uncomplicated Stanford type B aortic dissections treated by endovascular implantation of a Medtronic Talent stent-graft to best medical treatment. This trial, referred to as the INSTEAD trial (*IN*vestigation of *STE*nt in patients with type B *A*ortic *D*issection) will measure all-cause mortality as the primary outcome; secondary outcome variables will include conversion to stent and/or surgery, thrombosis of the false lumen, cardiovascular morbidity, aortic expansion, quality of life, and hospital stay. Given the relatively low 1-year mortality for uncomplicated type B dissections, the benefit for any interventional strategy may be difficult to prove. Results should be available in late 2006.[55]

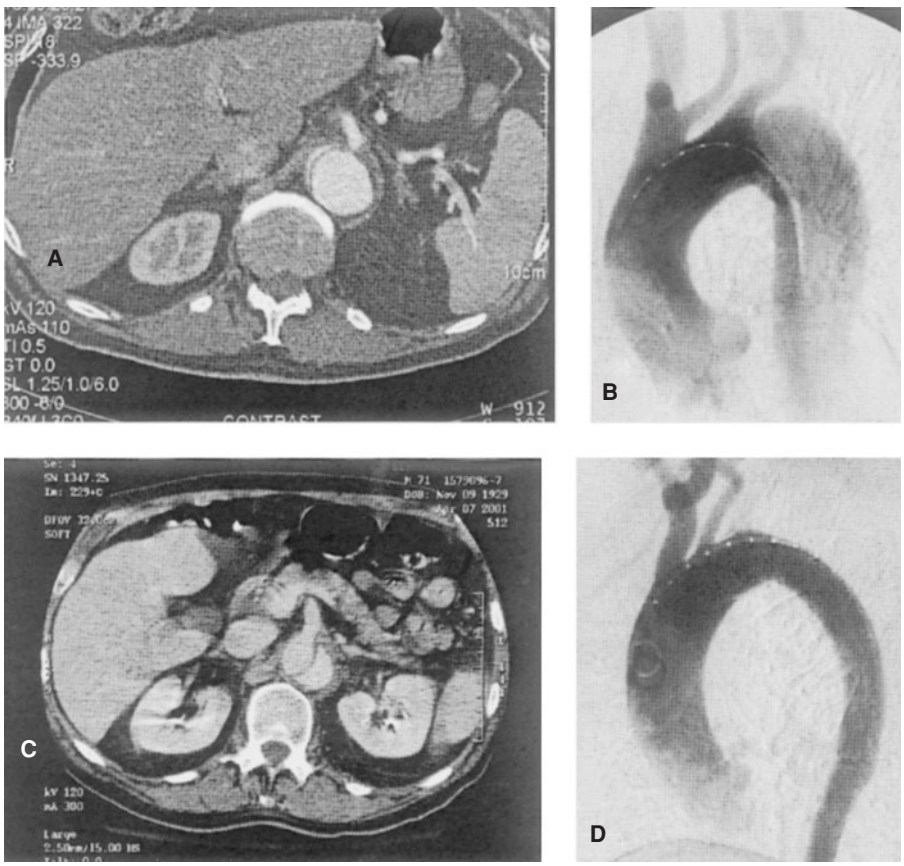

Figure 55-4. (A) Intravenous contrast-enhanced CT scan of the upper abdomen demonstrating an aortic dissection with compression of the true lumen. (B) Angiogram of the thoracic aorta demonstrating a type B dissection involving the descending thoracic aorta. (C) CT scan of the abdomen and (D) angiogram of the descending thoracic aorta after stent-graft implantation into the true lumen in the proximal descending thoracic aorta.

Penetrating atherosclerotic ulcers and intramural hematomas

IMH of the aorta is attracting growing interest as a variant of aortic dissection.[44] The evolution from IMH to overt dissection or rupture is not well understood and currently pure IMH of the descending thoracic aorta is not amenable to stent-graft repair. IMH of the ascending aorta is currently a surgically treatable disease with early intervention being warranted.[43,44] IMH, however, is often associated with or even precipitated by PAUs of the descending thoracic aorta.[42] Therefore, covering the PAU with a stent-graft may limit the progression of the IMH and allow healing to occur.[19,42] Unfortunately, even with successful stent-graft implantation using both first- and second-generation grafts, retrograde aortic dissection, new ulcer formation, and endoleaks have been noted in a significant percentage of patients, emphasizing the diffuse and severe nature of this disease.[56–59]

The Stanford group has reported their mid-term results treating PAU of the descending thoracic aorta, with an average of 51 months of follow-up[19] (Fig. 55-5). Using both first-generation and second-generation commercial devices, 26 patients were treated, 14 of whom were deemed nonoperative candidates. The primary success rate was 92% with actuarial survival estimates of 85%, 76%, and 70% at 1, 3, and 5 years, respectively. Perioperative mortality was 12%. Increasing aortic diameter and female gender were determinants of treatment failure. These risk factors reflect the importance of careful patient selection based on anatomic criteria and clinical factors. In addition, long-term follow-up with serial CT angiography is necessary to detect late complications.

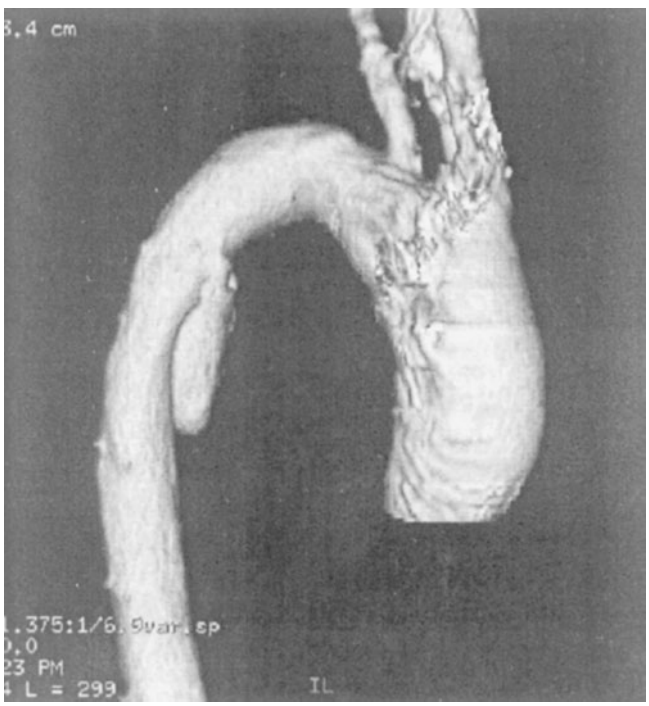

Figure 55-5. Three-dimensional CT scan of a giant penetrating ulcer involving the descending thoracic aorta that is perfectly suited to treatment with a thoracic stent-graft.

Thoracic aortic trauma

Aortic injuries secondary to nonpenetrating trauma are lethal lesions, with 80 to 90% of patients dying in the hour following the accident.[60] Urgent surgical graft replacement of the aorta is the standard treatment, but these patients frequently have other major injuries, including closed head injuries, pulmonary contusions, and other solid organ injuries that limit open surgical repair. Several authors have reported the improved results of stent-grafts over open repair for these acute injuries.[61,62] Although long-term durability may be a concern, there appear to be significant short-term benefits.[62,63] The major difficulty at present is the absence of thoracic stent-grafts sufficiently small in diameter as to be appropriate for these relatively normal-sized aortas, frequently less than 20 to 22 mm in diameter. Because of these limitations, our current strategy is to allow permissive hypotension, intervening only for those patients with signs of impending rupture, those with increasing mediastinal hematoma or hemothorax, or persistent pain. For these patients, conventional repair is preferred, using heparin-bonded circuits, unless closed head injury or pulmonary contusions contradict. Stent-graft repair is utilized for those patients in whom a conventional repair could not be tolerated.

The Stanford group has reported on their mid-term results of stent-graft repair of chronic traumatic aneurysm of the descending thoracic aorta[64] (Fig. 55-6). Among 15 patients treated with either first- or second-generation stent-grafts, deployment was successful in all patients without need for surgical conversion. No neurologic complications were reported. Actuarial survival estimates at 1 and 6 years were 93% and 85%. Freedom from reintervention on the descending thoracic aorta was 93% and 70% at 1 and 6 years, respectively. Freedom from treatment failure at 1 and 6 years was 87% and 51%, respectively. They therefore concluded that stent-grafts are safe in patients with chronic traumatic aneurysms, and are associated with satisfactory but not optimal mid-term durability. They state that younger, low-risk patients should be offered conventional, open surgery and stent-grafting should be reserved for those patients who are at prohibitive operative risk.[64]

CONCLUSIONS

Despite the many advances in the field of endovascular surgery, stent-grafting the thoracic aorta remains in a developmental phase.[20,65] This evolving technology has been applied to the treatment of thoracic aortic aneurysms, aortic dissections, IMHs, and PAUs, and traumatic injuries. The early outcomes are encouraging but middle- and long-term outcomes are a concern. Although device technology has certainly improved over the past 20 years, all devices are limited

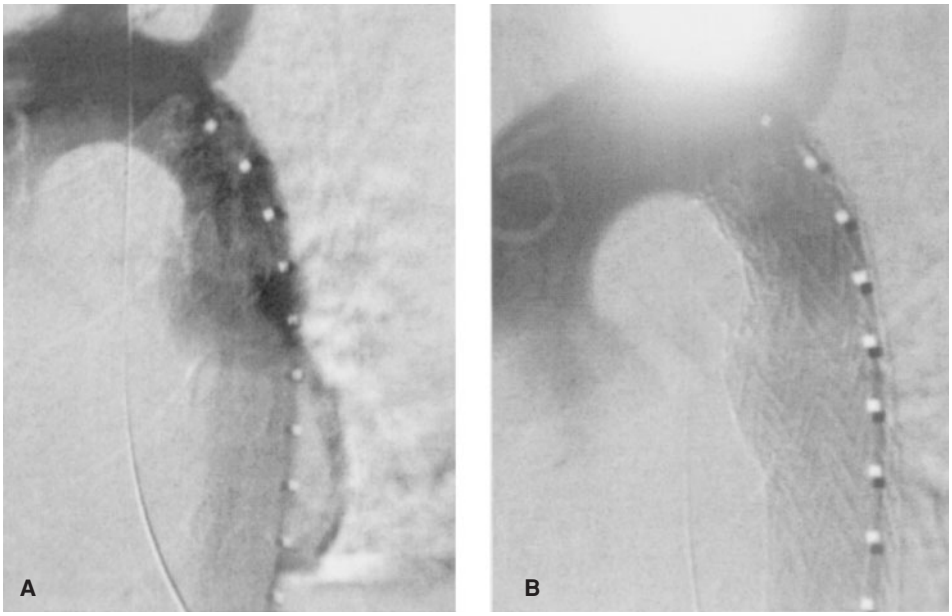

Figure 55-6. (A) Thoracic angiogram demonstrating a contained rupture of the descending thoracic aorta in a trauma victim. (B) Thoracic angiogram revealing repair of the aortic rupture with a thoracic stent-graft.

by their own structural flaws, lack of conformability, limited array of sizes, length of landing zones necessary to allow secure fixation, and structural integrity to withstand the severe physiologic milieu present in the thoracic aorta. Given the variable pathologies, it is likely that many different stent-graft configurations will be necessary for the various clinical indications.

Of utmost importance in the treatment of thoracic aortic pathology with stent-grafts is strict and dedicated follow-up. Patients need to be seen on a routine basis and new symptoms or findings need to be investigated. Serial CT angiography is an excellent tool to follow the areas of the thoracic aorta treated with the endograft, as well as to follow the evolution of the untreated portions of the aorta. Follow-up will allow endoleaks and device migration to be detected, and may further define the natural history of endovascular treatment strategies.

Diseases of the thoracic aorta pose a significant challenge to the surgeon because of the complexity of the disease and the characteristics of the patient population. Current literature supports the early advantage of endovascular technology in well-suited patients, but longer follow-up and results of ongoing trials will help define the indications for their use in the future.

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CHAPTER 56

Pulmonary Embolism and Pulmonary Thromboendarterectomy

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Pulmonary thromboendarterectomy (PTE) is the definitive treatment for chronic pulmonary hypertension as the result of thromboembolic disease. Although pulmonary embolism (PE) is one of the more common cardiovascular diseases affecting Americans, PTE remains an uncommon procedure, primarily because this form of chronic pulmonary hypertension remains an underdiagnosed condition. Patients affected by chronic thromboembolic pulmonary hypertension (CTEPH) may present with a variety of debilitating cardiopulmonary symptoms. However, once diagnosed, there is no curative role for medical management, and surgery remains the only option.

The exact incidence of PE remains unknown, but there are some valid estimates. Acute PE is the third most common cause of death (after heart disease and cancer). Approximately 75% of autopsy-proven PEs are not detected clinically.[1] Dalen and Alpert[2] calculated that PE results in 630,000 symptomatic episodes in the United States yearly, making it about half as common as acute myocardial infarctions, and three times as common as cerebrovascular accidents. This is, however, a low estimate, since in 70 to 80% of the patients in whom the primary cause of death was PE, premortem diagnosis was completely unsuspected.[3,4] The disease is particularly common in hospitalized elderly patients. Of all hospitalized patients who develop PE, 12 to 21% will die in the hospital, and another 24 to 39% die within 12 months.[5–7] Thus approximately 36 to 60% of the patients who survive the initial episode live beyond 12 months and may present later in life with a wide variety of symptoms.

More than 90% of clinically detected pulmonary emboli are associated with lower extremity deep vein thrombosis (DVT), but in two-thirds of patients with DVT and PE, the DVT is asymptomatic.[8,9] Greenfield estimates that approximately 2.5 million Americans develop DVT each year.[10]

For the most part, DVT and acute PEs are managed medically. Cardiac surgeons rarely become involved in management of acute PE, unless it is in a hospitalized patient who survives a massive embolus that causes life-threatening acute right heart failure with low cardiac output, with a large clot burden. Conversely, the mainstay of treatment for patients with chronic pulmonary thromboembolic disease is the surgical removal of the disease by means of pulmonary thromboendarterectomy. Medical management is only palliative, and transplantation surgery is an inappropriate use of resources with less than satisfactory results.

The prognosis for patients with pulmonary hypertension is poor, and it is worse for those who do not have intracardiac shunts. Thus patients with primary pulmonary hypertension and those with pulmonary hypertension due to pulmonary emboli fall into a higher risk category than those with Eisenmenger syndrome and encounter a higher mortality rate. In fact, once the mean pulmonary pressure in patients with thromboembolic disease reaches 50 mm Hg or more, the 3-year mortality approaches 90%.[11]

Surgical options are dependent on both the primary disease process and the reversibility of the pulmonary hypertension. With the exception of thromboembolic pulmonary hypertension, lung transplantation is the only effective therapy for patients with pulmonary hypertension when the disease reaches end stage. Pulmonary transplantation is also still used in some centers as the treatment of choice for those with thromboembolic disease. However, a true assessment of the effectiveness of any therapy should take into account the total mortality once the patient has been accepted and put on the waiting list. Thus the mortality for transplantation (and especially double-lung or heart-lung transplantation) as a therapeutic strategy is much higher than is generally appreciated because of the significant loss of patients awaiting donors. Considering also the long-term use of antirejection medications and their associated side effects, the higher

operative morbidity and mortality, the long waiting time, and inferior prognosis even after transplantation, transplantation is clearly an inferior option to pulmonary thromboendarterectomy. We consider it to be inappropriate therapy for this disease, leaving pulmonary thromboendarterectomy as the only curative option for patients with CTEPH.

DEEP VENOUS THROMBOSIS

DVT primarily affects the veins of the lower extremity or pelvis and rarely affects the venous system elsewhere. The process may involve superficial as well as deep veins, but superficial venous thrombosis does not generally propagate beyond the saphenofemoral junction and therefore very rarely causes PE.[9,12] Venous thrombosis of the upper extremity is almost always associated with trauma, indwelling catheters, or other pathologic states and is an uncommon cause of PE, but can be fatal. Pulmonary emboli that do not originate from the deep venous system of the legs and pelvis are thought to come from a diseased right atrium or ventricle or from retroperitoneal and hepatic systems.[12,13]

DVT is most common in hospitalized patients but may occur in ambulatory patients outside the hospital. In recent years improved understanding of the pathogenesis of the disease and better diagnostic tests have identified patients at risk, improved prophylaxis, and increased the percentages of patients who are diagnosed and treated.

Pathology

In careful autopsy studies microscopic thrombi may be found in the pockets of venous valve cusps, in vein saccules, and at vein junctions of pelvic, thigh, and calf veins.[12,14] Calf vein thrombi are most common, and multiple and bilateral thrombi at independent sites within the lower body venous system can occur simultaneously.[12] The initial thrombus grows by accretion of platelets, fibrin, and enmeshed red cells and may detach at any time. Six primary sites of origin of DVT are described: external iliac, common femoral, termination of either the superficial or deep femoral, popliteal, posterior tibial, and intramuscular calf veins.[12] Most calf vein thrombi either do not embolize or produce small, often asymptomatic emboli of little clinical significance. However, somewhere between 20 and 30% of calf vein thrombi propagate proximally into upper thigh veins.[9,15] The majority of PEs originate in thigh and pelvic veins.

Thrombi are composed of fibrin, platelets, and usually large numbers of red cells that may form lakes within the clot. In clots that do not embolize, the fibrinolytic system usually dissolves the thrombus. Incomplete dissolution results in the formation of granulation tissue at sites where the thrombus attaches to the vein wall. The organizing thrombus becomes incorporated into the vein wall, and usually destroys the adjacent valve as proliferating vascular channels and fibroblasts invade the site.[14,15]

Pathogenesis

In 1856 Rudolf Virchow made the association between DVT and PE and suggested that the causes of DVT were related to venous stasis, vein wall injury, and hypercoagulopathy. This triad of etiologic factors remains relevant today and is supported by an ever-growing body of evidence.

Injections of contrast material in foot veins require up to 1 hour to clear from venous valves in the soleus muscle of immobilized patients.[16] Venous stasis is also produced by mechanical obstruction of proximal veins, by low cardiac output, by venous dilatation, and by increased blood viscosity.[17] Some pelvic tumors, bulky inguinal adenopathy, the gravid uterus, previous caval or iliac venous disease, and elevated central venous pressures from cardiac causes also enhance venous stasis. Tourniquets, anesthetic agents, pregnancy, high-dose estrogens, and increasing age produce venous dilatation. Polycythemia, hyperfibrinogenemia, and some abnormal protein diseases increase the viscosity of blood.[17] It is not clear whether or not superficial varicosities increase the likelihood of DVT in deep veins. However, immobilization is by far the most important cause of venous stasis in hospitalized patients.

The role of vein wall injury is less clear since DVT often begins in the absence of mechanical trauma. Recent work shows that subtle vein wall injuries may occur during surgery in veins remote from the operative field.[18,19] In animals, endothelial cell tears have been found at junctions of small veins with larger veins at remote sites during hip replacement (Fig. 56-1). The mechanism is thought to be

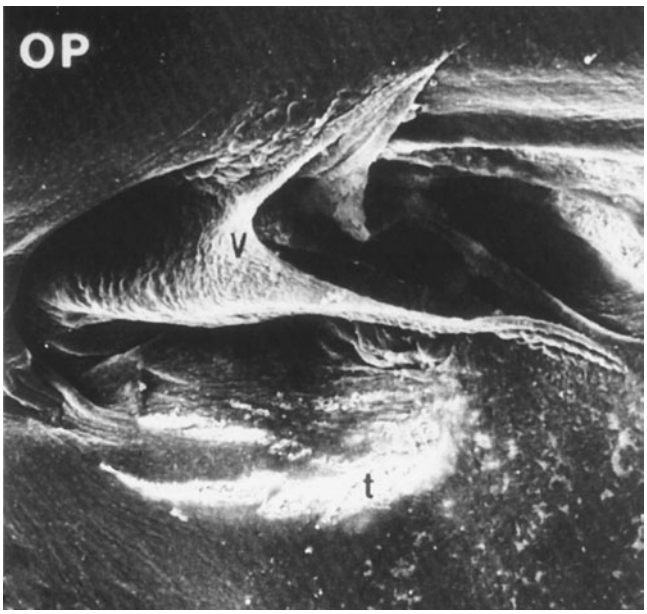

Figure 56-1. Scanning electron photomicrograph of a canine jugular vein after total hip replacement with significant operative venous dilatation. An endothelial cell tear (t) is visible near a valve cusp (V). *(Reproduced with permission from Comerota AJ, Stewart GJ, White JV: Combined dihydroergotamine and heparin prophylaxis of postoperative deep vein thrombosis: Proposed mechanism of action. Am J Surg 1985; 150:39.)*

venous dilatation mediated by the production of circulating vasoactive substances, including histamines, bradykinin, activated complement, and the leukotrienes during surgery.[20] Exposure of subendothelial tissue factor provides a powerful procoagulant stimulus by activating factor VII and the extrinsic coagulation pathway.[21] The cytokines interleukin-1 and tumor necrosis factor, produced by macrophages and other cells in various pathologic conditions, stimulate procoagulant activity of endothelial cells. In ways that are still not clear these processes may combine with venous stasis, microscopic endothelial tears, and blood procoagulant activity to localize the formation of the initial thrombus to venous saccules and valve pockets of the deep leg veins.

Simultaneous maintenance of the fluidity of blood and the integrity of the vascular system requires a balance between blood pro- and anticoagulants. Some patients with DVT have deficiencies in natural anticoagulants. Three uncommon familial deficiencies associated with venous thrombosis are in antithrombin, protein C, and protein S. Antithrombin is a natural plasma protease that inhibits thrombin after it is formed, and to a lesser extent before it is formed. Antithrombin is also the cofactor that is accelerated 1000-fold by heparin. Protein C is a potent inhibitor of factor V and platelet-bound factor VII and requires protein S as a cofactor for anticoagulant activity. Both protein C and S are vitamin-K–dependent zymogens that are activated by thrombin and accelerated by thrombomodulin produced by endothelial cells.

A much more common coagulation deficiency, resulting from a mutation of factor V (factor V Leiden) that prevents its degradation by protein C, has been described and is present in approximately 6 to 7% of study populations of Swedes and North American males.[22–24] Both the homozygous and heterozygous mutants are strongly associated with venous thrombosis and pulmonary embolism but are not associated with stroke, myocardial infarction, and other manifestations of arterial thrombosis.[24,25]

The presence of the lupus anticoagulant, which is an acquired IgG or IgM antibody against prothrombinase, increases the likelihood of venous thrombosis by poorly understood mechanisms.[25] The disease may be associated with lupus-like syndromes, immunosuppression, or intake of specific drugs, such as procainamide.

In addition to the three classic risk factors described above, decreased fibrinolytic activity in blood may also contribute to the development of DVT. Fibrinolytic activity is less in leg veins than in arm veins, particularly in older patients.[26] Decreased fibrinolytic activity may be due to decreased production of tissue plasminogen activator or increased concentrations of plasminogen-activator inhibitor-1.[27]

Risk Factors for DVT

The presence of major risk factors increases the likelihood of venous thromboembolism in proportion to the number of risk factors present. In patients with clinically suspected DVT, 50% of patients with three risk factors will have a proven diagnosis of DVT; however, without any risk factors DVT is proven in only 11%.[28] The rationale for aggressive prophylactic therapy against the disease is based on the strong association between major risk factors and venous thromboembolism.

Table 56–1.

Major Risk Factors for Venous Thromboembolism

Previous venous thromboembolism	Age over 4 years
Major hip or knee surgery	Bedrest 7 days or longer
Recent major surgery	Cancer
Congestive heart failure	Paralysis of lower extremity
Pelvis, hip, or leg fracture	Multiple trauma
High-dose estrogen therapy	

Table 56-1 presents a list of major risk factors for the development of DVT or PE. Previous thromboembolism, older age, immobilization for more than 1 week, orthopedic surgery of the hip or knee, recent surgery, multiple trauma, and cancer are strong risk factors. In patients with a history of venous thromboembolism the risk of developing a new episode during hospitalization is nearly eight times that of someone without a history.[9,29] Up to 10% of patients with a first episode of DVT or PE and up to 20% of those with a recurrent event develop a new episode of venous thromboembolism within 6 months.[30]

The incidence of DVT and PE increases exponentially with age (Fig. 56-2). Patients in the seventh and eighth decades of life are 200 times more likely to develop venous thromboembolism than patients below age 40. Males are at greater risk than females. Immobility from any cause and prolonged bedrest are major risk factors. Although usually other risk factors are present, the incidence of autopsy-proven venous thrombosis rises from 15 to 80% in patients at bedrest for more than 1 week.[30,31]

Surgeries, particularly orthopedic and abdominal, and multiple trauma are associated with a significant incidence of DVT and PE. Without prophylaxis the risk of DVT and PE after major abdominal surgery is approximately 25% and 2%, respectively.[8,31] The risk of venous embolism is also increased following urologic surgery and operations for gynecologic cancer.[9] After multiple trauma the risk of DVT and PE is over 50% in patients with pelvic, thigh, or leg injuries.

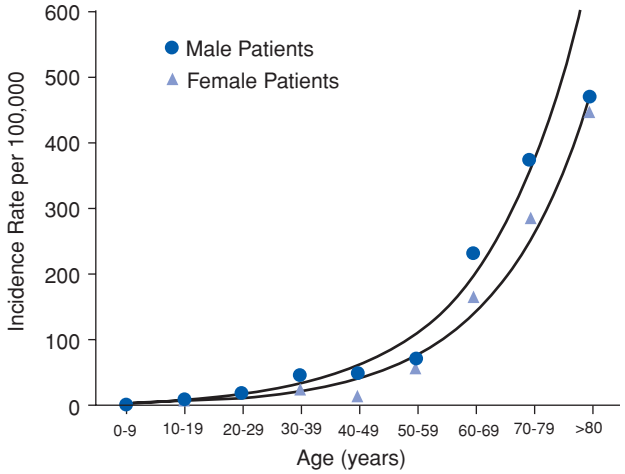

Figure 56-2. Annual incidence of venous thromboembolism in the United States stratified for age. Males have a significantly higher incidence rate of venous thromboembolism than females. Both curves fit an exponential function. *(Reproduced with permission from Anderson FA Jr, Wheeler HB, Goldberg RJ, et al: A population based perspective of the hospital incidence and case fatality rates of deep vein thrombosis and pulmonary embolism: The Worcester DVT study. Arch Intern Med 1991; 151:933.)*

The incidence of venous thromboembolism increases threefold in patients who have operations for cancer.[9] The incidence is highest in patients with advanced or metastatic disease and may be related to the production of procoagulant material or suppression of fibrinolytic activity by some tumors.[9] Patients with congestive heart failure are at higher risk of venous thromboembolism because of venous stasis and higher venous pressures, and if PE occurs are more likely to die because of reduced cardiac reserve. Acute myocardial infarction may be an independent risk factor for PE, but this is not clear because other risk factors usually are present.[9]

Although the risk of PE is low, women who have just given birth are at higher risk of PE than during pregnancy, and PE remains a major cause of maternal mortality.[17] High-dose estrogen given to treat some malignancies is associated with an increased risk of venous thromboembolism. It is not clear whether or not oral estrogen contraceptives increase the risk of thromboembolism. Low-dose estrogens, obesity, and varicose veins are probably not independent risk factors for DVT or PE but may be additive.[9]

Of particular interest to cardiac surgeons and cardiologists is the recent observation that clinically silent DVT develops during hospitalization in nearly 50% of patients after myocardial revascularization.[32] Nearly all of the thrombi occur in calf veins and are distributed equally between the saphenous vein donor leg and the opposite extremity. Patients are asymptomatic for DVT, there are no physical clues, but all thrombi in this small series were proven by duplex scanning.[32]

A follow-up study[33] found that the incidence of PE in hospital after coronary artery bypass operations was 3.2%. Risk factors included prolonged postoperative recovery, previous venous thromboembolism, obesity, and hyperlipidemia. Hospital mortality in patients with PE was 18.7%. Interestingly, valvular surgery was not associated with the development of PE. In a retrospective study of 5694 patients who had open heart surgery, Gillinov and colleagues found the risk of PE proven by ventilation-perfusion scan (20 patients), angiography (4 patients), or autopsy (8 patients) was 0.56% within 60 days. However, the mortality was 34% in patients with PE.[34]

Diagnosis

Approximately two-thirds of patients with DVT do not have clinical symptoms[9] and thus the diagnosis depends on a high degree of clinical suspicion and a variety of objective diagnostic tests. Venography remains the most reliable test for detecting thrombus in calf veins but competes with noninvasive tests for detecting DVT in thigh and pelvic veins. Venography, however, is invasive, not suitable for serial studies, and the contrast material may be thrombogenic if allowed to remain within the deep venous system.[10] With advances in technology and the accuracy of the noninvasive diagnostic tests that are widely accessible, venographies are very rarely performed.

The most popular noninvasive test, which can be done at the bedside, is a combination of ultrasound and color flow Doppler mapping, widely referred to as *duplex scanning*. The method does not detect fresh thrombi directly but infers the presence of clot by flow patterns and the inability to compress the vessel in specific locations.[10] In the hands of skilled examiners duplex scanning is highly accurate for the detection of thrombus in popliteal, deep femoral, and superficial femoral veins and has a sensitivity between 89 and 100% against venography in symptomatic patients. Diagnostic accuracy is much lower in asymptomatic patients for thrombi in these locations, and specificity is nearly 100% in both symptomatic and asymptomatic patients.[10,35] Against magnetic resonance imaging (MRI), duplex scanning has a sensitivity of 70% for pelvic veins and a specificity of nearly 100%.[35] The test is less accurate in the calf and also in patients suspected of recurrent DVT. MRI is a noninvasive method that can image the entire venous system, including upper extremity veins and mediastinum.[36] The method detects flow within the venous system and reliably separates flowing blood from stagnant blood or thrombus.

Impedance plethysmography assesses volume changes in the leg after occlusion of the vein with calf electrodes and a thigh cuff. It is clinically useful in symptomatic patients but has relatively low sensitivity and specificity in asymptomatic patients and calf thrombosis.[35] Injection of iodine 125–labeled fibrinogen with subsequent leg scanning is a sensitive test for detecting calf vein thrombus but does not detect iliofemoral vein thrombosis. The combination of these two tests improves sensitivity and specificity, but in most hospitals duplex scanning, venography, and MRI have superseded both tests.

Prophylaxis

The prevalence of DVT, its strong association with PE, and the identification of risk factors in the pathogenesis of the disease provide the basis and rationale for prophylactic measures that are recommended in patients with two or more major risk factors, such as age over 40 years and major surgery.[9] Innocuous measures such as compression stockings probably should be prescribed more often and be used in most nonambulating patients in the hospital. Intermittent pneumatic compression is more expensive and more cumbersome but is effective. Both methods reduce the incidence of DVT after general surgery to approximately 40% of that of control patients.[9] Low-dose subcutaneous heparin or low-molecular-weight heparin given once per day reduce the incidence of DVT to approximately 35% and 18% of controls, respectively.[9,31,37] The reduction in PE with subcutaneous standard heparin or low-molecular-weight heparin is similar.[31,37]

Calf vein DVT that does not propagate has a low risk of PE, and controversy exists as to whether or not these patients should be anticoagulated.[13] Of patients who have DVT diagnosed in hospital without PE, the probability of clinically diagnosed PE within the next 12 months is 1.7%.[5] If PE occurs, the probability of recurrent PE is 8.0%.[5] Six months of warfarin anticoagulation is recommended for patients who have DVT with or without PE as prophylaxis against recurrent disease.[38]

PULMONARY EMBOLISM

Pathology and Pathogenesis

Partial or complete occlusion of calf or thigh veins reduces the velocity of flow in the more proximal femoral and iliac veins, and enhances the propagation of thrombus toward the direction of the flow. The thrombus is attached to the vein wall at the site of origin, usually does not develop other sites of attachment immediately,[26] and may grow to fill most of the lumen of the vein and extend into the vena cava. The only firm attachment is at the site of origin, usually a venous saccule or venous valve pocket. The degree of organization within the thrombus varies, but recent clots are more likely to migrate than older thrombi that are more firmly attached to the vessel wall.

Detached venous thrombi are carried in the bloodstream through the right heart into the pulmonary circulation. Large thrombi may float as a single embolus or fragment into smaller clots along the way. In autopsy series the percentage of emboli that obstruct two or more lobar arteries (major) ranges between 25 and 67% of all emboli,[39] but this percentage varies with the thoroughness of the examination. In clinical trials based on angiographic data the percentage of major emboli is similar and ranges from 30 to 64%.[40] The majority of pulmonary emboli lodge in the lower lobes[12] and are slightly more common in the right lung than in the left. Soon after reaching the lungs emboli become coated with a layer of platelets and fibrin.[12]

Simple mechanical obstruction of one or more pulmonary arteries does not entirely explain the often devastating hemodynamic consequences of major or massive emboli. Humoral factors, specifically serotonin, adenosine diphosphate, platelet-derived growth factor, thromboxane from platelets coating the thrombus, platelet-activating factor, and leukotrienes from neutrophils are also involved.[41] In animal and early clinical studies serotonin inhibitors, cyproheptadine, and ketanserin partially block constriction of both pulmonary arteries and bronchi associated with PE.[42] Anoxia and tissue ischemia downstream to emboli inhibit endothelium-derived relaxing factor production and enhance release of superoxide anions by activated neutrophils. The combination of these effects contributes to enhanced pulmonary vasoconstriction.[41]

Natural History

The mortality of untreated PE is 18 to 33% but can be reduced to about 8% if diagnosed and treated.[7,43,44] Seventy-five to ninety percent of patients who die of pulmonary emboli do so within the first few hours of the primary event.[45] It is possible that those who die later do so of recurrent PE. In patients who have sufficient cardiopulmonary reserve and right ventricular strength to survive the initial few hours, autolysis of emboli occurs over the next few days and weeks.[46] On average, approximately 20% of the clot disappears by 7 days, and complete resolution may occur by 14 days.[44,46,47] For many patients, up to 30 days are needed to dissolve small emboli and up to 60 days for massive clots.[48] As the natural fibrinolytic system dissolves the embolic mass, the available cross-sectional area of the pulmonary arterial tree progressively increases, and pulmonary vascular resistance and right ventricular afterload decrease. In the vast majority of patients, pulmonary emboli continue to resolve and thus an immediate interventional therapy, particularly surgical embolectomy, is not necessary for survival except in a minority of patients.

In an unknown but small percentage of patients with acute PE the clot will not lyse, and chronic thromboembolic obstruction of the pulmonary vasculature develops. The reasons for failure of emboli to dissolve are unknown. Patients often are asymptomatic until symptoms of dyspnea, exercise intolerance, or right heart failure develop, mostly secondary to the pulmonary hypertension that ensues. Asymptomatic patients may have partial or complete chronic thrombotic occlusion of one or more segmental or lobar arteries. Symptomatic patients usually have over 40% of their pulmonary vasculature obstructed by organized and fresh thrombi; however, significant pulmonary hypertension can develop in patients despite lesser degrees of vascular obstruction.

ACUTE PULMONARY EMBOLISM

Clinical Presentation

Acute PE usually presents suddenly. Symptoms and signs vary with the extent of blockage, the magnitude of the humoral response, and the pre-embolus reserve of the cardiac and pulmonary systems of the patient.[49] Symptoms and signs vary widely, but the clinical diagnosis is often missed or falsely made. Most pulmonary emboli occur without sufficient clinical findings to suggest the diagnosis, and in autopsy series of proven emboli only 16 to 38% of patients were diagnosed during life.[39]

The acute disease is conveniently stratified into minor, major (submassive), or massive embolism on the basis of hemodynamic stability, arterial blood gases, and lung scan or angiographic assessment of the percentage of blocked pulmonary arteries.[40,49,50] Most pulmonary emboli are minor. These patients present with sudden, unexplained anxiety, tachypnea or dyspnea, pleuritic chest pain, cough, and occasionally streak hemoptysis.[39,45,50] Examination may reveal tachycardia, rales, low-grade fever, and sometimes a pleural rub. Heart sounds and systemic blood pressure are often normal; sometimes the pulmonary second sound is increased. Interestingly, less than one-third of patients will have evidence of clinical DVT.[39] Room air arterial blood gases indicate an arterial partial oxygen pressure (Pa_{O_2}) between 65 and 80 torr and a normal arterial partial carbon dioxide pressure (Pa_{CO_2}) around 35 torr.[45] Pulmonary angiograms show less than 30% occlusion of the pulmonary arterial vasculature.

Major PE is associated with dyspnea, tachypnea, dull chest pain, and some degree of hemodynamic instability manifested by tachycardia, mild to moderate hypotension, and elevation of the central venous pressure.[45,50] Some patients may present with syncope rather than dyspnea or chest pain. In contrast to massive PE, patients with major embolism (at least two lobar pulmonary arteries obstructed) are hemodynamically stable and have adequate cardiac output.[40] Room air blood gases reveal moderate hypoxia (Pa_{O_2} <65 and >50 torr) and mild hypocarbia (Pa_{CO_2} <30 torr).[50] Echocardiograms may show right ventricular dilatation. Pulmonary angiograms indicate that 30 to 50% of the pulmonary vasculature is blocked; however, in patients with pre-existing cardiopulmonary disorders, lesser degrees of vascular obstruction may produce similarly alarming symptoms.

Massive PE is truly life-threatening and is defined as a PE that causes hemodynamic instability.[40] It is sometimes associated with occlusion of more than 50% of the pulmonary vasculature but may occur with much smaller occlusions, particularly in patients with pre-existing cardiac or pulmonary disease. The diagnosis is clinical, not anatomic. Patients develop acute dyspnea, tachypnea, tachycardia, and diaphoresis and sometimes may lose consciousness. Both hypotension and low cardiac output (<1.8 L/m^2/per minute) are present. Cardiac arrest may occur. Neck veins are distended, central venous pressure is elevated, and a right ventricular impulse may be present. Room air blood gases show severe hypoxia (Pa_{O_2} <50 torr), hypocarbia (Pa_{CO_2} <30 torr), and sometimes acidosis.[40,45,50] Urine output falls; peripheral pulses and perfusion are poor.

Diagnosis

The clinical diagnosis of acute major or massive PE is unreliable and is wrong in 70 to 80% of patients who have angiography subsequently.[49,51] Even in postoperative patients and those with additional major risk factors for DVT, differentiation of major or massive PE from acute myocardial infarction, aortic dissection, septic shock, and other catastrophic states is difficult and uncertain. A plain chest x-ray, an electrocardiogram (ECG), and insertion of a bedside Swan-Ganz catheter may add confirmatory information but might not necessarily prove the diagnosis.

The chest film may be normal but usually shows some combination of parenchymal infiltrate, atelectasis, and pleural effusion. A zone of hypovascularity or a wedge-shaped pleural-based density raises the possibility of PE. In patients with massive PE and hemodynamic compromise the chest x-ray may actually appear normal. Usually the ECG shows nonspecific T-wave or RS-T segment changes with PE. A minority of patients with massive embolism (26%) may show evidence of cor pulmonale, right-axis deviation, or right bundle-branch block.[49] An echocardiogram showing right heart dilatation raises the possibility of major or massive PE. A Swan-Ganz catheter generally shows pulmonary arterial desaturation (Pa_{O_2} <25 torr) but usually does not show pulmonary hypertension over 40 mm Hg because of low cardiac output and cor pulmonale (the unprepared right ventricle cannot generate pulmonary hypertension).

Ventilation-perfusion (V/Q) scans will provide confirmatory evidence, but these studies may be unreliable, since pneumonia, atelectasis, previous pulmonary emboli, and other conditions may cause a mismatch in ventilation and perfusion and mimic positive results. In general, negative V/Q scans essentially exclude the diagnosis of clinically significant PE. V/Q scans usually are interpreted as high, intermediate, or low probability of PE to emphasize the lack of specificity but high sensitivity of the test (Fig. 56-3). Pulmonary angiograms provide the most definitive diagnosis, but collapse of the circulation may not allow time for this procedure, and pulmonary angiograms should not be performed if the patient's circulation cannot be stabilized by pharmacologic or mechanical means. In stable patients, angiograms are associated with a mortality of 0.2%, but similar to a V/Q scan, a normal angiogram will rule out a clinically significant PE.[52,53]

MRI and computed tomography angiographies are better noninvasive methods for the diagnosis of pulmonary emboli and provide specific information regarding flow within the pulmonary vasculature.[54] Unfortunately, these methods are expensive, somewhat time consuming, and not

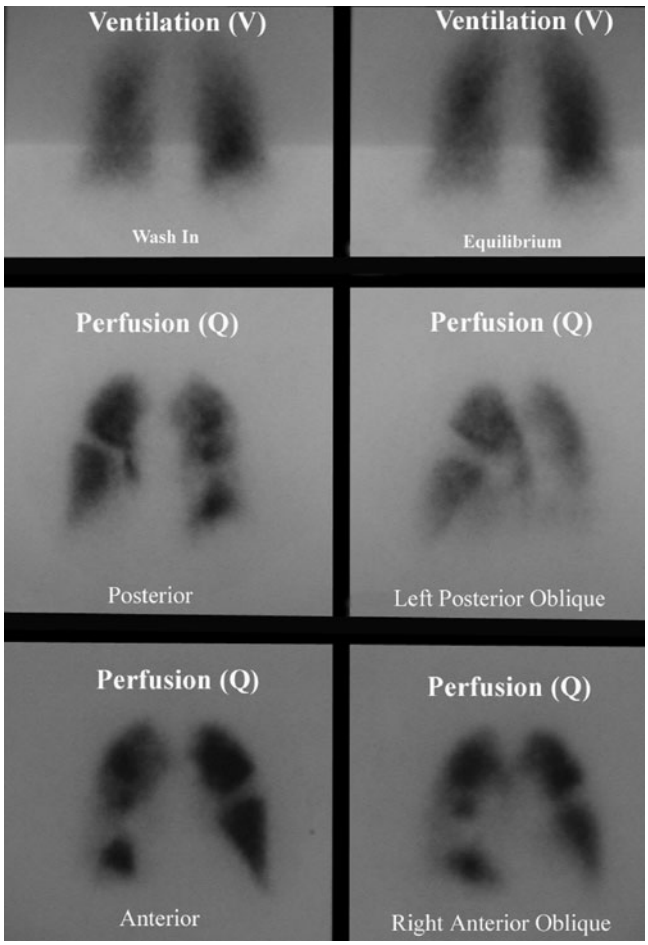

Figure 56-3. Anterior and posterior views from a radionuclide perfusion scan in a patient with chronic thromboembolic disease. Note the large punched-out defects.

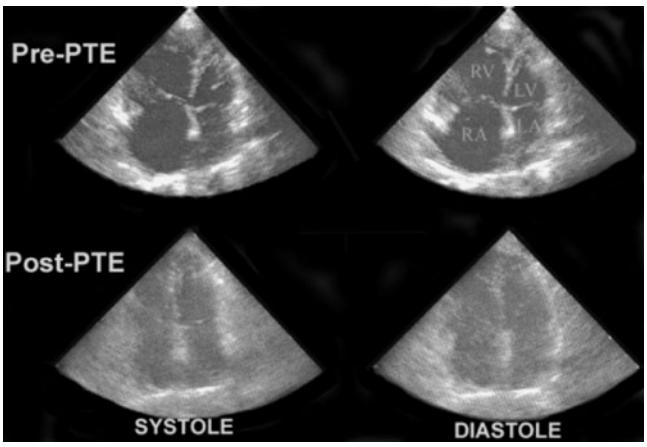

Figure 56-4. Appearance of echocardiography before and after the operation. The top images represent pre-PTE and the bottom images represent post-PTE. Note the shift of the intraventricular septum toward the left in the systole before the operation, together with the relatively small left atrial and left ventricular chambers. After the operation, the septum has normalized, and the right-sided chambers are no longer massively enlarged. LA = left atrium; LV = left ventricle; PTE = pulmonary thromboendarterectomy; RA = right atrium; RV = right ventricle.

widely available. Furthermore, they are not generally suitable for hemodynamically unstable patients. Transthoracic or transesophageal echocardiography with color flow Doppler mapping can provide reliable information about the presence or absence of major thrombi obstructing right-sided chambers or the main pulmonary artery. More than 80% of patients with clinically significant PE have abnormalities of right ventricular volume or contractility, or acute tricuspid regurgitation by transthoracic echocardiography (Fig. 56-4).[55] In some patients abnormal flow patterns can be discerned in major pulmonary arteries during transesophageal echocardiography.

Management of Acute Pulmonary Embolism

For the purposes of this chapter major or submassive PE is defined as an acute episode that causes hypoxia and mild hypotension (systolic arterial pressure >90 mm Hg), but that does not cause cardiac arrest or sustained low cardiac output and cardiogenic shock. By definition there is sufficient time in these patients to definitively establish the diagnosis and to attempt pharmacologic therapy and possibly removal of embolic material by catheter suction.

The first priority after sudden collapse of any patient is to establish adequate ventilation and circulation. The first may require intubation and mechanical ventilation. Pharmacologic agents, including cardiovascular pressors and vasoactive agents, are then used to help stabilize the patient's hemodynamics. Once the circulation has been stabilized, both arterial and central venous catheters are placed for access and for continuous pressure monitoring. Usually a Swan-Ganz catheter is also placed to monitor cardiac output and pulmonary arterial oxygen saturation. The ECG is monitored, a Foley catheter is placed for recording urine output, and blood gases are obtained.

If the patient's circulation can be stabilized, intravenous heparin is started with an initial bolus dose of 70 U/kg followed by 18 to 20 U/kg/per hour if there are no contraindications to heparin. Heparin will prevent propagation and formation of new thromboemboli, but does not dissolve the existing clot. In most instances the patient's own fibrinolytic system lyses fresh thrombi over a period of days or weeks.[46] Heparin is monitored by measurement of activated partial thromboplastin times, which are maintained between 51 and 68 seconds (twice control), every 6 to 8 hours. Platelet counts should be obtained at the beginning of heparin therapy and every 2 to 3 days to detect the presence or appearance of heparin-induced thrombocytopenia. Prothrombin times also are obtained at baseline to prepare for long-term anticoagulation with warfarin later.

The addition of lytic therapy (i.e., streptokinase, urokinase, or recombinant tissue plasminogen activator) increases the rate of lysis of fresh thrombi and is recommended in patients with a stable circulation and no contraindications.

Thrombolytic therapy increases the rate of lysis of fresh pulmonary clots over that of heparin alone during treatment,[56] but there is little difference in the amount of residual thrombus between the two treatments at 5 days or thereafter.[57–60] There is also no statistical difference in mortality or in the incidence of recurrent PE, but more recent experience shows a trend toward better results with thrombolytic therapy because of a more rapid reduction in right ventricular afterload and dysfunction.[56] Furthermore, there are no data that indicate that thrombolysis reduces the subsequent development of chronic pulmonary thromboembolism and pulmonary hypertension. Compared to heparin therapy alone, thrombolytic agents carry a higher risk of bleeding complications. Despite precautions, bleeding complications occur in approximately 20% of patients.[61,62] Contraindications to the use of these agents include patients with fresh surgical wounds, recent stroke, peptic ulcer, or bleeding disorders. Thrombolytics are also contraindicated in severely anemic patients and patients with potential sources of catastrophic intracranial, retroperitoneal, or gastrointestinal bleeding.[56]

Mechanical removal of pulmonary thrombi is possible by using a catheter device inserted under local anesthesia into the femoral (preferred) or jugular vein.[50,63,64,67,69] The catheter, which has a small terminal cup, is steered into the pulmonary artery using fluoroscopy for guidance. Syringe suction is applied to the cup as a thrombus is engaged, and the whole assembly is removed through the venotomy. The procedure may be repeated. Successful extraction of clot with meaningful reduction in pulmonary arterial pressure varies between 61 and 84%.[64,69]

Management of Massive Pulmonary Embolism

If the circulation cannot be stabilized at survival levels within several minutes or if cardiac arrest occurs after a massive PE, time becomes of paramount importance. Most deaths from acute PE occur before effective treatment is instituted, often as a result of failure of diagnosis. Eleven percent of patients with fatal PE die within the first hour, 43 to 80% within 2 hours, and 85% within 6 hours.[65] To a great extent, circumstances and the timely availability of necessary equipment and personnel determine therapeutic options. Mitigating factors such as advanced age, irreversible underlying health problems, and the likelihood of brain damage also enter into decision making. A decision to treat medically in an effort to stabilize the circulation at a survival level may preempt lifesaving surgery, but also may make surgery unnecessary. For many reasons retrospective studies are of limited relevance for this decision. Sometimes surgical treatment is not available immediately; at other times deteriorating patients are referred to surgery too late after failing medical therapy. The relative infrequency of treatment opportunities in massive PE, mitigating factors, and the lack of clear criteria for prescribing medical or surgical therapy leave the management of massive PE unsettled.

Better understanding of the condition and newer technology offer a reasonable, if untried, algorithm for dealing with "probable massive pulmonary embolism with life-threatening hemodynamic instability" in hospitalized patients. In otherwise healthy patients in whom surgery poses little risk or morbidity, emergency thromboembolectomy with preoperative confirmation of the diagnosis in the operating room by transesophageal echocardiography offers the best chance of survival, even though an occasional patient may undergo an unnecessary operation. When surgery is not immediately available or in patients who may not be surgical candidates, or in whom an alternate diagnosis seems more likely, emergency extracorporeal life support (ECLS) using peripheral cannulation is an attractive alternative.[72,73] In prepared institutions ECLS can be instituted rapidly outside the operating room. ECLS compensates for acute cor pulmonale and hypoxia and sustains the circulation until the clot partially lyses, pulmonary vascular resistance falls, and pulmonary blood flow becomes adequate.

Emergency Pulmonary Thromboembolectomy

Emergency pulmonary thromboembolectomy is indicated for suitable patients with life-threatening circulatory insufficiency as discussed earlier, but should not be done without a definitive diagnosis. A clinical diagnosis of PE is often wrong.[47,58,66,67] If a patient has been taken directly to the operating room without a definitive diagnosis, transesophageal echocardiography and color Doppler mapping can confirm or refute the diagnosis in the operating room. Transesophageal echocardiography permits good assessment of right ventricular volume, contractility, and tricuspid regurgitation, which are strongly associated with massive PE and acute cor pulmonale.[68] Echocardiographic detection of a large clot trapped within the right atrium or ventricle in a hemodynamically compromised patient with massive acute PE is another indication for emergency pulmonary thromboembolectomy.[74,75,77]

A midline sternotomy incision is used. The ascending aorta and both cavae are cannulated after full heparinization, and cardiopulmonary bypass is initiated. The heart may be electrically fibrillated or arrested with cold cardioplegic solution. Significant hypothermia may not be necessary since only a short period of complete bypass is needed. The main pulmonary artery is then opened 1 to 2 cm downstream to the valve, and the incision is extended into the proximal left pulmonary artery. Forceps and suction catheters remove the clot from the left pulmonary artery and behind the aorta to the right pulmonary artery. The right pulmonary artery can also be exposed and opened between the aorta and superior vena cava to allow better exposure in the distal segments, if necessary. If a sterile pediatric bronchoscope is available, the surgeon can use this instrument to locate and remove thrombi in tertiary and quaternary pulmonary vessels. Alternatively, pleural spaces are entered, and each lung is gently compressed to dislodge small clots into larger vessels and the clots are suctioned out. The pulmonary arteriotomy is then closed with a fine running suture (e.g., 6-0 polypropylene). After restarting the heart, the patient is weaned from bypass,

decannulated, and closed. Greenfield recommends placement of an inferior vena caval filter before closing the chest.[10,69,70,79] European surgeons generally clip the intrapericardial vena cava at the end of pulmonary thromboembolectomy to prevent migration of large clots into the pulmonary circulation.[77] This clip increases venous pressure and stagnant flow in the lower half of the body and causes considerable morbidity in over 60% of patients.[70,74,77]

Although recurrent PE is always a threat, the likelihood of this during the immediate postoperative period is statistically small. We feel that the diagnosis of proximal DVT, knowledge of risk factors, and efficacy of anticoagulant therapy permit brief deferral of the decision to place a filter. Anticoagulation for 6 months is recommended for most patients with PE, but an inferior vena caval filter is recommended for patients with contraindications to anticoagulation or with recurrent PE, or those who will require pulmonary thromboendarterectomy. The cone-shaped Greenfield filter is most widely used and is associated with a lifetime recurrent embolism rate of 5% and has 97% patency rate.[71]

Extracorporeal Life Support

The wider availability of long-term extracorporeal perfusion (termed extracorporeal life support, or ECLS) using peripheral vessel cannulation to stabilize the circulation offers a compromise position since most massive pulmonary emboli will dissolve in time. ECLS can be implemented outside the operating room, but extensive preparations must be made before ECLS is available for emergency therapy. An emergency team must be assembled and trained, and needed equipment and supplies must be collected. ECLS can be implemented within 15 to 30 minutes by an equipped team of trained personnel.[72]

The femoral vein and artery are rapidly cannulated under sterile conditions using local anesthesia. If the circulation is reasonably stable, both vessels can be cannulated over guidewires inserted via no. 16 angiographic needle punctures. A small skin incision is made to accommodate the cannulae, and after giving a bolus of heparin (1 mg/kg) first dilators and then cannulas are inserted. Alternatively, surgical cutdown and then cannulation using guidewires under direct vision can expose both femoral vessels. If pulses are absent or weak, a cutdown is usually faster; however, since patients need heparin and possibly fibrinolytic drugs, a minimal wound is preferred. The tip of the venous catheter is advanced into the right atrium to obtain flow rates of 2.5 to 4 L/min using an emergency pump-oxygenator circuit primed with crystalloid.[73] The perfusion circuit consists of a small venous reservoir with intravenous access tubes, a centrifugal pump, and membrane oxygenator. An arterial filter is not needed; and an electromagnetic flowmeter is usually placed on the arterial line. During ECLS, heparin is infused to maintain activated clotting times between 150 and 180 seconds. Activated clotting times are measured every 30 minutes initially and every hour thereafter.

Although the groin wound is minimal, some bleeding occurs. Usually the amount of bleeding is small, but it is often persistent. Theoretically, the addition of thrombolytic drugs accelerates clot lysis and may decrease the duration of ECLS; however, these drugs are likely to increase bleeding complications and are not needed once the circulation is stabilized. An alternative is to give low-dose fibrinolytic therapy directly into the thrombus via a pulmonary arterial catheter. ECLS should not be needed beyond a few hours or 1 to 2 days since clot lysis proceeds rapidly. Once pulmonary vascular resistance is adequately reduced, femoral cannulation sites should be closed surgically because of the need for heparin and long-term anticoagulation. ECLS should be discontinued in the operating room since vessels will need to be sutured closed because of the need for heparin and long-term anticoagulation.

Postoperative Care

Postoperative care is no different from care for other patients who require open cardiac surgery. Cardiac output is maintained by pharmacologic means and is usually adequate if the patient can be weaned from cardiopulmonary bypass and has not suffered irreversible myocardial damage. Reperfusion pulmonary edema is not a problem, but renal failure and ischemic brain damage from preoperative periods of inadequate circulation may become apparent. Antibiotics are required, particularly if sterile conditions were compromised in the resuscitation effort.

Results

Mortality rates for emergency pulmonary thromboembolectomy vary widely between 40 and 92%.[66,70,74–77] Results are best if cardiopulmonary bypass is used to support the circulation during pulmonary arteriotomy.[75] The eventual outcome depends largely on the preoperative condition and circulatory status of the patient. If cardiac arrest occurs and external massage cannot be stopped without ECLS, mortality ranges between 45 and 75%, and without cardiac arrest mortality ranges between 8 and 36%.[74,70,77] ECLS instituted during cardiac resuscitation is associated with survival rates between 43 and 56%.[74,66] Primary causes of death include brain damage, cardiac failure, bleeding complications, and sepsis. Recurrent embolism is uncommon,[70,78] but approximately 80% of survivors maintain normal pulmonary arterial pressures and exercise tolerance. In these patients postoperative angiograms are normal or show less than 10% obstructed vessels. A minority of patients have 40 to 50% of pulmonary vessels obstructed and have significantly reduced exercise tolerance and pulmonary function.[78]

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Incidence

The incidence of pulmonary hypertension caused by chronic PE is even more difficult to determine than that of acute PE.

There are more than 500,000 survivors per year of acute symptomatic episodes of acute pulmonary embolization.[79,80] The incidence of chronic thrombotic occlusion in the population depends on what percentage of patients fail to resolve acute embolic material. One estimate is that chronic thromboembolic disease develops in only 0.5% of patients with a clinically recognized acute PE.[79] If these figures are correct and counting only patients with symptomatic acute pulmonary emboli, approximately 2500 individuals would progress to chronic thromboembolic pulmonary hypertension in the United States each year. However, because most patients diagnosed with chronic thromboembolic disease have no antecedent history of acute embolism, the true incidence of this disorder is probably much higher, and in the range of 5 to 10 times our estimate.

Regardless of the exact incidence or the circumstances, acute embolism and its chronic relation, fixed chronic thromboembolic occlusive disease, clearly are much more common than generally appreciated and are seriously underdiagnosed. Houk and colleagues[81] in 1963 reviewed 240 reported cases of chronic thromboembolic obstruction of major pulmonary arteries but found that only 6 cases had been diagnosed correctly before death. Calculations extrapolated from mortality rates and the random incidence of major thrombotic occlusion found at autopsy support a postulate that more than 100,000 people in the United States currently have pulmonary hypertension that could be relieved by surgery.

Pathology and Pathogenesis

Although most individuals with chronic pulmonary thromboembolic disease are unaware of a past thromboembolic event and give no history of DVT, the origin of most cases of unresolved pulmonary emboli is from acute embolic episodes. Why some patients have unresolved emboli is not certain, but a variety of factors must play a role, alone or in combination.

The volume of acute embolic material may simply overwhelm the lytic mechanisms. The total occlusion of a major arterial branch may prevent lytic material from reaching, and therefore dissolving, the embolus completely. Repetitive emboli may not be able to be resolved. The emboli may be made of substances that cannot be resolved by normal mechanisms (already well-organized fibrous thrombus, fat, or tumor). The lytic mechanisms themselves may be abnormal, or some patients may actually have a propensity for thrombus or a hypercoagulable state. After the clot becomes wedged in the pulmonary artery, one of two processes occurs:[82]

1. The organization of the clot proceeds to canalization, producing multiple small endothelialized channels separated by fibrous septa (i.e., bands and webs), or
2. Complete fibrous organization of the fibrin clot without canalization may result, leading to a solid mass of dense fibrous connective tissue totally obstructing the arterial lumen.

In addition, there are other special circumstances. Chronic indwelling central venous catheters and pacemaker leads are sometimes associated with pulmonary emboli. More rare causes include tumor emboli; tumor fragments from stomach, breast, and kidney malignancies have also been demonstrated to cause chronic pulmonary arterial occlusion. Right atrial myxomas may also fragment and embolize.

As previously described and discussed, in addition to the embolic material, a propensity for thrombosis or a hypercoagulable state may be present in a few patients. This abnormality may result in spontaneous thrombosis within the pulmonary vascular bed, encourage embolization, or be responsible for proximal propagation of thrombus after an embolus. But, whatever the predisposing factors to residual thrombus within the vessels, the final genesis of the resultant pulmonary vascular hypertension may be complex. With the passage of time, the increased pressure and flow as a result of redirected pulmonary blood flow in the previously normal pulmonary vascular bed can create a vasculopathy in the small precapillary blood vessels similar to Eisenmenger syndrome.

Factors other than the simple hemodynamic consequences of redirected blood flow are probably also involved in this process. For example, after a pneumonectomy, 100% of the right ventricular output flows to one lung, yet little increase in pulmonary pressure occurs, even with follow-up to 11 years.[83] In patients with thromboembolic disease, however, we frequently detect pulmonary hypertension even when less than 50% of the vascular bed is occluded by thrombus. It thus appears that sympathetic neural connections, hormonal changes, or both, might initiate pulmonary hypertension in the initially unaffected pulmonary vascular bed. This process can occur with the initial occlusion either being in the same or the contralateral lung.

Regardless of the cause, the evolution of pulmonary hypertension as a result of changes in the previously unobstructed bed is serious, because this process may lead to an inoperable situation. Consequently, with our accumulating experience in patients with thrombotic pulmonary hypertension, we have increasingly been inclined toward early operation so as to avoid these changes.

Clinical Presentation

Chronic thromboembolic pulmonary hypertension is an uncommon and frequently underrecognized, but treatable cause of pulmonary hypertension. There are no signs or symptoms specific for chronic thromboembolism. The most common symptom associated with thromboembolic pulmonary hypertension, as with all other causes of pulmonary hypertension, is exertional dyspnea. This dyspnea is out of proportion to any abnormalities found on clinical examination. Like complaints of easy fatigability, dyspnea that initially occurs only with exertion is often attributed to anxiety or being "out of shape." Syncope, or presyncope (light-headedness during exertion) is another common symptom in pulmonary hypertension. Generally, it occurs in

patients with more advanced disease and higher pulmonary arterial pressures.

Nonspecific chest pains or tightness occur in approximately 50% of patients with more severe pulmonary hypertension. Hemoptysis can occur in all forms of pulmonary hypertension and probably results from abnormally dilated vessels distended by increased intravascular pressures. Peripheral edema, early satiety, and epigastric or right upper quadrant fullness or discomfort may develop as the right heart fails (cor pulmonale). Some patients with chronic pulmonary thromboembolic disease present after a small acute pulmonary embolus that may produce acute symptoms of right heart failure. A careful history brings out symptoms of dyspnea on minimal exertion, easy fatigability, diminishing activities, and episodes of angina-like pain or light-headedness. Further examination reveals the signs of pulmonary hypertension.

The physical signs of pulmonary hypertension are the same no matter what the underlying pathophysiology. Initially the jugular venous pulse is characterized by a large A wave. As the right heart fails, the V wave becomes predominant. The right ventricle is usually palpable near the lower left sternal border, and pulmonary valve closure may be audible in the second intercostal space. Occasional patients with advanced disease are hypoxic and slightly cyanotic. Clubbing is an uncommon finding.

The second heart sound is often narrowly split and varies normally with respiration; P_2 is accentuated. A sharp systolic ejection click may be heard over the pulmonary artery. As the right heart fails, a right atrial gallop is usually present, and tricuspid insufficiency develops. Because of the large pressure gradient across the tricuspid valve in pulmonary hypertension, the murmur is high pitched and may not exhibit respiratory variation. These findings are quite different from those usually observed in tricuspid valvular disease. A murmur of pulmonic regurgitation may also be detected.

Pulmonary function tests reveal minimal changes in lung volume and ventilation; patients generally have normal or slightly restricted pulmonary mechanics. Diffusing capacity is often reduced and may be the only abnormality on pulmonary function testing. Pulmonary arterial pressures are elevated and suprasystemic pulmonary pressures are not uncommon. Resting cardiac outputs are lower than the normal range, and pulmonary arterial oxygen saturations are reduced. Most patients are hypoxic; room air arterial oxygen tension ranges between 50 and 83 torr, the average being 65 torr.[84] CO_2 tension is slightly reduced and is compensated by reduced bicarbonate. Dead space ventilation is increased. Ventilation-perfusion studies show moderate mismatch with some heterogeneity among various respirator units within the lung and correlate poorly with the degree of pulmonary obstruction.[85]

Diagnosis

To ensure diagnosis in patients with chronic pulmonary thromboembolism, a standardized evaluation is recommended for all patients who present with unexplained pulmonary hypertension. This work-up includes a chest radiograph, which may show either apparent vessel cutoffs of the lobar or segmental pulmonary arteries, or regions of oligemia suggesting vascular occlusion. Central pulmonary arteries are enlarged, and the right ventricle may also be enlarged without enlargement of the left atrium or ventricle (Fig. 56-5). However, one should keep in mind that despite these classic findings, a large number of patients might present with a relatively normal chest radiograph, even in the setting of high degrees of pulmonary hypertension. The electrocardiogram demonstrates findings of right ventricular hypertrophy (right-axis deviation and a dominant R wave in V_1). Pulmonary function tests are necessary to exclude obstructive or restrictive intrinsic pulmonary parenchymal disease as the cause of pulmonary hypertension.

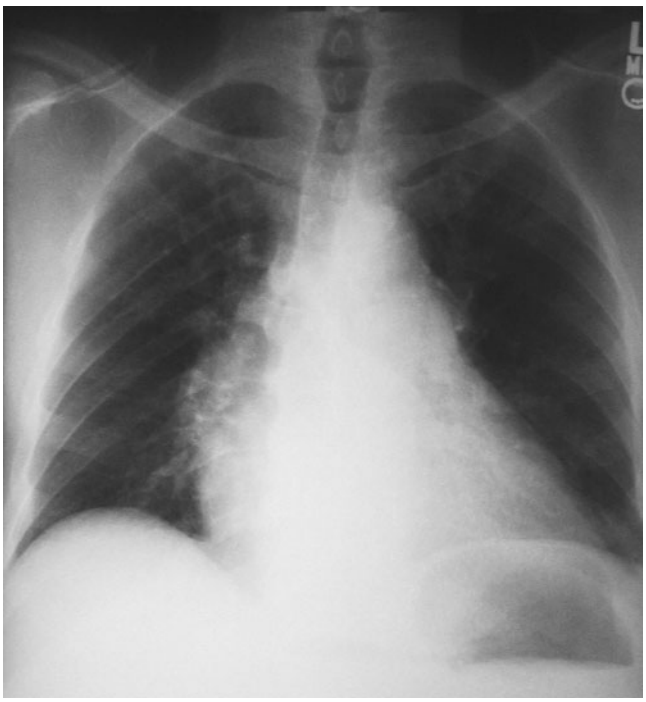

Figure 56-5. Chest radiograph of a patient with chronic thromboembolic pulmonary disease and evidence of pulmonary hypertension. Note the enlarged right atrium and right ventricle, disparity of size between the left and right pulmonary arteries, and the hypoperfusion in several areas of the lung fields.

The ventilation-perfusion lung scan is the essential test for establishing the diagnosis of unresolved pulmonary thromboembolism. An entirely normal lung scan excludes the diagnosis of both acute or chronic unresolved thromboembolism. The usual lung scan pattern in most patients with pulmonary hypertension either is relatively normal or shows a diffuse nonuniform perfusion.[84,85–87] When subsegmental or larger perfusion defects are noted on the scan, even when matched with ventilatory defects, pulmonary angiography is appropriate to confirm or rule out thromboembolic disease.

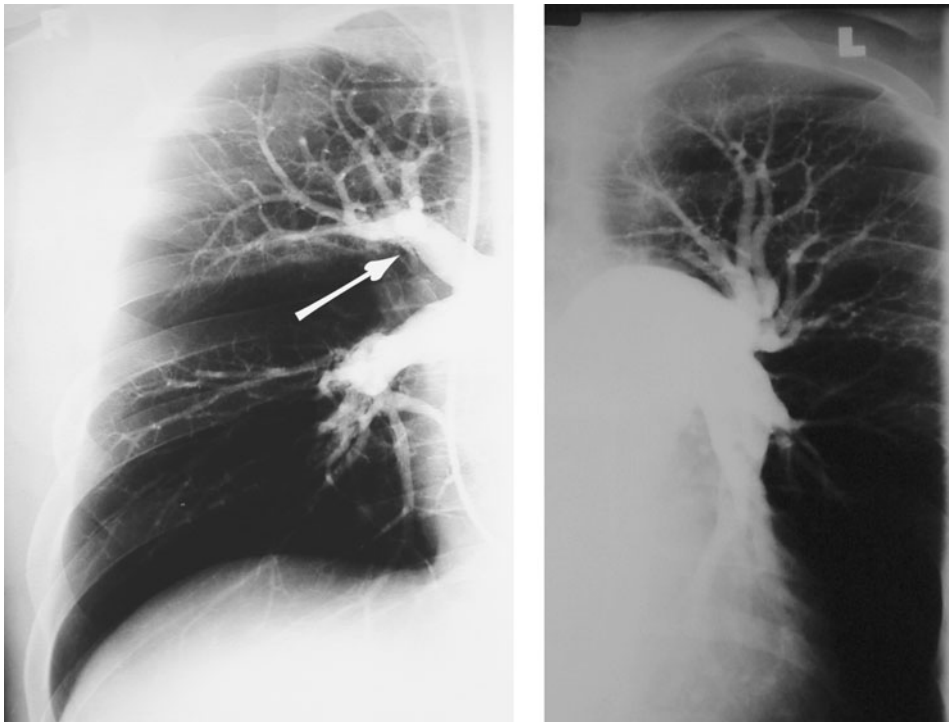

Figure 56-6. Right and left pulmonary angiograms demonstrate enlarged pulmonary arteries, poststenotic dilatation of vessels, lack of filling to the periphery in many areas, and abrupt cutoffs of branches. The arrow points to intraluminal filling defects representative of a web or band.

Currently, pulmonary angiography remains the gold standard for diagnosis of CTEPH. Organized thromboembolic lesions do not have the appearance of the intravascular filling defects seen with acute pulmonary emboli, and experience is essential for the proper interpretation of pulmonary angiograms in patients with unresolved, chronic embolic disease. Organized thrombi appear as unusual filling defects, webs, or bands, or completely thrombosed vessels that may resemble congenital absence of the vessel[87] (Fig. 56-6). Organized material along a vascular wall of a recanalized vessel produces a scalloped or serrated luminal edge. Because of both vessel-wall thickening and dilatation of proximal vessels, the contrast-filled lumen may appear relatively normal in diameter. Distal vessels demonstrate the rapid tapering and pruning characteristic of pulmonary hypertension (see Fig. 56-6).

Although some risk remains, the benefit of establishing the presence of a treatable cause of the hypertension far outweighs the small risk, and pulmonary angiography should be performed whenever there is a possibility that chronic thromboembolism is the etiology of pulmonary hypertension. Historically, angiography in those with pulmonary hypertension has been thought to carry disproportionate risk. We have found that not to be the case, and at our institution pulmonary angiographies are performed daily in these patients with minimal associated risks. Several thousand angiograms in pulmonary hypertensive patients have now been performed at our institution without mortality.

In addition to pulmonary angiography, patients over 40 undergo coronary arteriography and other cardiac investigation as necessary. If significant disease is found, additional cardiac surgery is performed at the time of pulmonary thromboendarterectomy.

In approximately 15% of cases, the differential diagnosis between primary pulmonary hypertension and distal and small-vessel pulmonary thromboembolic disease remains unclear and hard to establish. In these patients, pulmonary angioscopy is often helpful. The pulmonary angioscope is a fiberoptic telescope that is placed through a central line into the pulmonary artery. The tip contains a balloon that is then filled with saline and pushed against the vessel wall. A bloodless field can thus be obtained to view the pulmonary artery wall. The classic appearance of chronic pulmonary thromboembolic disease by angioscopy consists of intimal thickening, with intimal irregularity and scarring, and webs across small vessels. These webs are thought to be the residue of resolved occluding thrombi of small vessels, but are important diagnostic findings. The presence of embolic disease, occlusion of vessels, or the presence of thrombotic material is diagnostic.

Medical Treatment

Chronic anticoagulation represents the mainstay of the medical regimen. Anticoagulation is primarily used to prevent future embolic episodes, but it also serves to limit the development of thrombus in regions of low flow within the pulmonary vasculature. Inferior vena caval filters are used routinely to prevent recurrent embolization. If caval filtration and anticoagulation fail to prevent recurrent emboli, immediate thrombolysis

may be beneficial, but lytic agents are incapable of altering the chronic component of the disease.

Right ventricular failure is treated with diuretics and vasodilators, and although some improvement may result, the effect is generally transient because the failure is due to a mechanical obstruction and will not resolve until the obstruction is removed. Similarly, the prognosis is unaffected by medical therapy,[88,89] which should be regarded as only supportive. Because of the bronchial circulation, pulmonary embolization seldom results in tissue necrosis. Surgical endarterectomy therefore will allow distal pulmonary tissue to be used once more in gas exchange.

The only other surgical option for these patients is transplantation. However, we consider transplantation not to be appropriate for this disease because of the mortality and morbidity rates of patients on the waiting list, the higher risk of the operation, and the lower survival rate (approximately 80% at 1 year at experienced centers for transplantation versus 95% for pulmonary endarterectomy). Furthermore, pulmonary endarterectomy appears to be permanently curative, and the continuing risk of rejection and immunosuppression are absent.

Natural History

The natural history of chronic thromboembolic pulmonary hypertension is dismal, and nearly all patients die of progressive right heart failure.[11] Because of the insidious onset, the diagnosis is usually made relatively late in the progression of the disease when dyspnea and/or early symptoms of right heart failure develop and pulmonary hypertension is severe (>40 mm Hg mean). In the series of Riedel and associates of 13 patients, 9 died a mean of 28 months after the diagnosis of right heart failure.[11] Seven of the 13 had recurrent episodes of fresh emboli demonstrated by new perfusion defects or by autopsy. The severity of pulmonary hypertension at the time of diagnosis inversely correlates with duration of survival.[11]

Pulmonary Thromboendarterectomy

Although there were previous attempts, Allison and colleagues[90] did the first successful pulmonary "thromboendarterectomy" through a sternotomy using surface hypothermia, but only fresh clots were removed. The operation was 12 days after a thigh injury that led to PE, and there was no endarterectomy. Since then, there have been many occasional reports of the surgical treatment of chronic pulmonary thromboembolism,[91–94] but most of the surgical experience in pulmonary endarterectomy has been reported from the University of California, San Diego (UCSD) Medical Center. Braunwald commenced the UCSD experience with this operation in 1970, which now totals more than 2000 cases. The operation described below, using deep hypothermia and circulatory arrest, is the standard procedure.

Indications

When the diagnosis of thromboembolic pulmonary hypertension has been firmly established, the decision for operation is made based on the severity of symptoms and the general condition of the patient. Early in the pulmonary endarterectomy experience, Moser and colleagues[92] pointed out that there were three major reasons for considering thromboendarterectomy: hemodynamic, alveolorespiratory, and prophylactic. The hemodynamic goal is to prevent or ameliorate right ventricular compromise caused by pulmonary hypertension. The respiratory objective is to improve respiratory function by the removal of a large ventilated but unperfused physiologic dead space, regardless of the severity of pulmonary hypertension. The prophylactic goal is to prevent progressive right ventricular dysfunction or retrograde extension of the obstruction, which might result in further cardiorespiratory deterioration or death.[92] Our subsequent experience has added another prophylactic goal: the prevention of secondary arteriopathic changes in the remaining patent vessels.

Most patients who undergo surgery are classified as New York Heart Association (NYHA) class III or IV. The ages of the patients in our series have ranged from 7 to 85 years. A typical patient will have a severely elevated pulmonary vascular resistance (PVR) level at rest, the absence of significant comorbid disease unrelated to right heart failure, and the appearance of chronic thrombi on angiogram that appear to be relatively in balance with the measured PVR level. Exceptions to this general rule, of course, occur.

Although most patients have a PVR level in the range of 800 dynes/sec/cm^{-5} and pulmonary artery pressures less than systemic, the hypertrophy of the right ventricle that occurs over time makes pulmonary hypertension to suprasystemic levels possible. Therefore many patients (approximately 20% in our practice) have a level of PVR in excess of 1000 dynes/sec/cm^{-5} and suprasystemic pulmonary artery pressures. There is no upper limit of PVR level, pulmonary artery pressure, or degree of right ventricular dysfunction that excludes patients from operation.

We have become increasingly aware of the changes that can occur in the remaining patent (unaffected by clot) pulmonary vascular bed subjected to the higher pressures and flow that result from obstruction in other areas. Therefore, with the increasing experience and safety of the operation, we are tending to offer surgery to symptomatic patients whenever the angiogram demonstrates thromboembolic disease. A rare patient might have a PVR level that is normal at rest, although elevated with minimal exercise. This is usually a young patient with total unilateral pulmonary artery occlusion and unacceptable exertional dyspnea because of an elevation in dead space ventilation. Operation in this circumstance is performed not only to reperfuse lung tissue, but to re-establish a more normal ventilation-perfusion relationship (thereby reducing minute ventilatory requirements during rest and exercise), and also to preserve the integrity of the contralateral circulation and prevent chronic arterial changes associated with long-term exposure to pulmonary hypertension.

If not previously implanted, an inferior vena caval filter is routinely placed several days in advance of the operation.

Operation

PRINCIPLES: There are several guiding principles for the operation. Surgical treatment and endarterectomy must be bilateral, because this is a bilateral disease in the vast majority of our patients. Furthermore, for pulmonary hypertension to be a major factor, both pulmonary vasculatures must be substantially involved. The only reasonable approach to both pulmonary arteries is through a median sternotomy incision. Historically, there were many reports of unilateral operation, and occasionally this is still performed in inexperienced centers through a thoracotomy. However, the unilateral approach ignores the disease on the contralateral side, subjects the patient to hemodynamic jeopardy during the clamping of the pulmonary artery, does not allow good visibility because of the continued presence of bronchial blood flow, and exposes the patient to a repeat operation on the contralateral side. In addition, collateral channels develop in chronic thrombotic hypertension, not only through the bronchial arteries but also from diaphragmatic, intercostal, and pleural vessels. The dissection of the lung in the pleural space via a thoracotomy incision can therefore be extremely bloody. The median sternotomy incision, apart from providing bilateral access, avoids entry into the pleural cavities and allows the ready institution of cardiopulmonary bypass.

Cardiopulmonary bypass is essential to ensure cardiovascular stability when the operation is performed and to cool the patient to allow circulatory arrest. Excellent visibility is required, in a bloodless field, to define an adequate endarterectomy plane and to then follow the pulmonary endarterectomy specimen deep into the subsegmental vessels. Because of the copious bronchial blood flow usually present in these cases, periods of circulatory arrest are necessary to ensure perfect visibility. Again, there have been sporadic reports of the performance of this operation without circulatory arrest. However, it should be emphasized that although endarterectomy is possible without circulatory arrest, a complete endarterectomy is not. We always initiate the procedure without circulatory arrest, and a variable amount of dissection is possible before the circulation is stopped, but never complete dissection. The circulatory arrest periods are limited to 20 minutes, with restoration of flow between each arrest. With experience, the endarterectomy usually can be performed with a single period of circulatory arrest on each side.

A true endarterectomy in the plane of the media must be accomplished. It is essential to appreciate that the removal of visible thrombus is largely incidental to this operation. Indeed, in most patients, no free thrombus is present, and on initial direct examination, the pulmonary vascular bed may appear normal. The early literature on this procedure indicates that thrombectomy was often performed without endarterectomy, and in these cases the pulmonary artery pressures did not improve, often with the resultant death of the patient.

PREPARATION AND ANESTHETIC CONSIDERATIONS: Much of the preoperative preparation is common to any open-heart procedure. Routine monitoring for anesthetic induction includes a surface electrocardiogram, cutaneous oximetry, and radial and pulmonary artery pressures. After anesthetic induction a femoral artery catheter, in addition to a radial arterial line, is also placed. This provides more accurate measurements during rewarming and on discontinuation of cardiopulmonary bypass because of the peripheral vasoconstriction that occurs after hypothermic circulatory arrest. It is generally removed in the intensive care unit when the two readings correlate.

Electroencephalographic recording is performed to ensure the absence of cerebral activity before circulatory arrest is induced. The patient's head is enveloped in a cooling jacket, and cerebral cooling is begun after the initiation of bypass. Temperature measurements are made of the esophagus, tympanic membrane, urinary catheter, rectum, and blood (through the Swan-Ganz catheter). If the patient's condition is stable after the induction of anesthesia, up to 500 mL of autologous whole blood is withdrawn for later use, and the volume deficit is replaced with crystalloid solution.

SURGICAL TECHNIQUE: After a median sternotomy incision is made, the pericardium is incised longitudinally and attached to the wound edges. Typically the right heart is enlarged, with a tense right atrium and a variable degree of tricuspid regurgitation. There is usually severe right ventricular hypertrophy, and with critical degrees of obstruction, the patient's condition may become unstable with the manipulation of the heart.

Anticoagulation is achieved with the use of beef-lung heparin sodium (400 U/kg, intravenously) administered to prolong the activated clotting time beyond 400 s. Full cardiopulmonary bypass is instituted with high ascending aortic cannulation and two caval cannulas. These cannulas must be inserted into the superior and inferior vena cavae sufficiently to enable subsequent opening of the right atrium. The heart is emptied on bypass, and a temporary pulmonary artery vent is placed in the midline of the main pulmonary artery 1 cm distal to the pulmonary valve. This will mark the beginning of the left pulmonary arteriotomy.

When cardiopulmonary bypass is initiated, surface cooling with both the head jacket and the cooling blanket is begun. The blood is cooled with the pump-oxygenator. During cooling a 10°C gradient between arterial blood and bladder or rectal temperature is maintained.[93] Cooling generally takes 45 minutes to an hour. When ventricular fibrillation occurs, an additional vent is placed in the left atrium through the right superior pulmonary vein. This prevents atrial and ventricular distension from the large amount of bronchial arterial blood flow that is common with these patients.

It is most convenient for the primary surgeon to stand initially on the patient's left side. During the cooling period, some preliminary dissection can be performed, with full mobilization of the right pulmonary artery from the ascending aorta. The superior vena cava is also fully mobilized. The approach to the right pulmonary artery is made medial, not

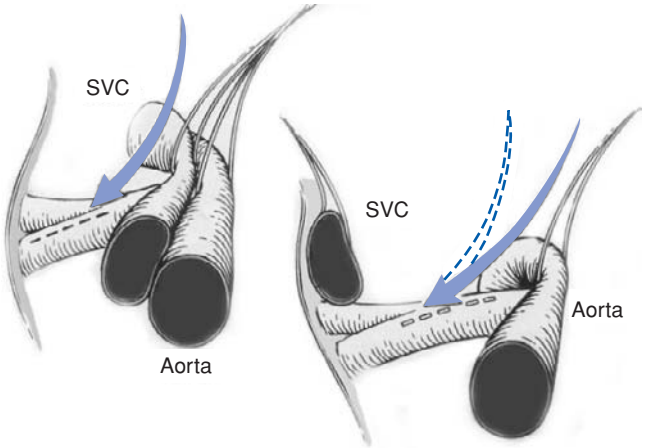

Figure 56-7. Recommended surgical approach on the right side. This approach, medial to the superior vena cava (SVC), between the superior vena cava and aorta, provides a direct view into the right pulmonary artery. Note that an approach on the lateral side of the superior vena cava will only provide a restricted view and should be avoided.

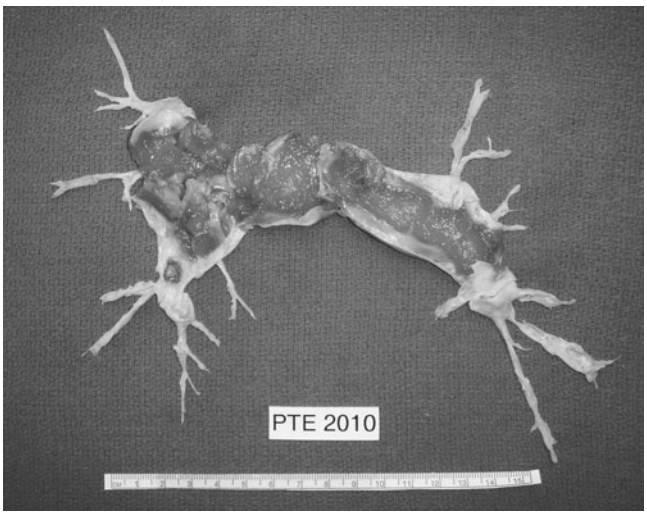

Figure 56-8. Surgical specimen removed from a patient showing evidence of some fresh and some old thrombus in the main and both right and left pulmonary arteries. Note that simple removal of the gross disease initially encountered upon pulmonary arteriotomy will not be therapeutic, and any meaningful outcome involves a full endarterectomy into all the distal segments.

lateral, to the superior vena cava. All dissection of the pulmonary arteries takes place intrapericardially, and neither pleural cavity should be entered. An incision is then made in the right pulmonary artery from beneath the ascending aorta out under the superior vena cava and entering the lower lobe branch of the pulmonary artery just after the takeoff of the middle lobe artery (Fig. 56-7). It is important that the incision stays in the center of the vessel and continues into the lower, rather than the middle lobe artery.

Any loose thrombus, if present, is now removed. This is necessary to obtain good visualization. It is most important to recognize, however, that first, an embolectomy without subsequent endarterectomy is quite ineffective, and second, that in most patients with chronic thromboembolic hypertension, direct examination of the pulmonary vascular bed at operation generally shows no obvious embolic material. Therefore, to the inexperienced or cursory glance, the pulmonary vascular bed may well appear normal even in patients with severe chronic embolic pulmonary hypertension.

If the bronchial circulation is not excessive, the endarterectomy plane can be found during this early dissection. However, although a small amount of dissection can be performed before the initiation of circulatory arrest, it is unwise to proceed unless perfect visibility is obtained because the development of a correct plane is essential.

There are four broad types of pulmonary occlusive disease related to thrombus that can be appreciated, and we use the following classification:[87,94] type I disease (approximately 10% of cases of thromboembolic pulmonary hypertension; Fig. 56-8) refers to the situation in which major vessel clot is present and readily visible upon opening the pulmonary arteries. As mentioned earlier, all central thrombotic material has to be completely removed before the endarterectomy. In type II disease (approximately 70% of cases; Fig. 56-9), no major vessel thrombus can be appreciated. In these cases only thickened intima can be seen, occasionally with webs, and the endarterectomy plane is raised in the main, lobar, or segmental vessels. Type III disease (approximately 20% of cases; Fig. 56-10) presents the most challenging surgical situation. The disease is very distal and confined to the segmental and subsegmental branches. No occlusion of vessels can be seen initially. The endarterectomy plane must be carefully and painstakingly raised in each segmental and subsegmental branch. Type III disease is most often associated with presumed repetitive thrombi from indwelling catheters (such as pacemaker wires) or ventriculoatrial shunts. Type IV disease (Fig. 56-11) does not represent primary thromboembolic pulmonary hypertension and is inoperable. In this entity there is intrinsic small-vessel disease, although secondary thrombus may occur as a result of stasis. Small-vessel disease may be unrelated to thromboembolic events ("primary" pulmonary hypertension) or occur in relation to thromboembolic hypertension as a result of a high-flow or high-pressure state in previously unaffected vessels similar to the generation of Eisenmenger syndrome. We believe that there may also be sympathetic "cross-talk" from an affected contralateral side or stenotic areas in the same lung.

When the patient's temperature reaches 20°C, the aorta is cross-clamped and a single dose of cold cardioplegic solution (1 L) is administered. Additional myocardial protection is obtained by the use of a cooling jacket. The entire procedure is now performed with a single aortic cross-clamp period with no further administration of cardioplegic solution.

A modified cerebellar retractor is placed between the aorta and superior vena cava. When blood obscures direct

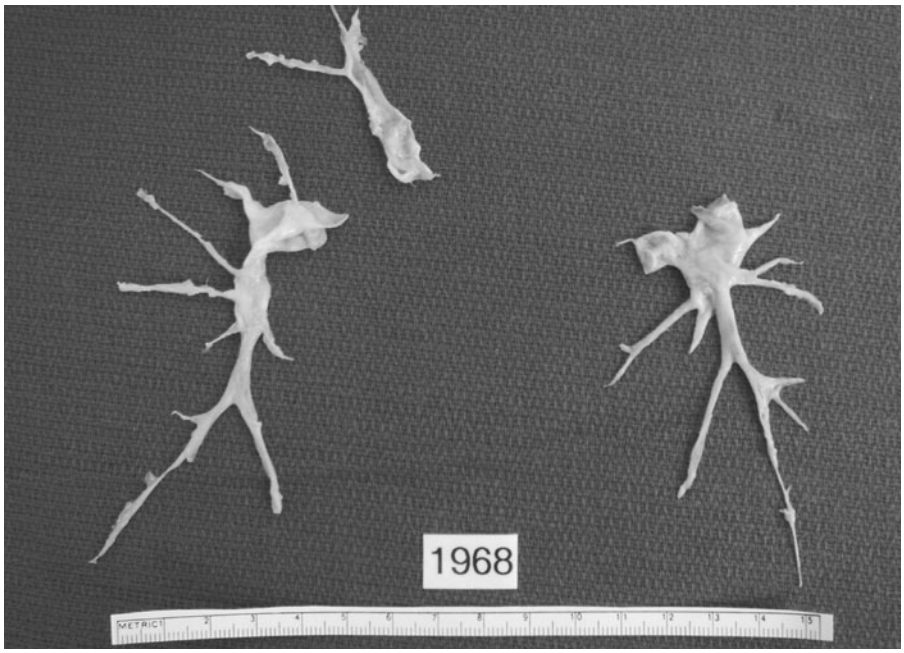

Figure 56-9. Specimen removed in a patient with type II disease. Both pulmonary arteries have evidence of chronic thromboembolic material. Note the distal tails of the specimen in each branch. Full resolution of pulmonary hypertension is dependent on complete removal of all the distal tails.

vision of the pulmonary vascular bed, thiopental is administered (500 mg to 1 g) until the electroencephalogram becomes isoelectric. Circulatory arrest is then initiated, and the patient undergoes exsanguination. All monitoring lines to the patient are turned off to prevent the aspiration of air. Snares are tightened around the cannulas in the superior and inferior vena cavae. It is rare that one 20-minute period for each side is exceeded. Although retrograde cerebral perfusion has been advocated for total circulatory arrest in other procedures, it is not helpful in this operation because it does

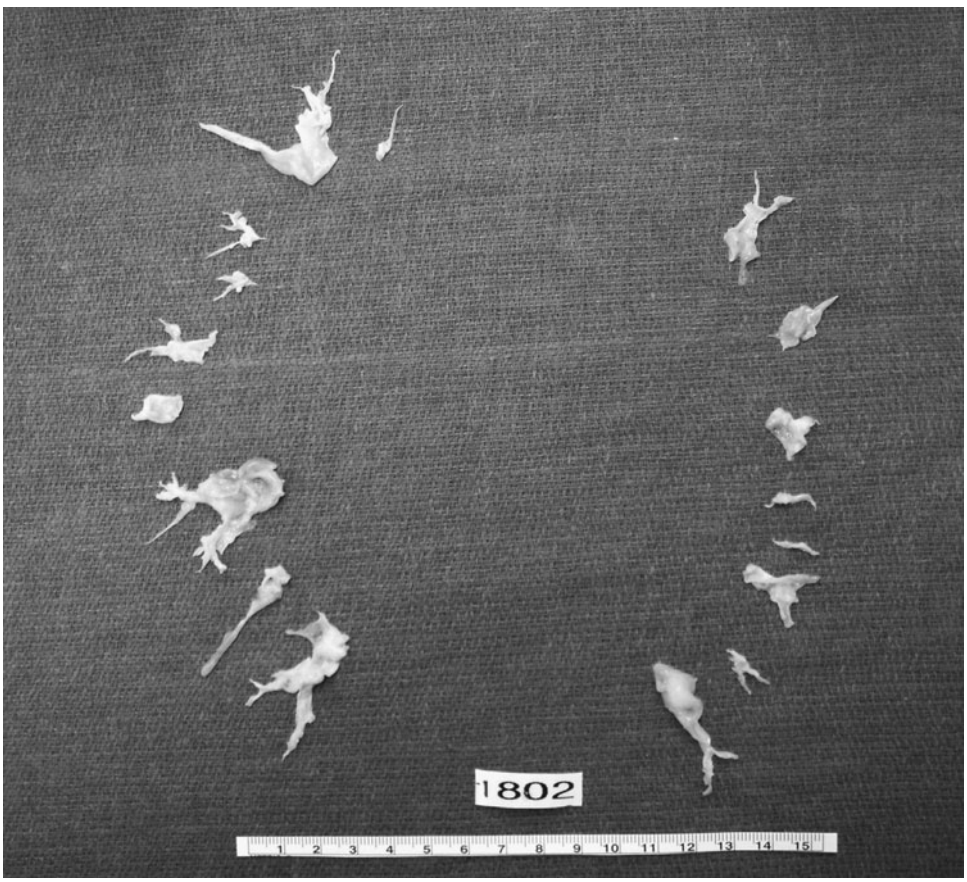

Figure 56-10. Specimen removed from a patient with type III disease. Note that the disease is distal, and the plane was raised at each segmental level.

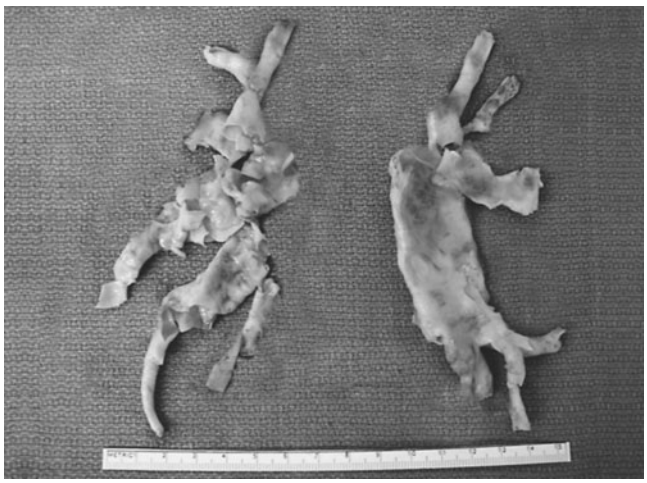

Figure 56-11. Note the absence of distal "tails" in this specimen removed from a patient with surgical classification type IV. All "tails" are replaced by "trousers." No clinical benefit was obtained from this procedure and the patient's postoperative hemodynamics were not improved, despite what appears to be an impressive endarterectomy specimen. The patient had primary pulmonary hypertension.

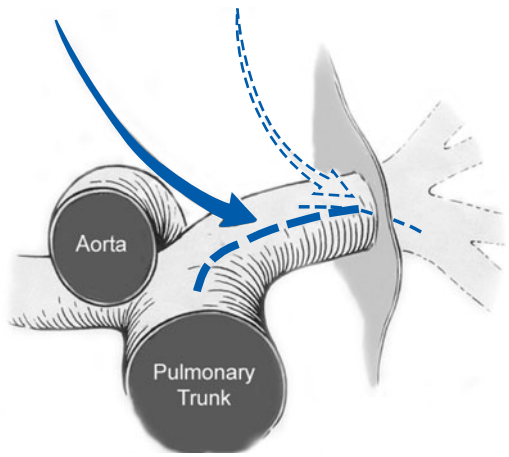

Figure 56-12. Surgical approach on the left side. The incision in the left pulmonary artery begins in the midpoint of the main pulmonary trunk, at the insertion site of the pulmonary artery vent. This incision provides better visibility than a more distal approach (dotted line and arrow). Care must be taken to avoid injury to the phrenic nerve.

not allow a completely bloodless field, and with the short arrest times that can be achieved with experience, it is not necessary.

Any residual loose thrombotic debris encountered is removed. Then a microtome knife is used to develop the endarterectomy plane posteriorly, because any inadvertent egress in this site could be repaired readily or simply left alone. Dissection in the correct plane is critical because if the plane is too deep the pulmonary artery may perforate, with fatal results, and if the dissection plane is not deep enough, inadequate amounts of the chronically thromboembolic material will be removed.

When the proper plane is entered, the layer will strip easily, and the material left with the outer layers of the pulmonary artery will appear somewhat yellow. The ideal layer is marked with a pearly white plane, which strips easily. There should be no residual yellow plaque. If the dissection is too deep, a reddish or pinkish color indicates that the adventitia has been reached. A more superficial plane should be sought immediately.

Once the plane is correctly developed, a full-thickness layer is left in the region of the incision to ease subsequent repair. The endarterectomy is then performed with an eversion technique. Because the vessel is everted and subsegmental branches are being worked on, a perforation here will become completely inaccessible and invisible later. This is why the absolute visualization in a completely bloodless field provided by circulatory arrest is essential. It is important that each subsegmental branch is followed and freed individually until it ends in a "tail," beyond which there is no further obstruction. Residual material should never be cut free; the entire specimen should "tail off" and come free spontaneously.

Once the right-sided endarterectomy is completed, circulation is restarted, and the arteriotomy is repaired with a continuous 6-0 polypropylene suture. The hemostatic nature of this closure is aided by the nature of the initial dissection, with the full thickness of the pulmonary artery being preserved immediately adjacent to the incision.

After the completion of the repair of the right arteriotomy, the surgeon moves to the patient's right side. The pulmonary vent catheter is withdrawn, and an arteriotomy is made from the site of the pulmonary vent hole laterally to the pericardial reflection, avoiding entry into the left pleural space. Additional lateral dissection does not enhance intraluminal visibility, may endanger the left phrenic nerve, and makes subsequent repair of the left pulmonary artery more difficult (Fig. 56-12).

The left-sided dissection is virtually analogous in all respects to that accomplished on the right. The duration of circulatory arrest intervals during the performance of the left-sided dissection is subject to the same restriction as the right.

After the completion of the endarterectomy, cardiopulmonary bypass is reinstituted and warming is commenced. Methylprednisolone (500 mg intravenously) and mannitol (12.5 g intravenously) are administered, and during warming a 10°C temperature gradient is maintained between the perfusate and body temperature, with a maximum perfusate temperature of 37°C. If the systemic vascular resistance level is high, nitroprusside is administered to promote vasodilatation and warming. The rewarming period generally takes approximately 90 to 120 minutes but varies according to the body mass of the patient.

When the left pulmonary arteriotomy has been repaired, the pulmonary artery vent is replaced at the top of the incision. The heart is retracted upward and to the left, and a posterior pericardial window is made between the

aorta and the left phrenic nerve. Alternatively, prior to closure a posterior pericardial drain can be placed and removed once drainage has substantially decreased.

The right atrium is then opened and examined. Any intra-atrial communication is closed. Although tricuspid valve regurgitation is invariable in these patients and is often severe, tricuspid valve repair is not performed. Right ventricular remodeling occurs within a few days, with the return of tricuspid competence. If other cardiac procedures are required, such as coronary artery or mitral or aortic valve surgery, these are conveniently performed during the systemic rewarming period. Myocardial cooling is discontinued once all cardiac procedures have been concluded. The left atrial vent is removed, and the vent site is repaired. All air is removed from the heart, and the aortic cross-clamp is removed.

When the patient has rewarmed, cardiopulmonary bypass is discontinued. Dopamine hydrochloride is routinely administered at renal doses, and other inotropic agents and vasodilators are titrated as necessary to sustain acceptable hemodynamics. The cardiac output is generally high, with a low systemic vascular resistance. Temporary atrial and ventricular epicardial pacing wires are placed.

Despite the duration of extracorporeal circulation, hemostasis is readily achieved, and the administration of platelets or coagulation factors is generally unnecessary. Wound closure is routine. A vigorous diuresis is usual for the next few hours, also a result of the previous systemic hypothermia.

Postoperative care

Meticulous postoperative management is essential to the success of this operation. All patients are mechanically ventilated for at least 24 hours, and all patients are subjected to a maintained diuresis with the goal of reaching the patient's preoperative weight within 24 hours. Although much of the postoperative care is common to more ordinary open-heart surgery patients, there are some important differences.

The electrocardiogram, systemic and pulmonary arterial and central venous pressures, temperature, urine output, arterial oxygen saturation, chest tube drainage, and fluid balance are monitored. A pulse oximeter is used to continuously monitor peripheral oxygen saturation. Management of cardiac arrhythmias and output and treatment of wound bleeding are identical to those used for other open-heart operations. In addition, a higher minute ventilation is often required early after the operation to compensate for the temporary metabolic acidosis that develops after the long period of circulatory arrest, hypothermia, and cardiopulmonary bypass. Tidal volumes higher than those normally recommended after cardiac surgery are therefore generally used to obtain optimal gas exchange. The maximum inspiratory pressure is maintained below 30 cm H_2O if possible.

Although we used to believe that prolonged sedation and ventilation were beneficial and led to less pulmonary edema, subsequent experience has shown this not to be so. Extubation should be performed on the first postoperative day, whenever possible.

DIURESIS: Patients have considerable positive fluid balance after operation. After hypothermic circulatory arrest, patients initiate an early spontaneous aggressive diuresis for unknown reasons, but this may in part be related to the increased cardiac output related to a now lower PVR level, and improved right ventricular function. This should be augmented with diuretics, however, with the aim of returning the patient to the preoperative fluid balance within 24 hours of operation. Because of the increased cardiac output, some degree of systemic hypotension is readily tolerated. Fluid administration is minimized, and the patient's hematocrit level should be maintained above 30% to increase oxygen-carrying capacity and mitigate against the pulmonary reperfusion phenomenon.

ARRHYTHMIAS: The development of atrial arrhythmias, at approximately 10%, is no more common than that encountered in patients who undergo other types of nonvalvular heart surgery. The small, inferior atrial incision, away from the conduction system of the atrium or its blood supply, may be helpful in the reduction of the incidence of these arrhythmias.

TRANSFUSION: Despite the requirement for the maintenance of an adequate hematocrit level, with careful blood conservation techniques used during operation, transfusion is required in only a few patients.

INFERIOR VENA CAVAL FILTER AND ANTICOAGULATION: A Greenfield filter is usually inserted before operation, to minimize recurrent pulmonary embolism after pulmonary endarterectomy. However, if this is not possible, it can also be inserted at the time of operation. If the device is to be placed at operation, radiopaque markers should be placed over the spine that correspond to the location of the renal veins to allow correct positioning. Postoperative venous thrombosis prophylaxis with intermittent pneumatic compression devices is used, and the use of subcutaneous heparin is begun on the evening of surgery. Anticoagulation with warfarin is begun as soon as the pacing wires and mediastinal drainage tubes are removed, with a target International Normalized Ratio of 2.5 to 3.

Complications

Patients are subject to all complications associated with open-heart and major lung surgery (e.g., arrhythmias, atelectasis, wound infection, pneumonia, and mediastinal bleeding) but also may develop complications specific to this operation. These include persistent pulmonary hypertension, reperfusion pulmonary response, and neurologic disorders related to deep hypothermia.

PERSISTENT PULMONARY HYPERTENSION: The decrease in PVR level usually results in an immediate and sustained restoration of pulmonary artery pressures to normal levels, with a marked increase in cardiac output. In a few patients, an

immediately normal pulmonary vascular tone is not achieved, but an additional substantial reduction may occur over the next few days because of the subsequent relaxation of small vessels and the resolution of intraoperative factors such as pulmonary edema. In such patients, it is usual to see a large pulmonary artery pulse pressure, the low diastolic pressure indicating good runoff, yet persistent pulmonary arterial inflexibility still resulting in a high systolic pressure.

There are a few patients in whom the pulmonary artery pressures do not resolve substantially. We do operate on some patients with severe pulmonary hypertension but equivocal embolic disease. Despite the considerable risk of attempted endarterectomy in these patients, since transplantation is the only other avenue of therapy, there may be a point at which it is unlikely that a patient will survive until a donor is found. In our most recent 500 patients, more than one-third of perioperative deaths were directly attributable to the problem of inadequate relief of pulmonary artery hypertension. This was a diagnostic rather than an operative technical problem. Attempts at pharmacologic manipulation of high residual PVR levels with sodium nitroprusside, epoprostenol sodium, or inhaled nitric oxide are generally not effective. Because the residual hypertensive defect is fixed, it is not appropriate to use mechanical circulatory support or extracorporeal membrane oxygenation in these patients if they deteriorate subsequently.

THE "REPERFUSION RESPONSE": A specific complication that occurs in most patients to some degree is localized pulmonary edema, or the "reperfusion response." Reperfusion response or reperfusion injury is defined as a radiologic opacity seen in the lungs within 72 hours of pulmonary endarterectomy. This unfortunately loose definition may therefore encompass many causes, such as fluid overload and infection.

True reperfusion injury that directly adversely impacts the clinical course of the patient now occurs in approximately 10% of patients. In its most dramatic form, it occurs soon after operation (within a few hours) and is associated with profound desaturation. Edema-like fluid, sometimes with a bloody tinge, is suctioned from the endotracheal tube.[95] Frank blood from the endotracheal tube, however, signifies a mechanical violation of the blood-airway barrier that has occurred at operation and stems from a technical error. This complication should be managed, if possible, by identification of the affected area by bronchoscopy and balloon occlusion of the affected lobe until coagulation can be normalized.

One common cause of the reperfusion pulmonary edema is persistent high pulmonary artery pressures after operation when a thorough endarterectomy has been performed in certain areas, but there remains a large part of the pulmonary vascular bed affected by type IV change. However, the reperfusion phenomenon is often encountered in patients after a seemingly technically perfect operation with complete resolution of high pulmonary artery pressures. In these cases the response may be one of reactive hyperemia, after the revascularization of segments of the pulmonary arterial bed that have long experienced no flow. Other contributing factors may include perioperative pulmonary ischemia and conditions associated with high permeability lung injury in the area of the now denuded endothelium. Fortunately, the incidence of this complication is much less common now in our series, probably as a result of the more complete and expeditious removal of the endarterectomy specimen that has come with the large experience over the last decade.

MANAGEMENT OF THE "REPERFUSION RESPONSE": Early measures should be taken to minimize the development of pulmonary edema with diuresis, maintenance of the hematocrit levels, and the early use of peak end-expiratory pressure. Once the capillary leak has been established, treatment is supportive because reperfusion pulmonary edema will eventually resolve if satisfactory hemodynamics and oxygenation can be maintained. Careful management of ventilation and fluid balance is required. The hematocrit is kept high (32 to 36%), and the patient undergoes aggressive diuresis, even if this requires ultrafiltration. The patient's ventilatory status may be dramatically position sensitive. The fraction of inspired oxygen level is kept as low as is compatible with an oxygen saturation of 90%. A careful titration of positive end-expiratory pressure is carried out, with a progressive transition from volume-limited to pressure-limited inverse ratio ventilation and the acceptance of moderate hypercapnia.[95] The use of steroids is discouraged because they are generally ineffective and may lead to infection. Infrequently, inhaled nitric oxide at 20 to 40 ppm can improve the gas exchange. On occasion we have used extracorporeal perfusion support (an extracorporeal membrane oxygenator or extracorporeal carbon dioxide removal) until ventilation can be resumed satisfactorily, usually after 7 to 10 days. However, their use is limited to patients who have benefited from hemodynamic improvement but are suffering from significant reperfusion response. Extracorporeal devices should not be used if there is no evidence or hope of subsequent hemodynamic improvement, since they carry mortality close to 100%, and will not play a role in improving irreversible pulmonary pressures.

DELIRIUM: Early in the pulmonary endarterectomy experience (before 1990), there was a substantial incidence of postoperative delirium. A study of 28 patients who underwent pulmonary endarterectomy showed that 77% experienced the development of this complication.[96,97] Delirium appeared to be related to an accumulated duration of circulatory arrest time of more than 55 minutes; the incidence fell to 11% with significantly shorter periods of arrest time.[96–98] With the more expeditious operation that has come with our increased experience, postoperative confusion is now encountered no more commonly than with ordinary open-heart surgery.

PERICARDIAL EFFUSION: Probably because of the lymphatic tissue that is encountered during the dissection of the hilum

and the mobilization of the superior vena cava, possibly combined with the diminution of cardiac size that occurs immediately after the operation, we have encountered significant pericardial effusions in several patients. It is now our practice to either create a posterior pericardial window at the end of the operation or place a posterior pericardial drain, which we usually keep longer. These techniques have essentially eliminated the problem, and in general it is much easier to treat the pleural effusion on the left side in the occasional patient who may develop this complication.

Results

More than 2000 pulmonary thromboendarterectomies have been performed at UCSD Medical Center since 1970. Most of these cases (over 1800) have been completed since 1990, when the surgical procedure was modified as described earlier in this chapter. The mean patient age in our group is about 52 years, with a range of 7 to 85 years. There is a very slight male predominance. In nearly one-third of the cases, at least one additional cardiac procedure was performed at the time of operation. Most commonly, the adjunct procedure was closure of a persistent foramen ovale or atrial septal defect (26%) or coronary artery bypass grafting (8%).[87]

HEMODYNAMIC RESULTS: A reduction in pulmonary pressures and resistance to normal levels and a corresponding improvement in pulmonary blood flow and cardiac output are generally immediate and sustained.[98,99] In general, these changes can be assumed to be permanent. Whereas before the operation, more than 95% of the patients are in NYHA functional class III or IV, at 1 year after the operation, 95% of patients remain in NYHA functional class I or II.[99,100] In addition, echocardiographic studies have demonstrated that, with the elimination of chronic pressure overload, right ventricular geometry rapidly reverts toward normal. Right atrial and right ventricular enlargement regress. Tricuspid valve function returns to normal within a few days as a result of restoration of tricuspid annular geometry after the remodeling of the right ventricle, and tricuspid repair is not therefore part of the operation.

OPERATIVE MORBIDITY: Severe reperfusion injury was the single most frequent complication in the UCSD series, occurring in 10% of patients. Some of these patients did not survive, and other patients required prolonged mechanical ventilatory support. A few patients were salvaged only by the use of extracorporeal support and blood carbon dioxide removal. Neurologic complications from circulatory arrest appear to have been eliminated, probably as a result of the shorter circulatory arrest periods now experienced, and perioperative confusion and stroke are now no more frequent than with conventional open-heart surgery. Early postoperative hemorrhage required re-exploration in 2.5% of patients, and only 50% of patients required intra- or postoperative blood transfusion. Despite the prolonged operation, wound infections are relatively infrequent. Only 1.8% experienced the development of sternal wound complications, including sterile dehiscence or mediastinitis.

DEATHS: In our experience, the overall mortality rate (at 30 days or in-hospital if the hospital course is prolonged) is about 7% for the entire patient group, which encompasses a time span of over 35 years. The mortality rate was 9.4% in 1989 and has been about 5 to 6% for the more than 1800 patients who have undergone the operation since 1990. Looking at our most recent experience over the last 5 years, the mortality rate has been about 4.5%. We generally quote an operative risk of less than 5%, but some patients predictably fall within a much higher-risk group. With our increasing experience and many referrals, we continue to accept some patients who, in retrospect, were unsuitable candidates for the procedure (type IV disease). We also accept patients in whom we know that the entire degree of pulmonary hypertension cannot be explained by the occlusive disease detected by angiography, but feel that they will be benefited by operation, albeit at higher risk. Residual causes of death are operation on patients in whom thromboembolic disease was not the cause of the pulmonary hypertension (50%) and the rare case of reperfusion pulmonary edema that progresses to a respiratory distress syndrome of long standing, which is not reversible (25%).

Late follow-up

A survey of the surviving patients who underwent pulmonary endarterectomy surgery at UCSD between 1970 and 1995 formally evaluated the long-term outcome.[100] Questionnaires were mailed to 420 patients who were more than 1 year after operation. Responses were obtained from 308 patients. Survival, functional status, quality of life, and the subsequent use of medical help were assessed. Survival after pulmonary thromboendarterectomy was 75% at 6 years or more. Ninety-three percent of the patients were found to be in NYHA class I or II, compared to about 95% of the patients being in NYHA class II or IV preoperatively. Of the working population, 62% of patients who were unemployed before operation returned to work. Patients who had undergone pulmonary endarterectomy scored several quality-of-life components just slightly lower than normal individuals, but significantly higher than the patients before endarterectomy. Only 10% of patients used oxygen, and in response to the question, "How do you feel about the quality of your life since your surgery?" 77% replied much improved, and 20% replied improved. These data appear to confirm that pulmonary endarterectomy offers substantial improvement in survival, function, and quality of life, with minimal later health care requirements.[100]

CONCLUSION

It is increasingly apparent that pulmonary hypertension caused by chronic PE is a condition which carries a poor prognosis. Medical therapy is ineffective in prolonging life and only transiently improves the symptoms. The only therapeutic alternative to pulmonary thromboendarterectomy is lung transplantation. The advantages of thromboendarterectomy

include a lower operative mortality rate and excellent long-term results without the risks associated with chronic immunosuppression and chronic allograft rejection. The mortality for thromboendarterectomy at our institution is now in the range of 4.5%, with sustained benefit. These results are clearly superior to those for transplantation both in the short and long term.

Although PTE is technically demanding for the surgeon and requires careful dissection of the pulmonary artery planes and the use of circulatory arrest, excellent short- and long-term results can be achieved. It is the successive improvements in operative technique developed over the last four decades which now allow pulmonary endarterectomy to be offered to patients with an acceptable mortality rate and excellent anticipation of clinical improvement. With this growing experience, it has also become clear that unilateral operation is obsolete and that circulatory arrest is essential.

The primary problem remains that this is an underrecognized condition. Increased awareness of both the prevalence of this condition and the possibility of a surgical cure should avail more patients of the opportunity for relief from this debilitating and ultimately fatal disease.

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CHAPTER 57

Trauma to the Great Vessels

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Vesalius was the first to report on a traumatic injury to the aorta manifesting as a posttraumatic aortic aneurysm in 1557.[1,2] Aortic rupture was a very uncommon injury until the latter half of the 20th century as travel by motor vehicles increased. Based on limited epidemiologic data, 85% of traumatic injuries to the great vessels in civilian practices were previously attributed to penetrating trauma with 57% caused by gunshot wounds and 25% by stab wounds.[3–6] A more recent Scottish population-based study suggests that over 70% of thoracic aortic trauma is caused by blunt trauma.[7] One percent of blunt chest trauma patients will have an aortic injury.[8–10]

TRAUMATIC AORTIC DISRUPTION

Epidemiology

Blunt aortic injury remains the second leading cause of death from vehicular trauma, representing 15% of motor vehicle–caused deaths.[11–13] Death occurs at the accident scene in 75 to 90% of cases.[1,11–14] Approximately 8% of patients survive more than 4 hours.[1] Those who survive aortic transection typically have two other associated serious injuries, while those who die have four or more serious injuries.[1,13] According to Parmley's landmark report published in 1958, 42% of patients with lethal aortic rupture had an associated cardiac injury.[1] The short duration of postaccident survival and the high incidence of fatal associated injuries preclude recovery in most of these patients. Recovery of the select few who survive the first few hours after aortic rupture depends on how they are managed in the hospital.

The true incidence of blunt aortic rupture is not known, but based on autopsy series aortic rupture occurs in 12 to 23% of deaths from blunt trauma.[1,15–18] According to national vehicular crash databases in the United States and the United Kingdom, the incidence of thoracic aortic injury among motor vehicle crash victims is 1.5% and 1.9%, respectively.[19] Seventy-three to 92% of all traumatic aortic disruptions involve motor vehicle drivers, passengers, or pedestrians hit by vehicles.[1,13,15,17,18] Alcohol or other substance abuse is involved in over 40% of these motor vehicle accidents.[15,17] Ejection from a vehicle doubles the risk of aortic rupture, and seat belt restraint reduces mortality risk by a factor of four.[15] Data confirm that active restraints (seat belts) are more effective than passive restraints (air bags) in preventing traumatic aortic injury.[20] Aortic rupture of both the ascending and descending aorta has been attributed to the deployment of an air bag, in some cases with cars going less than 10 mph.[21–24] The risk of an aortic injury is at least three times higher among unbelted than belted motor vehicle occupants.[19] Frontal and side impact crashes, regardless of the side of impact, have the highest risk.[14,19] Accidental or suicidal falls, crush injuries, airplane accidents, and rare cave-ins are among the other causes of aortic rupture.[1,13,16,25–27] Falls causing aortic rupture typically occur from heights greater than 3 meters.[1,25,26,28]

Seventy to eighty percent of these injuries occur in males with an average age of 36 to 40 years.[7,13,29,30] Seventy-five percent of patients with traumatic aortic rupture who make it to the hospital alive are initially hemodynamically stable,[13] but up to 50% die prior to definitive surgery.[29,31] Compared to autopsy series, patients who reach the hospital alive have fewer severe associated injuries.[1,12,13,16] Forty to 92% of patients are transferred from a hospital to a level I trauma center.[13,32,33]

Table 57-1 lists the frequency of associated injuries from data accrued throughout the 1970s into the late 1990s.[13,26,34–37] The most robust database was gathered prospectively from 50 trauma centers throughout the United States and Canada (American Association for the

Table 57–1.

Associated Injuries in Hospitalized Patients with Traumatic Aortic Disruption

	Associated (surgical) injuries						
	Schmidt et al[34] n = 80, %	Hilgenberg et al[35]; n = 51, %	Duhaylongsod et al[26]; n = 108, %	Kirsh et al[36] n = 43, %	Sturm et al[37] n = 37, %	Fabian et al[13] n = 274, %	Crestanello et al[163]; n = 72, %
Central nervous system	25	39	34	50	27	51	49
Thorax							
Diaphragm	13	2	12	9.3	7	—	8
Lung	38	41	43	58	19	38	35
Heart	10	10	18	19	—	4	3
Rib/clavicle fractures	40	39	55	65	35	46	—
Abdominal							49 (total)
Spleen	20	10	17		14	14	
Liver	10	12	15		22	22	
Kidney	9	12	11		5	—	
Bowel	10	—	15		3	7	
Other abdominal	11	—	9		8	14	
Skeletal							
Extremity	81	71	59		—	66	64
Spine	5	10	20		—	12	31
Pelvis	24	25	26		22	31	36
Maxillofacial	5	10	20		—	13	18

Surgery of Trauma [AAST] trial).[13] Fifty-one percent of patients have an associated closed head injury. Forty-six percent have multiple rib fractures, and 38% have pulmonary contusions. Compared to older autopsy series, which had demonstrated that the majority of patients have associated cardiac contusion, recent data suggest that the incidence is only 4%.[13] Orthopedic injuries remain common, occurring in 20 to 35% of cases. Mean injury severity score in the AAST trial was 42.1, which is significantly higher than that seen in older retrospective reports, implying that significantly more patients with these types of serious injuries make it to the hospital and are saved in the modern era.[13]

Pathology

Aortic disruptions occur in all aortic segments including, rarely, the abdominal aorta, but the most common site among patients who survive is at the aortic isthmus (Fig. 57-1). According to autopsy series, 36 to 54% occur at the aortic isthmus, 8 to 27% involve the ascending aorta, 8 to 18% occur in the arch, and 11 to 21% involve the distal descending aorta.[1,16,38,39] Alternatively, surgical series demonstrate that 84 to 97% of ruptures occur at the isthmus, while 3 to 10% occur in the ascending, arch, or distal descending aorta.[12,13,32,35,36,40–42] Among patients who survive, it is evident that the periadventitial tissues around the isthmus provide some protection against free rupture that allows for short-term survival and transfer to a hospital. The aorta is typically transected in a transverse fashion involving all three layers of the aortic wall with the edges often separated by several centimeters[1,16] (Fig. 57-2). Non-circumferential and partial aortic wall disruptions do occur and can vary from only a few millimeters to several centimeters.[1,16,43,44] Spiral lacerations or longitudinal extensions are uncommon. Intramural hematomas and focal dissections occur with partial-thickness disruptions but not transections.[1] Partial tears tend to occur posteriorly, involving the intima and media. Aortic wall structure at and around the transection does not differ from nearby uninvolved aorta, and atherosclerotic disease is generally not present.[1,15,16] The aortic adventitia provides the majority of its tensile strength, but there is no evidence to suggest that the adventitia at the aortic isthmus is any weaker than any other part of the aorta.[45,46]

Blunt trauma can also produce trauma to the other great vessels. Aortic disruption at the base of the innominate

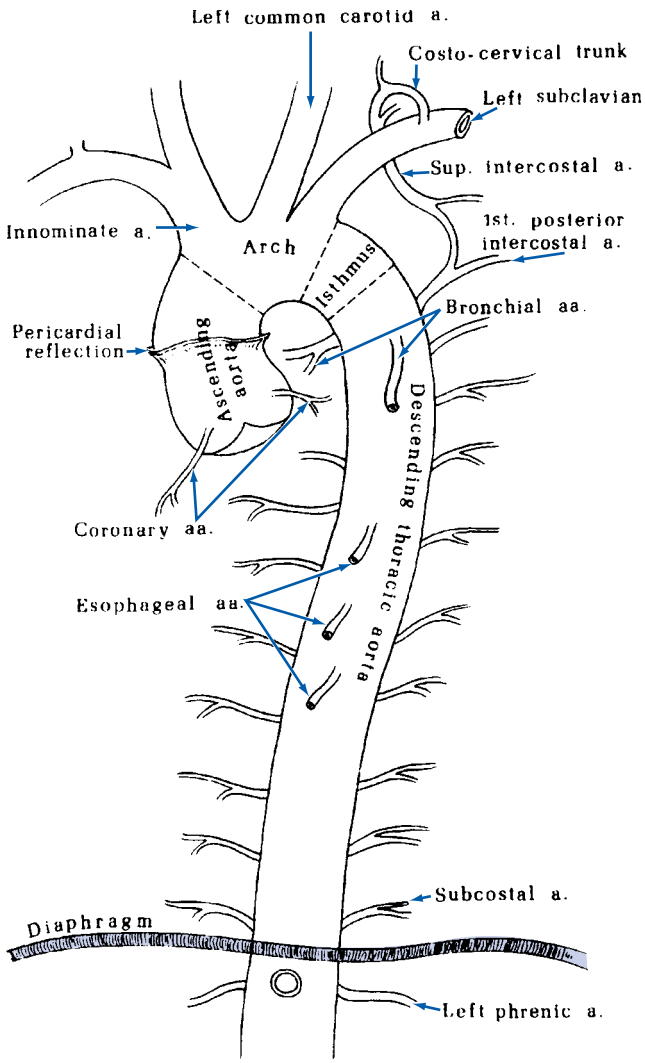

Figure 57-1. Anatomic diagram of the thoracic aorta and its major branches.

artery is the most common site of injury after the isthmus, followed by the base of the left subclavian artery, and then the base of the left carotid.[47] Central venous injuries are rarely injured with blunt trauma,[5] but they do occur with penetrating trauma.[48]

Approximately 2 to 5% of patients with aortic disruptions survive without operation, or even detection, to form chronic false aneurysms.[49] Little is known of the natural history of these chronic pseudoaneurysms because many go undetected. It is likely that an initial false aneurysm with blood flow partially thromboses and organizes to form a fibrous wall. This wall tends to calcify.[49–51] It can evolve into a saccular or fusiform aneurysm and late expansion or even rupture can occur. Ninety percent involve the aortic isthmus, again presumably reflective of the inherent protection afforded to this area by mediastinal periadventitial tissues around the isthmus.[52–54] The patients who develop chronic pseudoaneurysms have fewer associated injuries at the time of the traumatic event.[52–54] In fact, 35% have no other injuries, and 50% have only one.[50]

Pathogenesis of Blunt Aortic Injury

Despite extensive investigation, analysis, and debate, no consensus or unified understanding of the pathogenesis of aortic transection has emerged. Popular opinion has employed the "whiplash" theory posing that a combination of traction, torsion, shear, bending, and bursting forces secondary to differential deceleration of tissues within the mediastinum cause an appropriate stress to rupture the aorta at specific sites—the isthmus being the most common.[15,45,46,55–62] The ligamentum arteriosum, the left main stem bronchus, and the paired intercostal arteries limit the mobility of the aorta at the isthmus and just distal to it.

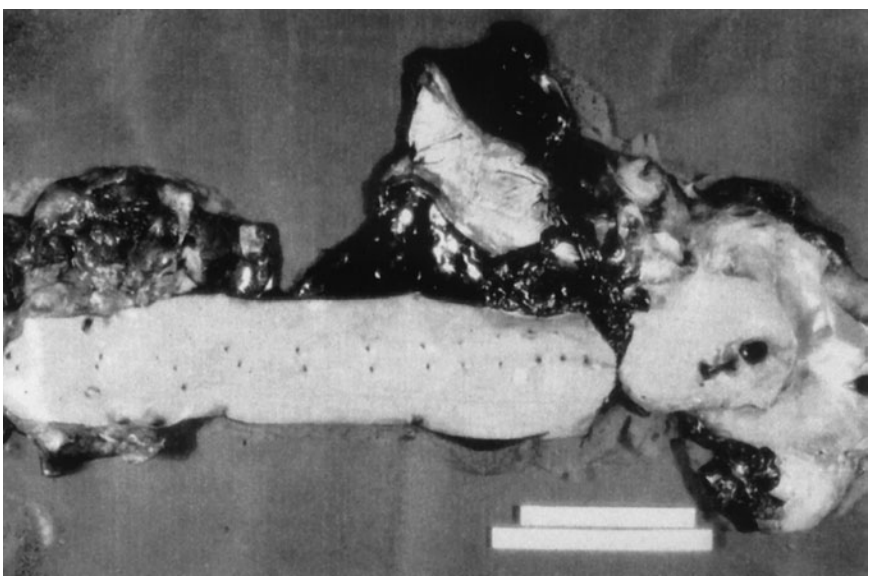

Figure 57-2. Photograph of a traumatic aortic disruption at the isthmus. (*Reproduced with permission from Strassman.*[44])

Experiments have suggested that the aorta can be displaced in a longitudinal (cranial or caudal) direction sufficient to cause traction tears at the isthmus.[57,59] It has also been apparently recognized that deceleration forces can reach several hundred times the force of gravity, producing injury without any direct impact on the chest.[55,56] Alternatively, a "shoveling mechanism" has been postulated to explain cranially directed traction stresses in drivers and front seat passengers in motor vehicle accidents.[63]

Contrarily, Crass and associates argue that the forces of differential deceleration, torsion, or hydrostatics alone have inadequate magnitude in vehicular accidents to result in aortic tearing given the inherent properties of the aorta.[64–66] Several studies have demonstrated that the gravitational forces of vehicular trauma do not approach the tensile strength of the aorta. Oppenheim and Zehnder showed that a normal aorta can withstand a 2000-mm Hg pressure before bursting.[67,68] Crass proposed a new mechanism he coined "the osseous pinch" based on thoracic compression that he tested in the laboratory. The hypothesis was that anterior thoracic osseous structures (manubrium, first rib, and clavicular heads) rotate posteriorly and inferiorly about the axes of the posterior rib attachments. When the force is large enough these anterior bony structures impact the vertebral column, and the portion of the aorta fixed overlying the spine (the isthmus and proximal descending aorta) is pinched between the bones. This causes a direct shearing of the aorta. Crass' group demonstrated in a canine model that a blunt force as small as 20,000 N transected the intima and media of the aorta.[64] In comparison, a 38-mph collision produces a force of 198,000 N in a normal-sized adult.[64] Some clinical data support the osseous pinch mechanism.[69]

Other forces may be important in ascending aortic injuries. The anterior location of the ascending aorta and the weight and ease of displacement of the heart downward and to the left facilitate traction stress on and above the aortic root.[59] Hyperextension of the spine and consequent shearing forces may play a role in the distal descending aorta.[64]

It is likely that the majority of victims of motor vehicle accidents experience some combination of differential deceleration forces and thoracic compression forces, causing aortic disruption.[70] It is clear that many different mechanisms of trauma (i.e., front impact, side impact, falls, crushing injury, and blasts) have caused aortic disruption. Each of these situations affords different circumstances and different forces, making it difficult to isolate a specific mechanism.

Natural History

The natural history of aortic transection in a given patient is dependent on many factors, not the least of which is how quickly a diagnosis is made. Our understanding of survival rates is based on data drawn from autopsy series and operative series. Autopsy studies tend to underestimate the rate of long-term survival, while operative studies tend to overestimate it. Parmley and associates observed that 86% of patients die at the scene, and 11% survive longer than 6 hours.[1] The only survivors in the Parmley series were in fact operated on. Mortality rates in most recent surgical series range from 0 to 50% variably dependent on the size of the series, although the attributable-mortality rates are not clearly defined.[12,13,25,29–32,71–75] Several groups have reported selective nonoperative or delayed operative management with aggressive antiimpulse therapy (beta-blockade) in patients deemed unsuitable candidates for surgery or in cases of apparent minimal aortic injury.[8,29,30,71,76–82] Those initially unsuitable for surgery in these series were elderly and morbid or had too severe associated injuries to tolerate operative repair and thus underwent delayed repair. When surgery has been delayed for stabilization of other injuries, the interim mortality rate prior to definitive repair appears to be between 30 and 50%, with the majority of deaths being attributed to head trauma or other complications.[79,81,83] Delays of up to 4 months prior to repair have been reported.[78,84–90] We conclude that aortic transection can be treated nonoperatively or with operative delay in carefully selected patients with severe associated injuries or significant comorbidities.

Numerous anecdotal reports confirm long-term survival in self-selected patients who were not diagnosed at the time of injury.[51,54,91–96] A review of the literature by Finkelmeier and colleagues demonstrated that among survivors like these, over 70% survive more than 5 years from the time of the injury.[50] The inherent survival bias of this group of patients is evident, but it does confirm that some patients can survive long-term without surgery. In Finkelmeier's review, the 60 patients who did not have operations for chronic traumatic aortic aneurysms had 5-year, 10-year, and 20-year survival rates of 71, 66, and 62%, respectively. Ninety-four percent of chronic traumatic aortic aneurysms were located at the aortic isthmus. Rarely, the arch and ascending aorta were involved.[50]

Clinical Presentation

The presentation of aortic rupture is protean. Aortic rupture itself manifests in the form of specific signs or symptoms in less than 50% of cases.[18,97–100] Patients may develop dyspnea, back pain, or differential hypertension in the lower as compared to the upper extremities.[66,97,98,100–104] Aortic injuries are more commonly identified in the backdrop of a multitrauma patient, and the diagnosis is made only if it is suspected. Consequently, aortic injury can easily be missed if patients are not appropriately screened. Identifying the character and mechanism of trauma is the critical first step in making the diagnosis of aortic disruption. If speeds or distances fallen suggest severe impact or significant deceleration forces, the possibility of aortic rupture exists, and it should

be ruled out. In all cases of motor vehicle crashes, falls, blasts, crush injuries, or other deceleration forces, aortic rupture should be considered.[8,11,25,77,105–108]

The initial management of a multitrauma patient is uniform regardless of whether aortic disruption is suspected. The patient's airway, breathing, and circulation are addressed first. Primary and secondary surveys are completed, and appropriate venous access is obtained concomitant with initial laboratory and radiographic studies. Priority of injury is based largely on the acute lethal potential of an injury. Exsanguinating hemorrhage in any body compartment, perforated viscus, or central neurologic injury take the usual priority. Most patients with aortic disruption also have one or more bone fractures. Fractures should be stabilized but not definitively treated prior to excluding the diagnosis or treating an aortic rupture. There are often clues evident in the initial evaluation of a trauma patient that suggest aortic disruption (Table 57-2). In the majority of trauma cases, a supine chest radiograph is obtained as part of the initial evaluation, and the constellation of grossly widened mediastinum, hemothorax, and transient hemodynamic instability upon arrival appear to be predictive of early in-hospital death from blunt thoracic aortic injury.[109]

Table 57–2.

Clues that Suggest Aortic Disruption

History
Motor vehicle crash >50 km/h
Motor vehicle crash into fixed barrier
No seat belt
Ejection from vehicle
Broken steering wheel
Motorcycle or airplane crash
Pedestrian hit by motor vehicle
Falls greater than 3 meters
Crush or cave-in injuries
Loss of consciousness
Physical signs
Hemodynamic shock (systolic blood pressure <90 mm Hg)
Fracture of sternum, first rib, clavicle, scapula, or multiple ribs
Steering wheel imprint on chest
Cardiac murmurs
Hoarseness
Dyspnea
Back pain
Hemothorax
Unequal extremity blood pressures
Paraplegia or paraparesis

Diagnostic Studies

Chest radiograph

A standard supine anteroposterior chest x-ray does not provide the diagnostic sensitivity to rule out aortic injury.[8,10,25,110] Nine to 40% of patients with aortic rupture have chest x-ray findings interpreted as normal at the time of initial evaluation in major trauma centers.[8,10,25,99,110–117] At least fifteen distinct signs on a standard anteroposterior chest x-ray are associated with blunt aortic injury or rupture (Table 57-3).[110] Unfortunately, none of these signs are sufficiently sensitive, specific, or predictive of aortic rupture. In a series of 188 consecutively evaluated multitrauma patients, 10 blunt aortic injuries were identified, and the sensitivities of these plain radiographic findings ranged from 0 to 90%.[110] The specificities ranged from 6 to 93%.[110] In lieu of obtaining an upright chest x-ray which is typically not possible in a multitrauma patient, reverse Trendelenburg 45° anteroposterior chest x-rays have been suggested to be more accurate than supine films at evaluating the mediastinum.[118]

Table 57–3.

Chest X-Ray Findings Associated with Blunt Aortic Disruption

Widened mediastinum (>8.0 cm)
Mediastinum-to-chest width ratio >0.25
Tracheal shift to the patient's right
Blurred aortic contour
Irregularity or loss of the aortic knob
Left apical cap
Depression of the left main bronchus
Opacification of the aortopulmonary window
Right deviation of the nasogastric tube
Wide paraspinal lines
First rib fracture
Any other rib fracture
Clavicle fracture
Pulmonary contusion
Thoracic spine fracture

Source: Data from Cook et al.[110]

Computed tomography

Volumetric helical or spiral computed tomography (CT) has become the standard screening tool to rule out aortic disruption, with sensitivity and negative predictive values of 100%.[8,10,25,116,119–121] The technology was introduced in the early 1990s, and since that time it has become the screening modality used in most institutions.[8–10,25,28,76,88,112,116,117,119,121–132] Its advantages over other sophisticated imaging techniques (e.g., transesophageal echocardiography, magnetic resonance imaging, or aortography) include its wide availability, its speed, its sensitivity, its reasonable cost, and its ease of interpretation.

Nonionic contrast media is typically used, and 50 to 150 images with slice thicknesses of 3 to 5 mm are acquired in less than 1.5 minutes.[10] Normal aorta is depicted with homogeneous enhancement. Several findings are indicative of aortic disruption, including wall thickening, extravasation of contrast, filling defects, para-aortic hematoma, intimal flaps, mural thrombi, pseudoaneurysm, or pseudocoarctation (Fig. 57-3).[10]

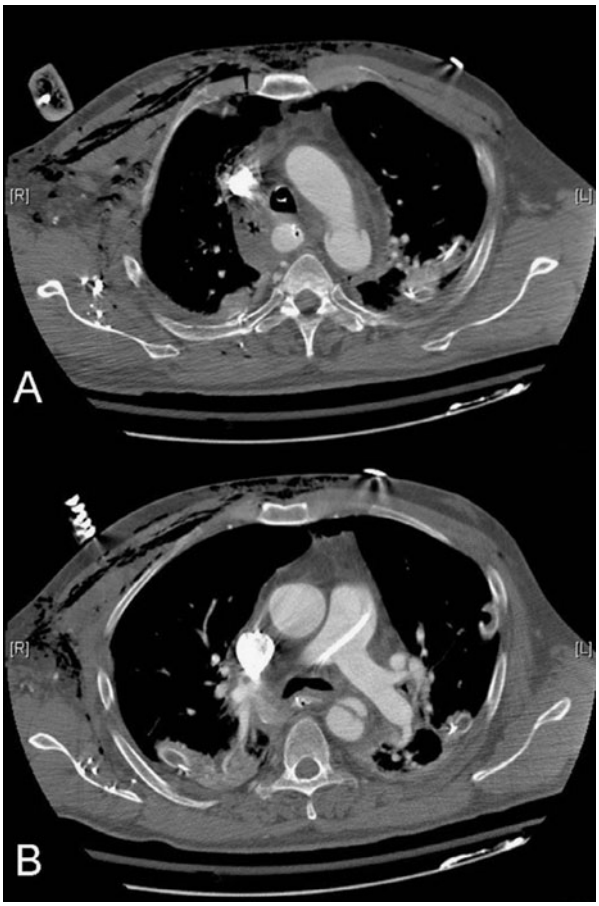

Figure 57-3. Helical computed tomography scan of the chest in a 30-year-old male after a high-speed motor vehicle accident. Slice A demonstrates circumferential disruption of the aortic wall just beyond the left subclavian. Slice B demonstrates an intimal flap in the proximal descending thoracic aorta. Both slices demonstrate periaortic hematoma.

Approximately 1% of blunt trauma patients have a thoracic aortic injury identified by helical CT.[8,123] False-positive CT studies do occur. The specificity, accuracy, and positive predictive value of helical CT range from 50 to 89%.[8,25,116,120] One uncommon finding that mimics aortic injury is a ductus diverticulum remnant.[10] Unlike an aortic injury, a ductus diverticulum will have no intimal irregularity or mediastinal hematoma. When there is a luminal or mural aortic irregularity without evidence of a periaortic hematoma, or when there is periaortic hematoma without obvious aortic luminal or mural irregularity, additional aortic imaging should be considered prior to intervention. Minimal aortic injuries (defined as small, less than 1-cm, intimal flaps) are being identified at an increasing rate because of the improved resolution of CT imaging and its widespread use.[8,10,76] These minimal injuries pose a management dilemma. Many of these minor aortic injuries can and probably should be managed medically with antiimpulse therapy.[76]

Transesophageal echocardiography

The development of multiplanar transesophageal echocardiography (TEE) has revolutionized cardiothoracic surgery such that its use is now necessary to plan and facilitate intraoperative management in most cardiothoracic surgical procedures. Its use in cases of aortic transection is no exception. TEE reliably images the entire thoracic aorta except the distal ascending aorta and proximal aortic arch, which can be obscured by tracheal and bronchial air artifact. Contrarily, transthoracic echocardiography cannot accurately evaluate the descending aorta. The accuracy of TEE for diagnosing aortic injury is operator-dependent. Some report its sensitivity and specificity to be approaching 100%,[120,133,134] while others demonstrate a sensitivity and specificity as low as 63 and 84%, respectively.[135] A recent prospective comparison of the use of helical CT to TEE in evaluating blunt aortic injury in 110 consecutive patients demonstrated a sensitivity, specificity, negative predictive value, and positive predictive value of 93, 100, 99, and 100%, respectively, for TEE compared to 73, 100, 95, and 100% for helical CT.[120]

A major advantage of TEE is its portability. The hemodynamically unstable patient who is taken to the operating room immediately can undergo exploratory laparotomy or other procedures while simultaneously being evaluated by TEE. The major disadvantage of TEE is that it requires an experienced operator. The risk of TEE is low.[120,133] It is contraindicated in cases of concomitant cervical spine, oropharyngeal, esophageal, or severe maxillofacial injury, or in patients with esophageal or pharyngeal lesions that would impede or complicate passage of the probe.

Multiplanar TEE probes permit acquisition of cross-sectional images at different angles along a single rotational axis (Fig. 57-4). The typical 5- or 7-MHz transducer permits adequate resolution of structures as small as 1 to 2 mm.

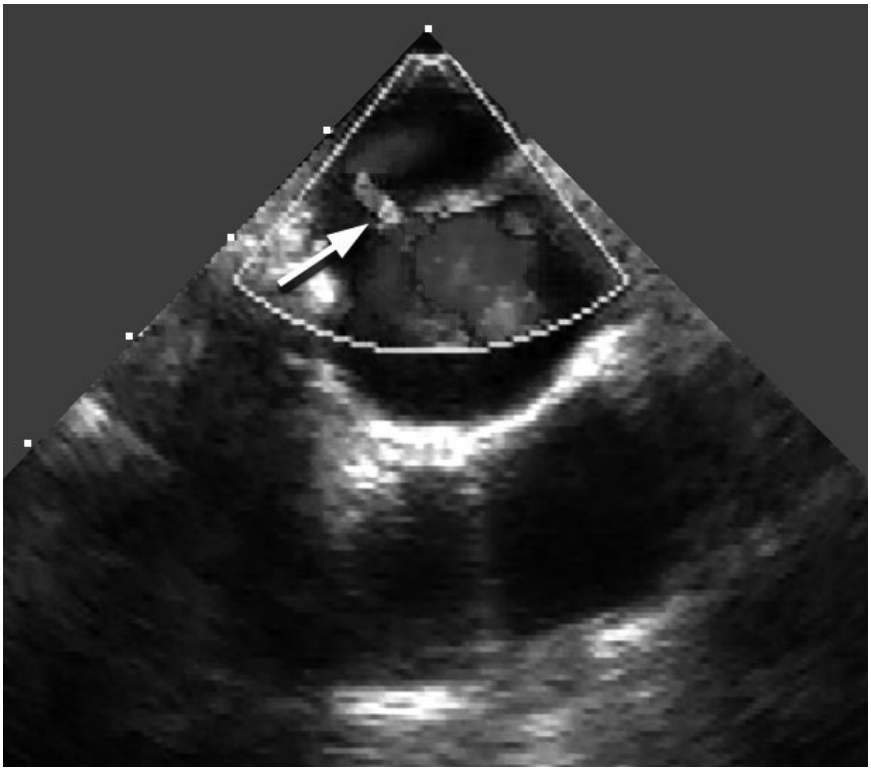

Figure 57-4. Transesophageal echocardiographic cross-sectional image in the short-axis with color flow Doppler depicting transection of the aortic isthmus. The transection appears as two distinct lumens, the "double-barrel" sign, and there is flow between the separated aorta. (*Courtesy of B. Milas, University of Pennsylvania.*)

Time-resolved imaging allows evaluation of the movement of anatomic structures and enhances the ability to determine the physiologic consequences of structural abnormalities. Doppler echocardiography is used to evaluate abnormal blood flow patterns which can aid in identifying intimal flaps.

The most common feature of aortic injury identified by TEE is a mural flap. Thickening of the vessel wall can represent a contained rupture or a mural thrombus. Color Doppler flow mapping can demonstrate alterations in flow patterns including turbulence at the site of injury. Chronic atheromatous changes can produce false-positive signs of intimal disruption. When aortic disruption is suspected on TEE there usually is a surrounding mediastinal hematoma, and its absence should prompt skepticism of the diagnosis.

Aortography

Aortography is the imaging modality by which all other techniques have been previously compared for evaluation of aortic injury. Its technique and role in evaluating aortic injuries or other vascular injuries was established long before any of the other sophisticated imaging methodologies. In experienced hands its sensitivity and specificity both approach 100%.[136] Its major disadvantages are that its use requires a highly skilled interventional radiology team, and it is time consuming, rendering the patient inaccessible during the time of the study. Rates of exsanguination and death of up to 10% in the angiography suite have been reported.[104,137,138] Complication rates attributed directly to aortography are low. Contrast reactions, renal insufficiency secondary to contrast material and groin hematomas or pseudoaneurysms do occur. In the pre–helical CT era, 85 to 95% of aortograms were negative, calling into question the cost- and time-effectiveness of the technique.[28,98,104,131,136,138] False-positive studies are usually attributed to atheromata or ductal diverticula. Though now only rarely used for diagnosis, aortography is becoming routine to facilitate endovascular stent grafting (EVSG) for traumatic disruptions (Fig. 57-5).

The technique of intra-arterial digital subtraction angiography is used by most groups and allows for faster generation of images. Intravenous digital subtraction angiography was used in the past by some as an even more rapid means of evaluating the aorta in the angiography suite.[138] This technique employs IV contrast instillation with time-delayed images of the arch and descending aorta. The time of a study can be reduced by up to fourfold when compared to conventional biplanar angiography. Unfortunately, the diagnostic quality of intravenous digital subtraction angiography is less than 70%,[138] and consequently with the near uniform availability of helical CT, the technique has become obsolete.

Magnetic resonance angiography

Magnetic resonance angiography provides excellent images of vascular structures, particularly the thoracic aorta, and its utility in the diagnosis and follow-up of complex aortic disease including aortic dissections and aneurysms is firmly established.[139–142] However, its use in

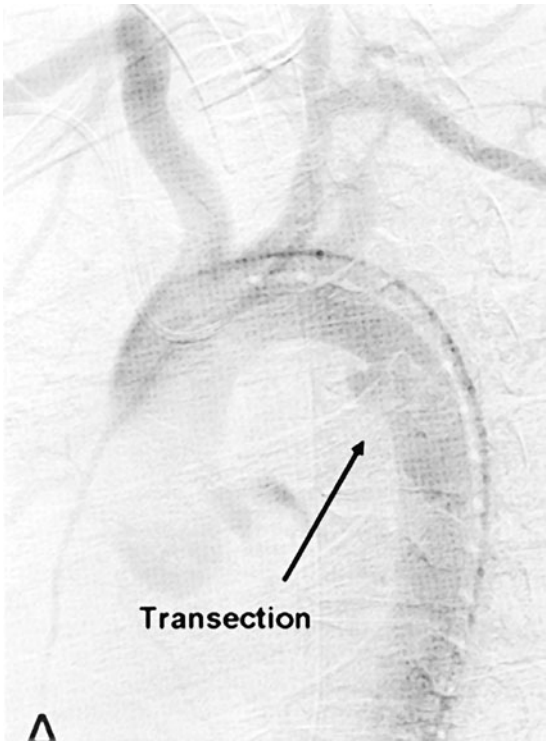

Figure 57-5. Intra-arterial digital subtraction angiogram of an acute traumatic aortic disruption near the isthmus. The left subclavian artery was transposed to the left common carotid artery prior to deployment of a stent graft.

the acute trauma patient has not been broadly justified. The time required to attain images and the confining nature of the scanners preclude its use in this patient population. If in the future magnetic resonance data acquisition time decreases and patient accessibility within a scanner increases, there may be a role for magnetic resonance angiography in acute trauma settings. Alternatively, it is reasonable to use magnetic resonance angiography for posttherapeutic surveillance of traumatic aortic injuries, particularly in those patients with minimal aortic injury who are treated nonoperatively.

Patient Assessment

Initial evaluation

Ninety-five percent of patients with aortic disruption have associated injuries, and consequently it is imperative that a comprehensive trauma evaluation occur prior to definitive imaging to rule out aortic injury.[12,13,77] However, the leading cause of death in patients with aortic injury who make it to the hospital remains exsanguinating aortic rupture, which occurs in at least 20% of patients.[13] Among patients who present hemodynamically stable with aortic injury, 4% die in the hospital of aortic rupture prior to surgical repair.[13] These data emphasize that a careful, planned, and expeditious team approach is mandatory in order to save as many of these patients as possible. The first steps include primary and secondary physical examinations with control of the airway, respiration, and hemodynamics. Intubation, cardiovascular resuscitation, chest x-ray, insertion of thoracostomy tubes, and identification and stabilization of head injuries take priority. Patients with nonlethal associated injuries who are hemodynamically stable should be diverted toward exclusion of aortic injury, and patients who are unstable require immediate direction toward life-saving operative intervention (e.g., laparotomy or thoracotomy), bypassing all time-consuming tests, in order to achieve the best chance of survival.

After initial trauma evaluation, a head CT should be obtained prior to any planned aortic operation in all patients with signs of an open- or closed-head injury. Relief of intracranial space-occupying lesions takes priority over nonbleeding aortic injuries. Hemodynamically unstable patients with signs of exsanguinating hemorrhage should go directly to the operating room for control of hemorrhage, and TEE should be used to evaluate for aortic injury. Identification of blunt aortic injuries in hemodynamically stable patients should be done in the most efficient manner for a given institution, depending on availability of experienced imaging diagnosticians and equipment, and should be coordinated with the evaluation of other life-threatening injuries. The usual scenario of a hemodynamically stable blunt trauma patient dictates leaving the emergency department to undergo head and abdominopelvic CT scan for identification of closed head injury and intra-abdominal injury. Patients with either an abnormal chest x-ray or a mechanism of injury that poses significant risk of aortic injury (e.g., falls greater than 3 m, motor vehicle crashes of greater than 50 km/h, or pedestrians hit by automobiles) should undergo simultaneous helical chest CT at the time of head and/or abdominopelvic CT. In most institutions, aortography is now reserved for use in patients with equivocal helical CT or TEE results or in patients with complex aortic injuries which cannot be accurately defined by these other imaging techniques. Occasionally thoracoscopy has been used to evaluate traumatic hemothoraces.[143] However, there is little role for thoracoscopy in the diagnosis of aortic disruption, because in experienced hands, the sensitivity and specificity of intraoperative TEE is so good.

In the preoperative period, patients with aortic injury should receive anti-impulse therapy for control of aortic wall tension and blood pressure.[8,77] Reduction of the change in pressure over the change in time ($\Delta P/\Delta t$) reduces wall stress significantly.[144] These measures have been shown to reduce in-hospital aortic rupture rates without adversely affecting the outcome of other injuries.[8] These control measures should be employed in patients going to the operating room and in patients undergoing delayed aortic repair for the treatment of other life-threatening injuries.

Timing of operation

Immediate aortic repair is recommended once the diagnosis of aortic injury is made in hemodynamically stable patients without severe associated injuries that require emergent laparotomy, craniotomy, or pelvic stabilization. Intracranial bleeding causing mass effect, and significant thoracic, abdominal, pelvic, or retroperitoneal hemorrhage should all be addressed prior to thoracotomy or stent grafting for contained aortic injury.[84,145] Contained aortic injuries should be aggressively managed with anti-impulse therapy if delayed aortic management is planned in order to address other life-threatening injuries. Delayed management may be appropriate in carefully selected patients with severe associated injuries or severe comorbidity.[29–31,71,79-83,146] Presentation of aortic disruption with ongoing aortic bleeding or signs of impending rupture requires immediate surgical intervention. Aortic injuries should be monitored by TEE during the surgical treatment of intracranial, thoracic, or abdominopelvic injuries. Treatment of all non–life-threatening injuries should be delayed until after definitive aortic repair.

Hemodynamically unstable patients should be taken to the operating room immediately, prior to definitive testing. Laparotomy or even thoracotomy may be required to locate and control ongoing hemorrhage. Patients with instability secondary to associated trauma who require laparotomy or thoracotomy for damage control to establish hemodynamic stability may be better served by subsequent immediate transfer to the intensive care unit for further resuscitation prior to definitive repair of contained aortic rupture until complete resuscitation and hemodynamic stability are achieved. Once stabilized, anti-impulse therapy with short-acting beta-blockade should be instituted and aggressively applied to reduce aortic wall stress.[8] Determining the optimal extent of delay for definitive aortic repair in patients with severe associated injuries is not clear. In rare cases, particularly extremely comorbid patients, nonoperative management has been extended for long periods of time with acceptable mortality.[82,83]

Operative Strategies

Conventional open repair of traumatic aortic disruption via interposition grafting for replacement of the injured segment is safe, effective, and durable. Historically, open repair via thoracotomy is the standard to which all other management strategies must be compared. However, as endovascular strategies for treating abdominal and more recently thoracic aortic pathology have evolved, there is growing enthusiasm for endovascular stent grafting (EVSG) of traumatic disruption because of its relative ease, reduced operative time required, and potentially reduced complication rate compared to conventional open repair. Consequently, but despite a lack of prospective clinical trials, recent trends around the world demonstrate a more liberal use of EVSG for acute traumatic aortic disruption, particularly for complicated cases with severe associated injuries. Retrospective reviews of single institutional experiences have demonstrated favorable short-term outcomes with endovascular strategies; however, the reported series are small, ranging from 5 to 29 cases per report.[29,30,72,73,80,147–151] Currently there are ongoing clinical trials of the use of new EVSG repair for traumatic aortic disruption, but these trials are not randomizing patients to open repair. An important limitation of the use of EVSG for traumatic transection is that the currently available thoracic aortic stent grafts were designed to treat aneurysmal disease, not traumatic disruption. Unlike aneurysms, aortic transection typically occurs in younger patients (average age 36 to 40 years)[7,29,30,152] with normal-caliber descending aortas in the range of 18 to 24 mm. The currently available stent grafts are not optimally suited for this size thoracic aorta. Consequently, groups have often resorted to the use of homemade or improvised materials that were originally designed for other purposes like extension cuffs of abdominal stent grafts. The long-term durability of these rudimentary, rigged devices or even the newest available devices designed for the thoracic aorta is not known. Despite these limitations, it is becoming clearer that EVSG can safely be used in a significant percentage of trauma patients. In many cases, simply bridging a patient with a stent graft to a more stable, chronic pseudoaneurysm may have an advantage over thoracotomy in a multitrauma patient. Because EVSG techniques continue to evolve and are not uniformly applicable, surgeons treating thoracic aortic disruption must be comfortable with conventional open repair techniques.

Open repair

The technical aspects of repairing aortic disruptions are straightforward. Although no one method of repair of aortic transection has been proven superior, standards are established. There remains some controversy surrounding the issue of spinal cord protection and what means of protection are optimal.[12,13,32,36,40,42,66,77,86,88,99,108,115,153–161] There are two general perspectives: (1) that "clamp-and-sew" techniques are sufficiently safe, and (2) that some form of lower body perfusion provides added spinal cord and visceral protection against the ischemia of the aortic cross-clamp. Paraplegia has historically occurred at an overall rate of approximately 10%.[12,40,42,99,152,162] More recently, data from multiple institutions demonstrate a marked reduction in paraplegia rates with the use of adjuvant perfusion techniques.[8,13,25,77,163]

SPINAL CORD PROTECTION: The spinal cord is supplied blood flow by anterior and posterior spinal arteries that consist of anatomic vascular chains that run the length of the cord.[164] The anterior spinal artery supplies the anterior two-thirds of the cord and is well developed in the upper thorax. Collateral arterial vessels also feed off of the left subclavian

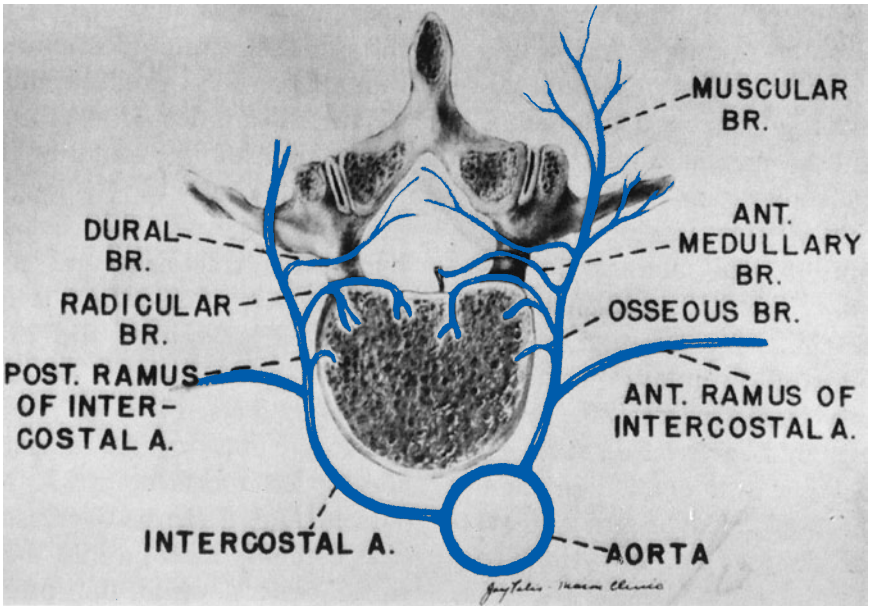

Figure 57-6. Cross-sectional diagram showing a medullary (radicular) arterial branch to the anterior spinal artery.

artery, including the vertebral artery, and consequently its occlusion during repair may have added implications toward a heightened risk of spinal cord ischemia. In the lower thorax and upper abdomen the anterior spinal artery is less developed and relies on segmental branches from intercostal and lumbar arteries. The anterior artery is supplied by 7 to 10 unpaired anterior medullary branches that vary in location along the cord (Fig. 57-6). Usually at least two anterior medullary vessels supply the cervical cord, two or three supply the thoracic cord, and two supply the lumbar cord. At the level of the first lumbar vertebra (variations T8 to L4) the anterior spinal artery receives the arteria radicularis magna (or artery of Adamkiewicz), which is essential for cord blood supply in this zone in at least 25% of patients.[164,165]

Aortic cross-clamping near the aortic isthmus produces profound hypotension to the lower body and spinal cord below this region, and spinal cord injury is proportional to aortic cross-clamp time (Fig. 57-7).[166] Clamping the aorta above the takeoff of the left subclavian artery may increase the risk of paraplegia since the collateral vessels fed by the internal thoracic, vertebral, and subscapular vessels all emanate from the subclavian.[167] Paraplegia has occurred after only 9 minutes of aortic cross-clamping without extracorporeal perfusion of the lower body.[168]

Several adjuncts have been proposed to reduce the risk of paraplegia in cases of elective repair of thoracic or thoracoabdominal aneurysms, but many of these techniques are not practical in the trauma patient requiring repair of aortic

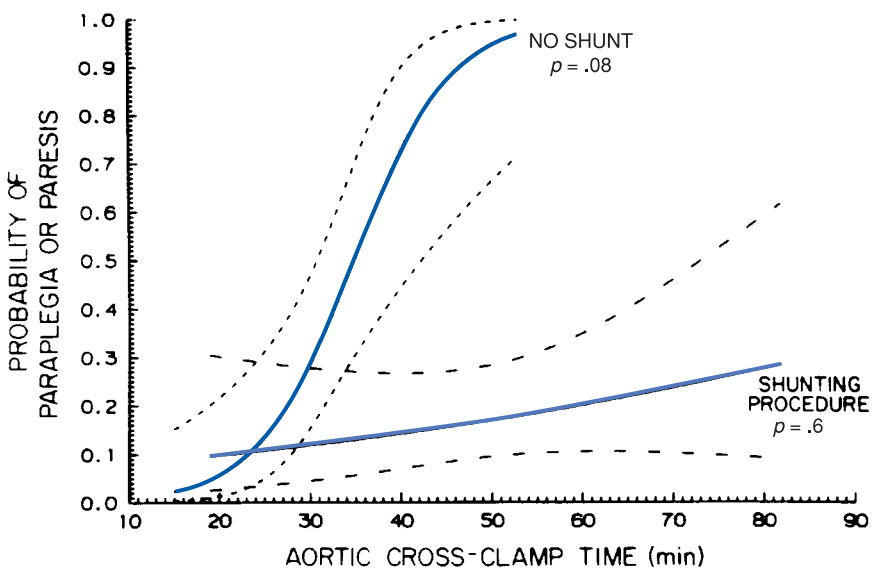

Figure 57-7. Probability of paraplegia in relation to aortic cross-clamp time with and without lower body perfusion in patients with traumatic aortic disruption at the isthmus. (*Reproduced with permission from Katz et al.*[166])

Table 57–4.

Incidence of Postoperative Paraplegia in Relation to Surgical Management: Meta-Analysis

Operative technique	Patients, n	Paraplegia, %	Clamp time, minutes
No shunt	443	19.2	31.8
Passive shunt	424	11.1	46.8
CPB*	490	2.4	47.8
Partial bypass†	71	1.4	39.5

**CPB, cardiopulmonary bypass with oxygenator and heparin.*
†Partial bypass, partial left heart, or femoral vein to artery without systemic heparin.
Source: Reproduced with permission from von Oppell et al.[40]

transection. These include monitoring of somatosensory evoked potentials and lumbar cerebrospinal fluid drainage, both of which require added time and expertise in the preoperative setting which is often not available to trauma patients.[162,169–175] Hypothermia, while attractive as a means of spinal cord protection, is not practical in partial bypass systems which rely on the heart to perfuse the upper body. On rare occasions when aortic injury involves the aortic arch, hypothermic circulatory arrest techniques are required for repair and may actually offer added spinal cord protection.[176–179] Selective retrograde spinal cord hypothermia and perfusion has been studied in the laboratory, but to date these techniques have not been employed in humans.[180,181] Epidural cooling has been used for thoracoabdominal aortic resections, but is not practical in trauma patients.[182] Experience with theoretical neuroprotective pharmaceuticals like steroids, lidocaine, or magnesium have not been thoroughly studied in this patient population.

Based on the currently available data from the surgical community as a whole, it appears that cross-clamp times exceeding 30 minutes and utilization of the "clamp-and-sew" technique alone yield higher rates of paraplegia than techniques that include extracorporeal lower body perfusion (Tables 57-4 and 57-5).[152,162,163] Certainly there are groups that have had success with low paraplegia rates using exclusively a simple cross-clamping technique,[12,32] but these results have not been reproducible throughout many institutions, and their results rely on short cross-clamp times (average 20 to 25 minutes) with little margin for difficult cases. Recent data suggest that the paraplegia rate approaches zero when cross-clamp times are short (less than 30 minutes) *and* lower body perfusion techniques are employed.[13,156,162] We have employed some form of lower body perfusion, typically left heart bypass, during aortic cross-clamping for these injuries since 1994. In our experience, there have been no cases of paraplegia with open repair since this strategy was implemented (over 50 patients, unpublished data).

SIMPLE AORTIC CROSS-CLAMPING: Simple aortic cross-clamping probably still has a role in the management of traumatic aortic rupture. The only advantage to this technique is its simplicity. In particular, it may be useful to the general, vascular, or trauma surgeon who is not experienced in the utilization of extracorporeal perfusion circuits or the cannulation of cardiac chambers or great vessels when thoracic surgical expertise is unavailable. It may also be useful in unstable patients who are actively bleeding from the aortic tear; in these patients there may be no time to employ a distal aortic perfusion system.

When aortic cross-clamp times are less than 25 to 30 minutes, low paraplegia rates have been achieved.[12,13,32] However, the average cross-clamp time reported in the literature is 41.0 minutes.[40] Many cases of aortic transection require more than 30 minutes to repair because of extravasated blood, fragility of the aorta, and difficulty in identifying local anatomy within a large hematoma. This is especially true if the tear extends proximally to involve the orifice of the left subclavian artery. These patients require clamping the aorta proximal to the left subclavian artery,

Table 57–5.

Incidence of Postoperative Paraplegia in Relation to Surgical Management: AAST Prospective Trial

Operative technique	Patients, n	Paraplegia, %
Bypass	134	4.5*
Gott shunt	4	0
Full bypass	22	4.5
Partial bypass	39	7.7
Centrifugal pump	69	2.9†
Clamp and sew	73	16.4*,†

**$p < .004$, bypass versus clamp and sew.*
†$p < .01$, centrifugal pump versus clamp and sew.
Source: Data from Fabian et al.[13]

which may increase the incidence of paraplegia in the absence of distal aortic perfusion.

ADJUVANT PERFUSION METHODS: Optimally, both right radial and femoral arterial catheters should be in place to allow for monitoring of upper and lower body perfusion. Both active and passive shunting systems have been successful with both full systemic heparinization and no heparinization.[13,32,34,36,108,153–155,157,158,160,169,183–185] Despite the theoretical risk of bleeding with heparinization in the trauma setting, most groups, including our own, that employ active partial left heart bypass techniques use full systemic heparinization and have not seen bleeding complications.[8,13,75] Pulmonary venous cannulation near its confluence with the left atrium has a lower complication rate than cannulation of the left atrial appendage.[186] It is important to be well versed in the various lower body perfusion systems because distinct circumstances may require alterations in routine practice.

The system used by any one group should be simply applied, and reliable and routine for that group. Distal perfusion pressure should be maintained at 60 to 70 mm Hg.[158] Full heparinization is relatively contraindicated in cases of intracranial hemorrhage and severe lung injury, but is otherwise safely used by many groups.[12,13,40,75,99,158,183,187] Use of a centrifugal pump with heparin-bonded tubing and active partial left heart bypass or use of a heparin-bonded passive shunt is an option that does not require systemic heparinization.[154,158,185,187] It is helpful to employ the use of a heat exchanger within extracorporeal circuits in order to maintain core temperatures above 35°C in these patients that cool quickly.

PARTIAL LEFT HEART BYPASS: A small single- or dual-stage cannula is placed into the left atrium through the left inferior pulmonary vein to provide inflow to the pump (Fig. 57-8). Arterial cannulation size is determined by body size and site of cannulation. We preferably use a high-flow, atraumatic, aortic cannula in the distal descending aorta or less commonly place a femoral arterial cannula. Distal aortic cannulation has the advantage of convenience and speed. Partial left heart bypass serves several purposes: (1) to unload the left heart and control proximal hypertension at the time of cross-clamping, (2) to maintain lower body perfusion, (3) to allow rapid infusion of volume, and (4) to control (remove) intravascular volume. The lower body is perfused at a flow rate of 2 to 3 L/min with lower body mean arterial pressure of 60 to 70 mm Hg while maintaining an upper body mean arterial pressure of 70 to 80 mm Hg. All field blood is returned to the circuit via a pump reservoir or is accumulated and returned by cell saver.

Ventricular arrhythmias pose a major risk since the native heart perfuses the upper body. Single-lung ventilation does not increase postoperative pulmonary problems

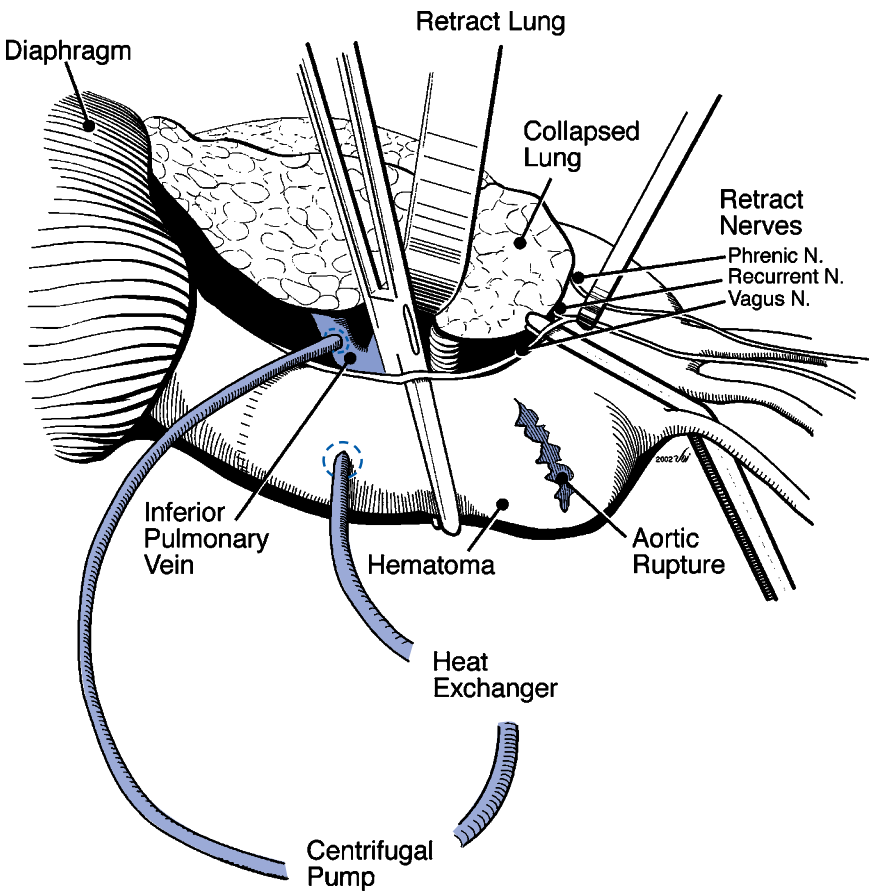

Figure 57-8. Diagram showing a typical setup for partial left heart bypass in a patient with aortic disruption at the isthmus.

after left heart bypass. If the system is used without systemic heparinization, heat exchangers and oxygenators should be removed from the circuit to minimize surface area and thrombotic risks, but in doing so great care must be taken to reduce heat losses and maintain near-normal temperatures.

FULL OR PARTIAL CARDIOPULMONARY BYPASS: Direct right atrial cannulation at the inferior vena cava–right atrial junction from a left thoracotomy by simple, transverse, inferior pericardiotomy below the left phrenic nerve is straightforward and provides excellent venous drainage. Alternatively, a long venous catheter with multiple side holes via the left common femoral vein into the right atrium can be placed with a guidewire. Right atrial–femoral arterial bypass has been used with or without an oxygenator like partial left heart bypass. When no oxygenator is used blood is returned with a partial arterial oxygen pressure of approximately 40 mm Hg (saturation 45 to 65%), and this has been shown to be adequate for lower body tissue oxygen needs provided the hemoglobin concentration is maintained above 10 g/dL.[169,188] Full cardiopulmonary bypass support is most useful in cases in which the aortic arch is involved in the injury to allow for systemic cooling.[189,190]

Right femoral venous to arterial bypass has the distinct advantage of allowing for establishment of partial or complete bypass prior to entering the chest. This technique may be preferred when there is concomitant right lung contusion in order to ensure adequate tissue oxygenation during repair. Rarely, there may be a need to perform a proximal anastomosis under deep hypothermic circulatory arrest (HCA) because an injury involves the mid-aortic arch. In cases of aortic arch transection in proximity to the innominate or left common carotid, anterior exposure via sternotomy or thoracosternotomy may offer better exposure for total arch replacement.[189,190] Use of HCA in trauma patients should proceed with caution and only after other serious associated injuries have been addressed to avoid bleeding complications. If HCA is required, it is essential to confirm the lack of significant aortic valvular insufficiency. When HCA is utilized within the left chest, the left ventricle should be vented, and we typically do this via the left atrium.

PASSIVE (GOTT) SHUNT: Of predominantly historical interest, this technique shunts blood from the proximal aorta to the distal aorta with a tapered, heparin-coated polyvinyl tube.[154] The proximal end is placed in the ascending or arch of the aorta or the left subclavian artery and the distal end is placed in the descending aorta or femoral artery. Ventricular cannulation had been used in the past; however, it was abandoned due to a high rate of ventricular dysrhythmias, reduced shunt flows, and a higher rate of paraplegia.[34,154,155,184,191,192] The diameter of the shunt is obviously fixed, and therefore flow is passive, unmonitored, and dependent on a pressure gradient. Femoral arterial monitoring, as with all of these techniques, is recommended.[184] The Gott shunt is easy to use, although it requires a more extensive dissection of either the aortic arch or ascending aorta. It offers no left ventricular unloading or loading advantage that partial bypass systems do, and therefore blood pressure control is left to pharmacology alone.

OPERATIVE TECHNIQUES: A standard fourth interspace posterolateral thoracotomy with or without fifth rib notching usually provides excellent exposure to the aortic isthmus and proximal descending aorta. The incision should be long enough to facilitate dissection of the descending aorta below the level of the inferior pulmonary vein and dissection of the arch of the aorta between the left common carotid and left subclavian arteries. Dissection near the isthmus or tear should be avoided until both proximal and distal aortic control is established. Depending on the stability of the patient, lower body perfusion can be established prior to aortic exposure by gaining access to the left groin.

If cannulation is planned in the chest, proximal and distal aortic control is established first. The left inferior pulmonary vein–left atrial junction is dissected after gaining aortic control when using left heart bypass. Excessive compression or traction of the lung should be avoided, particularly when dissecting out the aortic arch, because the left pulmonary artery may be easily disrupted at this location (see Fig. 57-8).

The mediastinal pleura is incised along the anterior surface of the proximal left subclavian artery. The subclavian artery is isolated. The pleura overlying the distal aortic arch is incised lateral to the vagus nerve. Great care is taken to avoid injury to either the phrenic or vagus nerves as they pass over the aortic arch, which can be difficult since they are often obscured by the hematoma. They should be reflected off the aorta with the overlying pleura and retracted medially by attaching stay sutures to the pleura just lateral to the vagus nerve. Loops around the nerves themselves should be avoided, as even stretch of these nerves can result in paresis. This reflection exposes the arch of the aorta between the left common carotid and left subclavian arteries, which is the point needed for proximal aortic control in the majority of cases. Inferiorly, the vagus nerve and its branching left recurrent laryngeal nerve are reflected medially as well. This exposes the ligamentum arteriosum which can be sharply divided. The aortic arch between the left carotid and subclavian artery superiorly and medial to the ligamentum inferiorly is encircled with a tape after establishing a plane between the posterior arch and the trachea using a combination of sharp and gentle finger dissection. There should be no dissection distal to either the left subclavian or the ligamentum in order to avoid free disruption of the hematoma.

Distal aortic control is established at an adequate distance from the aortic injury to facilitate repair. The overlying pleura is incised, and the aorta isolated. The left inferior pulmonary vein is dissected out anteriorly. Opening the pericardium just anterior to the vein allows better exposure and a better site of pulmonary venous cannulation. Heparin, if employed, is given. We establish arterial cannulation first. Distal aortic purse-string sutures are fashioned below the

distal clamp site, or the femoral artery is cannulated by Seldinger technique with serial dilatation to the desired cannula size. The inferior pulmonary vein is then cannulated with a dual-stage catheter. The circuit for left heart bypass is de-aired and connected. Lower body perfusion is initiated, and once systemic blood pressure is stabilized the left subclavian artery is clamped followed by the proximal aorta, then the distal aorta. We prefer to always clamp the proximal aorta *between* the left common carotid artery and the left subclavian artery because the tear frequently extends quite close to the ostium of the left subclavian artery. Upper and lower body pressures are stabilized with the bypass circuit to maintain upper body mean arterial pressures of 70 to 80 mm Hg and a lower body pressure of 60 to 70 mm Hg with flows of 2 to 3 L/min (see Fig. 57-8).

The periaortic hematoma is then entered, and the edges of the transected aorta identified. Usually the aorta is completely transected, and the edges are separated by 2 to 4 cm.[1,16] Less frequently the transection is partial. Some authors advocate primary repair at this point;[34,193] however, we advocate placing a short interposition graft after débridement of the torn edges.[12,13,32,35,42,103,155,157,159–161] Collagen-coated woven polyester grafts or gelatin-impregnated grafts are used most commonly. Use of intraluminal prostheses has been abandoned by most groups.[194] Grafts are sewn using a running polypropylene suture with the proximal anastomosis performed first, followed by the distal. Generous amounts of adventitial tissue are included in each bite. If the proximal anastomosis is done under HCA, cardiopulmonary bypass and reperfusion of the arch should be reinstituted immediately after completion of the proximal anastomosis for optimal neurocerebral protection. This requires cannulation of the graft just beyond the proximal anastomosis, and then the distal anastomosis is completed using a dual arterial-inflow perfusion setup perfusing the arch and lower body simultaneously. The left subclavian can either be incorporated into the proximal anastomosis or grafted separately as appropriate.

If the aorta is already ruptured with bleeding into the hemithorax, proximal aortic dissection between the left carotid and subclavian arteries is rapidly performed, and a cross-clamp quickly applied. The descending aorta is then clamped below the injury, and the hematoma opened. No attempt is made to establish lower body perfusion, but every attempt is made at maintaining adequate mean arterial pressure during clamping. The aortic repair is done as expeditiously as possible to minimize clamp time. Repair sutures are placed accordingly after clamps are removed. Hemostasis is achieved after continuity of the aorta is reestablished.

SPECIAL CONSIDERATIONS

PREVIOUS LEFT THORACOTOMY: Emergency department thoracotomies are usually done in haste by inexperienced nonthoracic surgeons and are often placed at sites too inferior to effectively repair an aortic transection. Given this situation it is usually best to enter the chest through a fourth interspace thoracotomy even if this means creating a second intercostal incision (using the same skin incision). When a patient with a history of prior left thoracotomy presents with an aortic injury the associated scarring offers both an advantage and disadvantage to the patient. The adhesions between the lung and mediastinum help contain the rupture making it less likely to exsanguinate, but the adhesions also make the dissection considerably more difficult and time consuming. Optimally, dissection in these cases should be done prior to heparinization.

EXTENSION OF THE TEAR INTO THE LEFT SUBCLAVIAN ARTERY: Traumatic aortic disruptions that occur in close proximity (<1 cm) from the left subclavian artery portend a higher mortality risk and greater operative difficulty than injuries further away from the left subclavian ostium.[195] We recommend routinely placing the proximal aortic clamp proximal to the left subclavian artery since most aortic ruptures tear close to it. This allows for an easier, more precise proximal anastomosis. The subclavian should also be controlled by encircling it with a tape just distal to its origin. Occasionally, the aortic tear will extend into the left subclavian orifice, and in this case the proximal clamp may have to partially or totally occlude the left common carotid. The left subclavian can then be completely detached from the aorta, the proximal anastomosis completed, and the clamp then moved distally onto the graft. The left subclavian is then reattached to the aortic graft with an interposition graft after completing the distal aortic anastomosis. The left common carotid artery will usually tolerate occlusion for 10 to 15 minutes without sequelae. The left subclavian interposition graft is fashioned with an end-to-end anastomosis distally and an end-to-side anastomosis proximally.

Endovascular stent grafting (EVSG)

There are now many reports of the efficacy of EVSG in the setting of acute traumatic aortic disruption.[29–31,72,73,80,147–151,196–199] Most groups placing EVS grafts for aortic disruption are doing so selectively based on the prediction of higher risk with conventional repair due to severity of illness, age, comorbidity, or associated injuries. Open- or closed-head injury, bleeding abdominal visceral injury, retroperitoneal bleeding, and pulmonary contusions are commonly cited factors that may favor an EVSG approach.[29–31,72,73,80,149]

EVSG for traumatic aortic disruption should be performed in either a hybrid operating room/angiosuite with a fluoroscopy unit designed for endovascular surgery or a conventional operating room with a portable C-arm fluoroscopy unit. The rate of conversion from EVSG to open repair is higher with management of aortic disruption than aneurysms,[72] and the operative team involved must be ready and capable of making the conversion immediately. General anesthesia is used most commonly. Aortic access is retrograde via either the femoral or iliac artery. Percutaneous and femoral arterial cutdown or direct iliac arterial puncture or iliac access via a silo graft sewn to the iliac artery have all been used. One theoretical advantage of an endovascular approach may be the use of a very low dose or no heparin in trauma patients. A floppy J-tipped wire is advanced under

fluoroscopic and/or TEE guidance, and an aortogram is performed using steep anterior oblique projection with a marked catheter to accurately assess and measure the aortic arch anatomy relative to the site of transection. *Diameter* of the prosthesis used should be based on aortic measurements obtained preoperatively by CT angiography. *Length* of graft coverage should be based on intraoperative angiographic measurements. Intravascular ultrasound is likely to improve our ability to accurately determine the extent of coverage and the size of grafts needed in the operating room.[200,201] Based on the proximity to the aortic injury, the left subclavian artery may need to be covered, and if covered, it may need to be embolized and bypassed or transposed to the left common carotid artery in order to ensure a proximal EVS graft seal and avoid problems of ischemia to the left arm or vertebrobasilar system (see Fig. 57-5).[202–205]

Stent graft collapse is a problem that can occur in nearly any setting, but EVSG for transection may be particularly prone because of the fact that the available grafts may be relatively oversized for the normal-sized aorta adjacent to an injured segment. There are several unpublished reports of EVS graft collapse during or immediately after deployment for transection including events from our own institutions. Idu and colleagues reported a case of delayed EVS graft collapse that was identified on CT angiogram 3 months after repair of a traumatic transection.[206]

There is little doubt that as devices are designed better and more suitably for aortic transection, EVSG will become part of the standard of care. Currently we employ a selective strategy whereby most patients that are young and have limited associated injuries are treated by conventional open grafting, recognizing the durability of this approach. Alternatively, elderly, comorbid patients or those with severe associated injuries are treated with EVSG.

Nonisthmic Aortic/Arterial Disruptions

The incidence of acute rupture of the ascending aorta among motor vehicular or other trauma patients is not known, as most of these patients do not survive beyond the site of the accident. However, there are reports of successful repairs of these injuries.[22,33,207] Most commonly the proximal ascending aorta at or just above the sinotubular junction is involved.[33] There are a few case reports of ascending aortic ruptures associated with the deployment of air bags.[22,23] Ascending aortic ruptures require full heparinization and cardiopulmonary bypass for repair. These injuries are approached through a median sternotomy. The survival among cases reported in the literature of those undergoing repair is about 85%.[33] They have been repaired either primarily or with an interposition graft. Rarely, a concomitant aortic valve replacement is required.[33]

Lacerations to the base of the innominate or left common carotid arteries should be approached through a median sternotomy and may require cardiopulmonary bypass depending on the degree of aortic involvement.[47] Extension of the incision into the right or left neck including detachment of the sternocleidomastoid from the sternum is usually helpful in obtaining adequate exposure. When the base of the left carotid or innominate is injured, the safest option is to oversew the base and create an interposition graft to the ascending aorta in an end-to-side fashion.[108,208,209] Injury to the base of the left subclavian artery can be approached either by sternotomy or left posterolateral thoracotomy, the latter of which typically provides better exposure.[208] Alternatively, when injuries extend out onto either the left or right subclavian artery a thoracosternotomy, cervicosternotomy, or cervicosternothoracotomy "trap door" incision provides good exposure depending on the level of the injury.[5] Finally, the transverse anterior thoracosternotomy, "clam-shell" incision provides good exposure to the mediastinal structures and both hemithoraces when multiple injuries require repair.[5]

Aortic injuries of the descending aorta distal to the isthmus to the level of T8 should be approached through a posterolateral thoracotomy in the fourth, fifth, or sixth interspace, depending on the level of injury. These types of aortic injuries from blunt trauma are rare. More commonly, this segment of aorta is injured by penetrating trauma. These patients rarely make it to the hospital alive. When the distal thoracoabdominal aorta is injured below T8, it should be approached by thoracoabdominal incision. This can be done either retroperitoneally or intraperitoneally. An intraperitoneal approach offers the advantage of allowing for abdominal exploration; however, retraction of the abdominal contents with a thoracoabdominal incision and a violated peritoneum can be cumbersome. We use partial left heart bypass with left atrial to femoral arterial or distal aortic cannulation for all thoracoabdominal aortic procedures unless active bleeding precludes its setup, or there is an absolute contraindication to heparinization.

Postoperative Care

Postoperative care after aortic repair is similar to that given patients who have other major cardiothoracic surgery. Immediately following aortic repair in the operating room, patients should undergo flexible bronchoscopy for evacuation of bloody secretions to avoid plugging and atelectasis of the left lung. Respiratory function, ventricular filling pressures, blood pressure, cardiac output, renal function, chest tube output, nasogastric drainage, body temperature, neurologic status, and coagulation function should be monitored closely. Pulmonary toilet is extraordinarily important, and once clinically stable an epidural catheter may be advantageous to facilitate good pulmonary recovery. Antibiotics are given in a standard prophylactic fashion. Patients are extubated as soon as is clinically indicated. Chest tubes are removed when any air leak has stopped and drainage is less than 150 to 200 mL of serous fluid per day.

Complications

Complications after aortic repair occur at a rate of 40 to 50%.[13,34,36,42,108] Pneumonia is the most common complication and occurs at a rate of 17 to 34%.[13,34,36,42,108] Other complications include bacteremia, renal insufficiency, and paraplegia. Rates of frequency for several series are listed in

Table 57–6.

Major Postoperative Complications

	Schmidt et al[34] n = 73, %	Cowley et al[42] n = 51, %	Kodali et al[108] n = 50, %	Fabian et al[13] n = 207, %
Paraplegia	5.4%	19.6	10	8.7
Renal failure	9.6	9.8	4	8.7
Sepsis	13.7	9.8	—	—
ARDS/pneumonia	21.9	17.7	34	33
Left vocal cord paralysis	4.1	13.7	14	4.3
Left phrenic nerve palsy	1.4	5.9	—	—
Stroke	2.7	—	4	—
Re-exploration for bleeding	1.4	9.8	4.0	—
Pulmonary embolism	1.4	3.9	—	—
Deep vein thrombosis	2.7	—	—	—
Empyema	—	—	—	1.9
Wound infection	—	3.9	—	—
Chylothorax	—	3.9	—	—
Deaths	8.8	43.1	28.0	14 (31.3)*

ARDS = acute respiratory distress syndrome.

**Twenty-nine deaths (14%) occurred among the 207 patients who presented in stable condition. An additional 46 patients presented either in extremis or with free rupture, and all of these patients died in the hospital. All told there were 86 deaths among 274 patients included in the AAST trial (31.3%).*

Table 57-6.[13,34,36,42,108] Left vocal cord paralysis has been reported to occur at a rate of 4 to 14% percent, although recurrent nerve injuries are probably underreported. Late complications are rare in these patients. Aortobronchial fistula following repair of transection has been reported.[210,211]

Patients who survive an undiagnosed aortic injury may develop a chronic traumatic aortic aneurysm.[26,49–54,92–96] Among those patients with initial pseudoaneurysm formation, most develop progressive dilation with symptoms of pain referable to aneurysmal expansion. Other symptoms include dyspnea or cough secondary to compression of the left main stem bronchus, hoarseness due to stretching of the recurrent nerve, hemoptysis, or dysphagia. These chronic traumatic aortic aneurysms, once discovered, should be repaired regardless of size unless there are contraindications due to age or comorbidity.

Results

The mortality rate of patients with aortic rupture who reach the hospital ranges from 7 to 65% depending on whether or not the injury is repaired.[12,13,29–32,40] The large discrepancy is likely due to underreporting of patients who make it to the hospital but not to the operating room, as most series only report operative results. Among hemodynamically stable patients undergoing open repair or EVSG repair, the hospital mortality rate ranges from 0 to 20% in the modern era (Tables 57-6 and 57-7).[13,29,30,80,163] The mortality rate of nonoperative patients with associated injuries precluding initial aortic repair was 55% in the AAST trial.[13] All patients who either presented in extremis or with free rupture died of aortic rupture. A few small series have demonstrated acceptable survival rates of 67 to 72% in select, high-risk patients treated nonoperatively.[82,83] In his meta-analysis of 1492 patients, Von Opell reported an average of 7.8% of patients dying during aortic repair, and 13.5% dying in the postoperative period.[40]

Paraplegia or paraparesis occurred in an average of 9.9% of patients in the meta-analysis.[40] However, paraplegia rates vary widely depending on the operative technique utilized, with a range of 0 to 20% (see Tables 57-4 and 57-7).[12,13,29–32,40,42,72,73,80,86,108,147,149,163,198] Although there are several groups that have reported very low paraplegia rates

Table 57–7.

Results of Endovascular Stent Grafting (EVSG) for Aortic Transection (with Comparison to Open Repair)

Author, year	Study period (years)	# of Cases		Mortality		Paraplegic	
		Open repair	EVSG	Open repair (%)	EVSG (%)	Open repair (%)	EVSG (%)
Cook et al[29]	20	79	19	24.1	21.1	4	0
Pacini et al[80]	23	51	15	7.8	0	5.9	0
Rousseau et al[30]	18	35	29	17	0	5.7	0
Andrassy et al[72]	14	16	15	18.8	13.3	12.5	0
Ott et al[149]	11	12	6	17	0	17	0
Morishita et al[73]	3	11	18	9	17	0	5.6
Reed et al[31]	5	9	13	11	23	0	0
Lachat et al[198]	N/A	N/A	12	N/A	0	N/A	0
Peterson et al[147]	4	N/A	11	N/A	0	N/A	0
Pooled data		214	138	16.8	8.7	5.6	0.7

using the "clamp-and-sew" technique, these results have not been widely reproduced.[13,32] It is clear that increasing cross-clamp time, particularly beyond 30 minutes, increases the rate of paraplegia.[13,166] Alternatively, use of extracorporeal lower body perfusion systems have facilitated low rates of paraplegia.[13,163] Our own institutional data similarly demonstrate that since the practice of partial left heart bypass for all open repairs of aortic transection was instituted in 1994 (over 50 patients), there have been no cases of paraplegia (unpublished data). The preponderance of data suggests that the combination of partial left heart bypass for lower body perfusion with short, less than 30 minutes, cross-clamp time affords the lowest rate of paraplegia.[13,40] The early results of EVSG repair suggest that it may reduce the risk of paraplegia further (see Table 57-7), although to date the data are limited and comparisons are retrospective.

NONAORTIC GREAT VESSEL INJURY

The majority of injuries to the great venous structures and the pulmonary arteries are a result of penetrating trauma. Blunt trauma to these structures is rare, presumably because of their distensibility and low pressure. The incidence of injury to the nonaortic great vessels among cases of penetrating thoracic trauma is not known; however, the overall incidence of great vessel injury with thoracic gunshot wounds is approximately 5% and with stab wounds is 2%.[212] Wounds penetrating the thoracic "box" bordered by the midclavicular lines, the thoracic outlet, and xiphoid process should be explored operatively. Chest tubes should be inserted as a diagnostic and therapeutic measure, and an echocardiogram or a subxiphoid pericardial window performed to rule out hemopericardium. Patients with a high index of suspicion of mediastinal great vessel injury or with a confirmed hemopericardium should undergo sternotomy. Patients with central venous or pulmonary arterial rupture will decompensate from pericardial tamponade. Expeditious pericardial decompression will often provide enough stability to facilitate definitive repair. Exsanguination from a venous or pulmonary arterial injury into one of the hemithoraces requires immediate massive volume resuscitation and transfer to the operating room. Choice of incision should be made based on clinical suspicion of site of injury or objective data (arteriography, chest radiograph, or bleeding site). When the site of injury is not clear, median sternotomy provides excellent access to the heart and great vessels, and it can be extended across a hemithorax or up the neck along either sternocleidomastoid to facilitate exposure of any vascular structure in the chest. Most venous injuries and pulmonary arterial injuries when localized and simple can be repaired without cardiopulmonary bypass. Large or complex venous, and particularly pulmonary arterial, injuries are often more easily repaired on full cardiopulmonary

bypass with a decompressed heart. When repairing pulmonary venous injuries it is important to safeguard against air embolus, the result of which can be devastating. Therefore, complex pulmonary venous injury may require aortic cross-clamping with cardioplegia to prevent embolus to the brain.

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PART

VI

Surgery for Cardiac Arrhythmias

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CHAPTER 58

Interventional Therapy for Atrial and Ventricular Arrhythmias

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Therapy available for the treatment of heart rhythm disorders has gone through significant evolution. Although previously limited to pharmacologic therapy, the transformation and adaptation of surgical procedures to a minimally invasive catheter-based approach, and subsequent hybridization of the approach has led to new possibilities in arrhythmia management. A fundamental understanding of the invasive diagnostic and therapeutic strategy for treating heart rhythm disorders is critical to surgical specialties exposed to these rhythm disorders. This chapter will focus on catheter-based ablation, predominantly radiofrequency (RF) ablation, the most common type, but will also briefly explore alternative energy sources. It will also review diagnostic strategies and localization of specific tachyarrhythmias to appropriately target the energy delivery.

HISTORICAL EVOLUTION

The recording of intracardiac signals through electrodes, and subsequent stimulation of the cardiac tissue using these same electrodes, allowed for development of the concept of ablation. In 1967, Durrer and associates first described reproducible initiation and termination of tachycardia in a patient with atrioventricular re-entrant tachycardia (AVRT) using a bypass tract.[1] In 1969, the His bundle was first reproducibly recorded using a transvenous electrode catheter.[2] The continued advancements allowing localization of intracardiac signals led to the study of a variety of tachyarrhythmias.

The idea emerged that critical regions of cardiac tissue were necessary for the initiation and propagation of tachyarrhythmias. If these regions could be interrupted, the tachyarrhythmia could then be clinically cured. Once catheter mapping could localize arrhythmogenic foci, surgical excision was contemplated. In 1968, a description of such a surgical procedure for the elimination of an accessory pathway was first published.[3] This heralded an era of nonpharmacologic treatment of tachyarrhythmias.

Surgical Ablation

A variety of arrhythmogenic foci and circuits were successfully mapped and ablated using surgical techniques in the 1970s. Resection of an atrial focus felt to be responsible for an atrial tachycardia was reported in 1973.[4] Identification of re-entry circuits within the atrioventricular (AV) node allowed surgical dissection to treat AV nodal re-entrant tachycardia (AVNRT) without causing complete heart block.[5] Although surgical ablation was therapeutic for a variety of tachyarrhythmias, the morbidity and mortality associated with thoracotomy and open-heart surgery limited its application. Because most supraventricular tachycardias (SVTs) are not life-threatening, the risk of the procedure was hard to justify. Rather, ablation procedures were an option of last resort in highly symptomatic patients refractory to medical therapy. With these limitations of the surgical approach, catheter-based ablation procedures were explored.

Catheter Ablation

In attempts to minimize the morbidity associated with ablation, a method of using a catheter to delivery energy to cardiac tissue to achieve local tissue injury was sought. In 1981, Scheinman and colleagues reported the first catheter-based ablation procedure, describing the ablation of the His bundle in dogs.[6] This same group, in March 1981, performed the first closed-chest ablation procedure in a human. A patient with atrial fibrillation and rate control refractory to medical therapy was placed under general anesthesia and a catheter was advanced to the His bundle region. Using a standard external direct-current (DC) defibrillator, they attached one of the defibrillator pads to the intracardiac catheter and used the second defibrillator pad as a cutaneous grounding pad. A

series of DC shocks was delivered between the two pads and complete heart block, and thereby rate control, was achieved.[7]

This closed-chest catheter-based procedure was quickly adopted to treat a variety of SVTs dependent on the AV node.[8] However, to restore quality of life, these patients undergoing AV node ablation frequently required pacemakers, which at the time were not the small devices we are accustomed to today. As experience was gained and specific catheters were developed, energy could be more precisely directed to allow ablation of accessory pathways, atrial tachycardia, single limb of AVNRT, and ventricular tachycardia.

Although DC shock ablation allowed for the initiation of catheter-based ablation, it had its own limitations. The mechanism for DC shock ablation is such that a high-energy discharge from the catheter tip is developed. This results in the formation of a plasma ball at the distal electrode and subsequent "explosion" at the electrode tip. Because energy delivery was not titratable, such treatment had variable outcomes, including cardiac rupture and perforation. Since DC energy was delivered from the intracardiac electrode toward a cutaneous site, general anesthesia was required.

The introduction of RF energy as an ablative energy source heralded a new era in the nonpharmacologic, nonsurgical treatment of arrhythmias. RF energy had been used for decades by surgeons for surgical cutting and cautery and had a long history of safety and efficacy. Animal studies using RF energy were first described in 1987.[9] Intracardiac RF energy produces controlled lesions at the catheter tip over a period of 40 to 120 seconds. The improved safety and efficacy of RF catheter-based ablation procedures quickly replaced DC shock ablation techniques.

BIOPHYSICS OF ABLATION

Ablation using RF as an energy source involves the delivery of sinusoidal alternating current between the catheter tip at the endocardial surface and a large grounding pad on the skin. The current has a frequency of 350 to 700 kHz. The principal method of tissue injury with RF delivery is thermal. As the RF energy passes through the tissue at the distal electrode of the ablation catheter, resistive heating produces coagulation necrosis. The lesions produced are well demarcated and are 5 to 6 mm wide by 2 to 3 mm deep when a standard catheter tip is used. To achieve irreversible tissue injury, a tissue temperature of about 55° to 58°C is required.[10] At temperatures above 100°C, plasma reaches the boiling point and coagulates on the catheter tip. Coagulum and desiccated tissue act as an insulating barrier to energy delivery, resulting in a rise in impedance and the prevention of tissue heating. If subendocardial tissue temperature exceeds 100°C, steam may be formed within the tissue, resulting in a rapid expansion and crater formation and an audible "pop" during ablation. Much like DC shocks, such steam "pops" can cause unpredictable injury (e.g., to surrounding normal conduction tissue) as well as rupture of thin-walled structures. Thus it is important to regulate the temperature of the catheter-tissue interface by regulating the energy delivered. Contemporary RF ablation catheters have a thermistor or thermocouple that allows for automatic adjustment of the temperature at the electrode tip–tissue interface through adjustment of power. This allows the maximal energy delivery without the buildup of excessive temperature that results in coagulum and increases in impedance.

A limitation in lesion size places some epicardial foci and arrhythmia circuits out of reach of endocardial ablations. One method to increase lesion size and depth uses the principle of limiting coagulum size by increasing the electrode-tissue interface by increasing tip size. In vitro studies have shown that 8-mm catheter tips produced lesions that are twice as deep and four times larger than lesions produced by standard 4-mm tips.[11] A limitation of larger catheter tips is that the larger surface area makes it difficult to regulate power delivery and achieve even temperatures. High current densities develop at the edges of the electrode resulting in higher temperatures and coagulum formation. The larger catheter tips have been shown clinically to significantly reduce procedural and fluoroscopy time for some types of ablation.[12]

Cooling the ablation catheter tip with saline irrigation, either through the catheter or external to the catheter, can also prevent coagulum formation at the tissue interface. This prevents a rise in impedance and allows for more energy delivery deep into the tissue, resulting in deeper and larger lesions.[13] Irrigated RF catheters bathe the catheter tip internally using recirculating saline (Chilli II, Boston-Scientific, Natick, Mass) or externally through a porous electrode tip (Navistar Thermocool, Biosense-Webster, Inc., Diamond Bar, Calif). These catheters continue to utilize RF as an energy source; however, maximization of power delivery has demonstrated deeper lesions with a greater volume than with standard RF.[14]

Since the effects of RF ablation are usually irreversible, some ablations, such as for AVNRT, carry a 1% risk of complete heart block. Because of this concern, alternative energy sources have been developed that allow for reversible tissue injury prior to placement of permanent lesions.

One such catheter system (Freezor MAX, CryoCath, Montreal, Quebec, Canada) relies on gradual cooling of tissue to allow for an estimation of injury effect, and can be followed up by a more permanent cryoablation. Hypothermia has been the preferred method of delivering linear lesions in surgical ablation. This technique utilizes pressurized nitrogen or nitrogen oxide flow through a catheter tip nozzle. As the gas expands beyond the obstruction, there is a temperature drop to as much as –90°C. The advantage to the system rests entirely in its ability to deliver both transient and permanent injury to the tissue. The "cooling" phase (CryoMapping) allows one to assess not only the impact on pathologic tissue (e.g., anteroseptal accessory pathways, the slow limb of a dual AV node), but also to assess the impact of potential lesion placement on surrounding normal

conduction tissue.[15] If the CryoMapping phase yields desirable results, then the temperature is lowered even further to a "freezing" stage. Of interest is that during the "cooling" phase, an ice ball actually forms on the tip of the catheter and becomes mildly adherent to the tissue. This enhances stability of the catheter despite cardiac motion. The ability to deliver reversible injury and catheter stabilization has made CryoCath increasingly popular in those cases in which the pathologic lesion is in close proximity to the AV node and in younger patients in whom a pacemaker would be less than desirable.[16]

A second potential disadvantage to RF as an energy source is the risk of extracardiac tissue injury. Although constantly evolving, the inclusion of pulmonary vein (PV) isolation for treatment of atrial fibrillation is increasingly common.[17] There were early reports of PV stenosis following PV ostial RF ablation and concerns about atrioesophageal fistula following RF ablation in the left atrium.[18,19] Interestingly, the rate of intraoperative atrioesophageal perforation was as high as 1.3% in one open-chest series of patients undergoing linear lesions between PV ostia, to include the posterior wall overlaying the esophagus.[20,21] This has led to less anatomic, more functional, approaches in some centers, with the intent of avoiding extracardiac structures placed at risk by older techniques.[22,23]

The complexity of a nonanatomic approach to atrial fibrillation ablation has left many in search of alternatives allowing for PV isolation without risk of damage to extracardiac structures. One such approach may be through the use of energy-delivering balloons. Previous work with RF in delivery of linear ablations was limited by the exponential increase in the power supply necessary with increasing electrode length. However, the placement of a cryothermy balloon in a pulmonary vein ostium has been shown to cause a significant transmural lesion, without extracardiac injury.[24] However, the means by which extracardiac tissue is left uninjured is also a minor setback for this technology. The placement of a lesion is only in those areas with direct contact with the energy source. Since the target is unlikely to be the perfect circular shape built into a balloon, any flow around the balloon will be an area in which there will be no injury, and therefore acts as a potential source for continued atrial-PV electrical connectivity. Recent European approval and ongoing clinical trials in the United States of an endocardial deflectable catheter-based high-intensity focused ultrasound balloon (ProRhythm, Ronkonkoma, NY) may allow for the placement of transmural linear lesions without the need for direct tissue contact, and animal trials into the use of laser balloon therapy are ongoing.[25]

ELECTROPHYSIOLOGY STUDY PROCEDURAL PROTOCOL

Catheter ablation of tachyarrhythmias is typically an elective procedure with the patient presenting on an outpatient basis. As with any invasive procedure, patients need to be thoroughly evaluated and informed of the risks, benefits, and alternatives regarding the specific planned procedure. Occasionally, electrophysiology procedures are performed on an emergency basis in patients with recurrent or incessant hemodynamically unstable arrhythmias (e.g., ventricular tachycardia or atrial fibrillation with a rapidly conducting accessory bypass tract) that are refractory to drugs or overdrive suppression through a temporary wire.

Electrocardiographic (ECG) recording of the clinical tachyarrhythmia is crucial to planning the procedure. In the absence of hemodynamic instability, every attempt should be made to obtain an ECG prior to pharmacologic arrhythmia suppression. A patient may present to a physician's office or to an emergency department with the tachyarrhythmia, allowing the recording of a 12-lead ECG. A loop recorder or 24-hour Holter monitor is sometimes helpful to record symptomatic tachyarrhythmias.[26] The recording of onset and termination of the tachyarrhythmia, either spontaneously, with vagal maneuvers, or with drugs, is also very helpful in determining the mechanism of the tachycardia.[27–29]

Additional studies to be considered when evaluating the patient with a known or suspected arrhythmia include an echocardiogram to identify the presence of structural heart disease; a graded exercise test to determine catecholamine sensitivity with possible imaging to assess for ischemic burden; and right heart and left heart catheterization and coronary angiography to assess for stability of known disease, or to further seek etiology of a new arrhythmia. Because a diagnostic study can invoke hemodynamically unstable arrhythmias, it is important to know beforehand if there is myocardium at risk for either demand-related ischemia or for low-flow conditions.

All antiarrhythmic medications are usually discontinued at least four half-lives prior to the procedure to allow for induction of tachyarrhythmias. In most cases, AV nodal–blocking medications (commonly beta blockers and nondihydropyridine calcium channel blockers like diltiazem and verapamil) should also be stopped when the AV node may be involved in the re-entrant circuit. Anticoagulation medications should also be stopped, and depending on the indication, the patient may be bridged for the procedure with subcutaneous low molecular weight heparin or admitted to the hospital for intravenous heparin. Because of the need for systemic anticoagulation for ablative procedures that require left heart access, premenopausal women should avoid scheduling procedures that conflict with the first day of menses. Routine complete blood count, electrolyte status, and coagulation profile should be obtained before undergoing the elective procedure. Additional laboratory tests that are sometimes useful are thyroid function tests in patients with a history suggestive of hyperthyroid state, and a pregnancy test in women of childbearing age.

Patients should present on the day of the procedure in a fasting state in preparation for intravenous conscious sedation. Drugs typically used include short-acting benzodiazepines and narcotics in combination (e.g., midazolam and

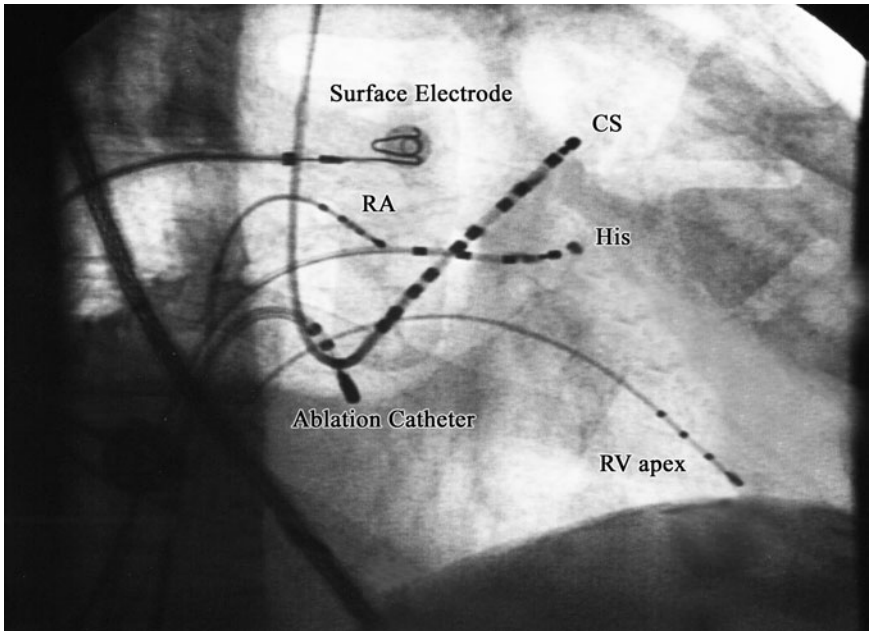


Figure 58-1. Radiograph in the right anterior oblique projection showing catheters positioned for a standard diagnostic electrophysiology procedure. Three nonsteerable diagnostic catheters are introduced from the inferior vena cava into the right heart. Two 4F catheters with four electrodes are positioned in the region of the right atrial appendage (RA) and right ventricular apex (RV apex). A 5F catheter with six electrodes is positioned across the tricuspid annulus to obtain a His bundle recording (His). A nonsteerable 6F catheter is introduced via the right internal jugular vein into the coronary sinus (CS) to obtain left atrial and ventricular recordings. Finally, a deflatable 7F ablation catheter is positioned in the region of the low right atrium.

fentanyl). Because sedation may suppress arrhythmias, or alter the conduction properties of the heart, administration of these agents should be at the discretion of the electrophysiologist. Although general anesthesia is rarely required, it may be used in those undergoing prolonged procedures or in high-risk unstable patients.

Patient Monitoring

Continuous monitoring is performed using surface ECG, noninvasive or invasive blood pressure monitoring, continuous pulse oximetry, and capnography. An external defibrillator is available and attached to the patient with "hands-free" patches throughout the procedure. Intubation and resuscitation supplies should be readily available. Electrophysiologic procedures are typically divided into diagnostic and ablative phases. The diagnostic phase involves obtaining venous access, passage of multiple catheters into the heart to record intracardiac electrograms, and induction and mapping of tachyarrhythmias. Only after mechanistic determination of a tachyarrhythmia is ablation considered.

Diagnostic Electrophysiology Study

Diagnostic localization of tachyarrhythmias involves positioning catheters in strategic locations within the heart to obtain intracardiac recordings from all four chambers of the heart as well as from the His bundle. Venous access is typically obtained in the bilateral groins via the right and left femoral veins. Catheters of 4F to 6F in size are passed into the right atrium and right ventricle as well as positioned just across the tricuspid valve to obtain His bundle recordings under fluoroscopic guidance. To obtain recordings of the left atrium and ventricle, a catheter is guided into the coronary sinus, which passes posteriorly in the AV groove and drains into the right atrium. Because of the angle of the entrance into the coronary sinus, cannulation is easier via the superior vena cava and thus previously venous access has been obtained from the right internal jugular, left subclavian, or left antecubital vein. However, steerable catheters allow for reliable access from the inferior approach and are now being used more frequently (Fig. 58-1).

Anticoagulation and Electrophysiology Studies

Direct recordings of the left heart are sometimes necessary and accomplished either by transseptal cannulation via the intra-atrial septum from the right atrium, or via a retrograde approach from the femoral artery and across the aortic valve. Systemic anticoagulation with heparin is maintained during catheter manipulation in the left heart because of the risk of thromboembolic events. Animal models have determined that mural thrombus is evident in up to 50% of cases immediately following RF ablation.[9,30] The Multicentre European Radiofrequency Survey conducted from 1987 until 1992 revealed that 84% of institutions used unfractionated heparin during the procedure, and 56% used either postprocedural heparin for a mean of 3.4 $\pm$ 2.8 days, or warfarin for a mean of 29 $\pm$ 11 days following ablation.[31] In addition to the risk of mural thrombus at the site of ablation, there is mounting evidence of a systemic prothrombotic condition following RF ablation.[32,33]

Once diagnostic catheters are positioned, programmed electrical stimulation is performed to induce and study the tachyarrhythmia. Sometimes modulation of the autonomic nervous system is required to induce tachyarrhythmias with the infusion of atropine or isoproterenol.[34] As will be described later, there are specific pacing maneuvers to initiate and evaluate the mechanism of a variety of

tachyarrhythmias. Once an optimal site for ablation is determined, steerable ablation catheters are positioned at the target site. These catheters come with a variety of curvatures. Specifically shaped long vascular sheaths may also be used to direct catheters. Once RF energy is delivered to the target site, re-induction of the tachycardia is attempted.

At the end of the procedure, all catheters and sheaths are removed and manual pressure held to achieve hemostasis. If the patient was heparinized for the procedure, sheath removal is delayed until anticoagulation reverses. The patient is placed on bedrest for 4 or more hours. During this recovery period, the patient is monitored for hemodynamic stability and recovery from sedation, and to assess for bleeding from puncture sites. The patient may be discharged to home the same day or be observed overnight in the hospital. Routine follow-up studies are not warranted unless required to assess for a complication. As mentioned previously, because of the risk of thromboembolic events, patients are frequently sent home on aspirin, thienopyridines, low molecular weight heparin, warfarin, or a combination of risk-appropriate antithrombotic therapies.

Complications Associated with Electrophysiology Studies

In referring patients for catheter ablation, it is important to weigh the risks and benefits of the procedure for the individual patient. Most tachyarrhythmias, although causing a variety of symptoms, are generally hemodynamically well tolerated and are not life-threatening. Thus an awareness of the potential complications of catheter ablation is necessary prior to referring a patient. Complications can be divided into those involving access, catheter manipulation within the heart, and ablation.

Access-related complications include pain, adverse drug reaction from anesthesia and sedation, infection, thrombophlebitis, and bleeding at the site of access. Complications associated with bleeding include hematoma or arteriovenous fistula formation. Arterial damage or dissection may also result. Systemic or pulmonary thromboembolism can occur, most seriously resulting in transient ischemic attack or stroke.

Complications associated with placement of intracardiac catheters can be more life-threatening. These include trauma of a cardiac chamber or the coronary sinus resulting in myocardial infarction, perforation, hemopericardium, and cardiac tamponade. Programmed electrical stimulation can result in the induction of life-threatening tachyarrhythmias such as ventricular tachycardia or fibrillation. Catheter manipulation can also result in usually transient but sometimes permanent damage to valvular apparatus or to the conduction of the right or left bundle branches due to mechanical trauma.

RF delivery within cardiac structures carries with it its own set of risks as alluded to previously. Inadvertent ablation of the normal conduction system could result in complete heart block requiring permanent pacing. Perforation of a cardiac chamber or vascular structure can also occur with RF delivery. Collateral damage to coronary circulation could result in myocardial infarction, heart failure, or cardiogenic shock. Phrenic nerve paralysis can occur. Ablation near the pulmonary veins within the left atrium can result in venous stenosis and pulmonary hypertension. Finally, new tachyarrhythmias can arise over the next 1 to 2 months due to what is likely a profound inflammatory process at the site of ablation, as well as from the scars induced by RF ablation.

An 8-year prospective study of 3966 procedures found an overall complication rate of 3.1% for ablative and 1.1% for diagnostic procedures. Complications are more likely to occur in elderly patients and those with systemic disease.[35] No deaths were reported in this series and other studies have shown very low mortality rates directly attributable to the electrophysiology study. Body dosimetry studies have shown that the lifetime excess risk per 60 minutes of fluoroscopy exposure is 294 per million cases or 0.03% per patient. The risk is higher for obese patients and the lungs are the most susceptible organs.[36]

DIAGNOSTIC ELECTROPHYSIOLOGY TECHNIQUES

A variety of techniques have been developed to elucidate the origin and mechanism of tachyarrhythmia propagation. These techniques are necessary to reveal targets for ablation. They involve pacing in a specific chamber at particular intervals to initiate a tachyarrhythmia, assess its response to pacing maneuvers, or terminate it.[37] Thus some of these techniques involve pacing in sinus rhythm while others are performed during the tachyarrhythmia.

Activation Mapping

Activation mapping is a technique of localizing focal tachycardias and accessory pathways. It involves positioning the mapping/ablation catheter during the tachyarrhythmia in such a way that activation at the catheter electrode tip precedes any other intracardiac activation or corresponding surface P wave or QRS. The earliest site of activation during a focal tachycardia must by definition be the source of the tachycardia.[38,39] The use of electroanatomic mapping systems allows for logging of local activation times in a three-dimensional model.[40] Earliest activation can then be easily relocated for stable re-entrant rhythms.

Accessory pathways can also be mapped using this technique by tracing the tricuspid and mitral annulus with the ablation catheter. The atrial insertion can be localized by determining the earliest site of retrograde atrial activation during AVRT or in sinus rhythm during ventricular pacing. The ventricular insertion can be localized in patients with preexcitation by determining the site of earliest ventricular activation during sinus rhythm.

Pace Mapping

Pace mapping is performed during sinus rhythm after obtaining a 12-lead surface ECG during tachycardia. By pacing at different sites and comparing the resulting paced ECG to the tachycardia ECG, the disparity can be assessed and the catheter can be repositioned until a perfect 12-lead match is obtained.[41] These sites are then the targets for ablation. This technique is typically used for focal ventricular tachycardias, especially those of right ventricular outflow origin.[42]

Mapping of local electrogram potentials requires recording an intracardiac signal from the structure targeted for ablation. For instance, to achieve complete heart block, the His bundle is the target and the ablation catheter is positioned such that the distal tip is recording a His bundle potential. Similarly for bundle-branch re-entry, the right bundle potential is used to target the right bundle to achieve right bundle-branch block. Sometimes an accessory pathway potential can be recorded and used to localize a target for ablation.[43]

Anatomic Mapping

Anatomic mapping is yet another way to localize potential targets for ablation by using fluoroscopy to localize anatomic landmarks for ablation. Catheters placed through the inferior vena cava into the coronary sinus and across the tricuspid valve delineate these structures. In typical atrial flutter that is dependent on the cavotricuspid isthmus, anatomic landmarks are used for the delivery of a line of lesions to prevent conduction across this isthmus. Bidirectional conduction block across this isthmus terminates flutter and prevents its reinitiation.[44]

Entrainment Mapping

Entrainment mapping is a technique of localizing re-entrant circuits for ablation. It involves positioning the catheter in a region thought to be involved in a re-entrant tachycardia. This is confirmed by pacing during the tachycardia slightly faster than the tachycardia rate. If the pacing site is within the circuit, then activation should proceed orthodromically, or in the same direction as the tachycardia, around the circuit resulting in an identical activation pattern. The resultant QRS or P wave should match that of the tachycardia. At the termination of the pacing the activation wavefront proceeds around the circuit. Therefore, if pacing was in the circuit, the first beat should be close to the cycle length of the tachycardia.

In clinical situations a combination of these mapping techniques is used to localize an arrhythmia for ablation. Usually an anatomic approach is used to find the general region and then more precise mapping is used to specifically localize the focal arrhythmia or re-entrant circuit.

Advanced Mapping Techniques

The success of ablation is very much dependent on localization of arrhythmogenic foci and circuits. The previously mentioned mapping techniques are useful for arrhythmias that originate from specific anatomic locations or have characteristic endocardial electrograms. Conventional fluoroscopy and the use of a single roving mapping catheter have limited success in ablation of complex arrhythmias that may originate from sites without characteristic fluoroscopic landmarks or have variable electrograms as recorded from the catheter tip. Advanced mapping techniques have been developed as adjuncts to conventional methods to improve the efficacy of catheter ablation for arrhythmias that are transient, focal, or hemodynamically unstable and thus require rapid mapping.

The multielectrode "basket" catheter (Constellation, Boston-Scientific, Natick, Mass) is a system with eight splines each with eight electrodes. The splines expand within a cardiac chamber to provide recordings from all 64 electrodes simultaneously to enable reconstruction of activation maps such that a single ectopic beat can be mapped online rapidly. Although these catheters are still fluoroscopically guided, multiple data points are acquired simultaneously, limiting procedure times, especially in patients with hemodynamically unstable arrhythmias.[45] Low spatial resolution limits this technology to larger macro re-entrant arrhythmias.

An electroanatomic mapping system (CARTO, Biosense, Diamond Bar, Calif) uses a magnetic field to localize the mapping catheter tip in three-dimensional space. Three coils in a locator pad located beneath the patient's chest generate ultra-low-intensity magnetic fields in the form of a sphere that decays in strength. A sensor in the catheter tip measures the relative strength and hence the distance from each of the coils. This allows for the recording of the spatial and temporal location of the catheter. Electrodes at the catheter tip record local electrograms, and this information is displayed on screen as a three-dimensional map of the local activation times relative to a reference catheter in a color-coded fashion. Data from multiple single mapping points acquired during tachycardia can be reconstructed to show animated sequences of arrhythmia propagation. Voltage maps can be obtained to delineate regions of scar and diseased myocardium.[46]

A similar endocardial mapping system (EnSite NavX, St. Jude Medical, St. Paul, Minn) consists of a catheter with a woven braid of 64 insulated 0.003-mm-diameter wires with 0.025-mm breaks in the insulation that serve as electrodes. A locator signal is generated between the array and a standard mapping catheter to permit nonfluoroscopic localization of the catheter to regions of interest. The position of the roving catheter is acquired over time to construct a three-dimensional map of the endocardial surface. The woven braid also acts to obtain and then reconstruct a virtual electrogram of the chamber of interest. Over 3360 virtual electrograms are simultaneously acquired by this system, allowing high-density maps to be acquired from a single beat. Thus this system is very useful for mapping in unstable or transient, nonsustained arrhythmias.[47]

The largest advantages to these mapping systems are the increase in patient and operator safety through the reduction of fluoroscopy while preserving precise localization of the catheter tip. In addition, recordings of catheter position allow for the repositioning of the catheter to previously mapped sites of interest.

Intracardiac echocardiography (ICE) has extended the principles of intravascular ultrasound (IVUS) for electrophysiologic use.[48] In contrast to IVUS catheters, ICE catheters use lower-frequency (5.5 to 10 MHz) transducers to extend the imaging range. Newer ICE catheters are steerable and have Doppler capability (Acuson, Mountain View, Calif), allowing for hemodynamic evaluation of intracardiac structures. For electrophysiologic use, ICE catheters are useful for visualization of endocardial structures such as the fossa ovalis and for guiding transseptal catheterization.[49–51] As the recognition of the importance of anatomy in the genesis of arrhythmias has grown, so has the importance of imaging. ICE catheters allow the accurate targeting of anatomic sites such as the crista terminalis and pulmonary vein ostia.[52] They are useful for imaging diagnostic and ablation catheter positions and visualization of tissue contact for optimal ablation. Through visualization of pericardial effusions, rapid diagnosis of perforation and other complications is feasible.

CLINICAL APPLICATIONS

Using the techniques described above, a variety of tachyarrhythmias can be targeted for percutaneous catheter-based ablation, including both atrial and ventricular arrhythmias that are either focal or that utilize re-entrant circuits.

Atrioventricular Nodal Re-entrant Tachycardia

The most common SVT is AVNRT.[53] Of patients with SVT, AVNRT represents up to 60% of cases that present to tertiary centers for electrophysiologic studies. This tachycardia can present at any age, although most patients who present for medical attention are in their 40s and the majority are female.[54,55] Advances in RF catheter ablation of this tachycardia has made it a first-line therapy for those symptomatic patients not wishing to take medications.[56]

This tachycardia has a re-entrant mechanism utilizing two pathways within the AV nodal tissue. The pathways are known as the "slow pathway" and "fast pathway" based on their relative conduction velocities. The anatomic location of these pathways is variable but generally located within the triangle of Koch. The Koch triangle is bounded by the tricuspid annulus and the tendon of Todaro with the coronary sinus at the base. The apex of the triangle is the His bundle at the membranous septum where it passes through the central fibrous body. The anterior third of the triangle contains the compact AV node and the fast pathway, and the middle and posterior portion, near the coronary sinus os, contains the slow pathway (Fig. 58-2).[57]

In the typical form of AVNRT, antegrade conduction from the atrium to the ventricle occurs over the slow pathway, and the retrograde conduction from the ventricle to the atrium occurs over the fast pathway. Since conduction in the

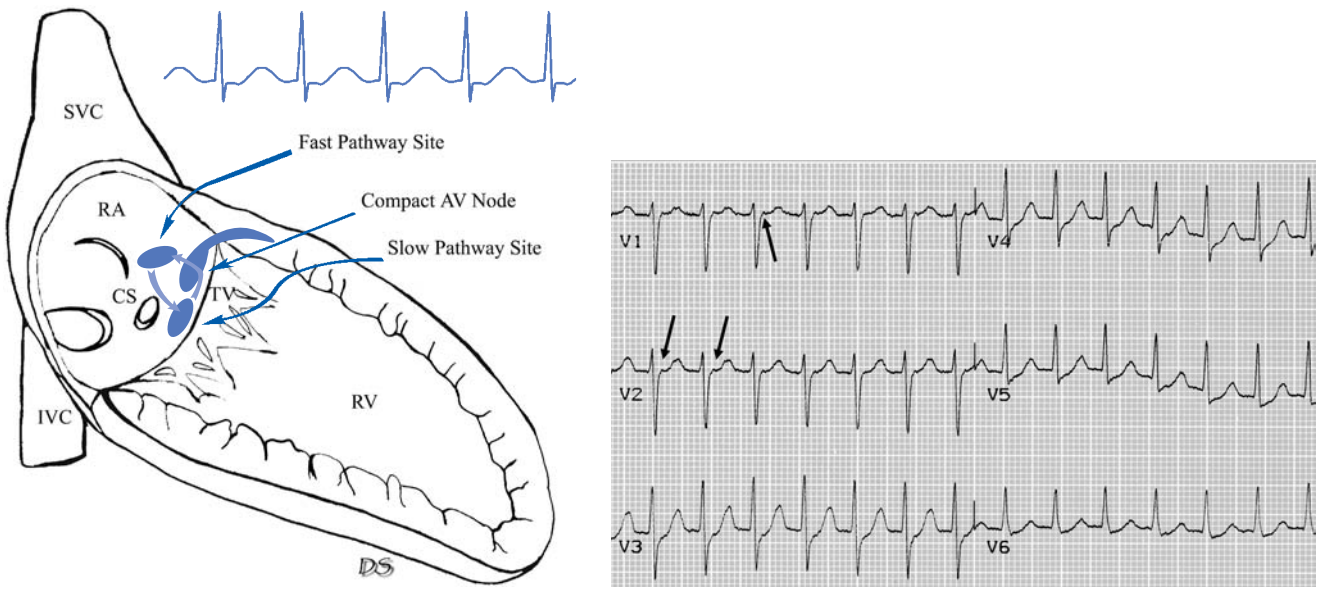


Figure 58-2. (A) Diagrammatic representation of typical atrioventricular nodal re-entrant tachycardia. Surface ECG shows narrow complex tachycardia with no clear P waves. The re-entrant circuit (gray arrows) consists of the posterior slow pathway region acting as the antegrade limb, and the anterior fast pathway region acting as the retrograde limb. The slow pathway target site is located between the coronary sinus os (CS) and the tricuspid valve annulus (TV). IVC = inferior vena cava; RA = right atrium; RV = right ventricle; SVC = superior vena cava. (B) Surface ECG showing precordial leads in AVNRT. This demonstrates that the retrograde P waves are barely discernible in some leads. In V_1, it forms a pseudo r′ wave (arrow). P waves are also visible in the terminal portions of QRS complexes in V_2 and V_3 but not in the lateral leads.

retrograde direction is fast, the atria and ventricle are depolarized almost simultaneously. Thus the electrocardiographic feature of this tachycardia is P waves that are inscribed within the QRS and thus not seen or barely discernible at the termination of the QRS complex.[58]

In less than 10% of cases, the circuit is reversed. In *atypical* AVNRT, antegrade conduction occurs over the fast pathway and retrograde conduction occurs over the slow pathway. Thus the ECG of this tachycardia shows inverted P waves in the inferior leads denoting retrograde activation of the atria with short PR segment due to rapid antegrade conduction.[59]

In the early days of catheter ablation therapy, highly symptomatic patients who had failed drug therapy underwent AV junctional ablation utilizing DC shocks with the insertion of a permanent pacemaker. While this greatly improved quality of life, it made patients pacemaker-dependent. Initial attempts to selectively eliminate AVNRT while leaving antegrade AV nodal conduction intact were performed with DC energy.[60] While selective pathway DC shocks were being studied, RF as an energy source was developed and quickly replaced DC shocks as a mode of therapy.

Early procedures utilizing RF energy targeted the fast pathway. While successful in up to 90% of patients, there was still a 5 to 10% incidence of inadvertent complete heart block.[61] In addition, ablation of the fast pathway left the patients with prolonged AV conduction (a long PR interval). In some, this led to symptomatic atrial contraction during ventricular contraction (pseudopacemaker syndrome), especially during sinus tachycardia when they were unable to shorten the AV conduction interval. Subsequently it was determined that the slow pathway could instead be reliably targeted in the posterior triangle of Koch.[62]

Slow pathway ablation has a high degree of success with a recurrence rate in the range of 2 to 7%, with the complication of complete AV block occurring about 1% (range 0 to 3%) of the time.[63] The North American Society of Pacing and Electrophysiology (NASPE) self-reported surveys on 4249 patients who underwent slow pathway ablations had success rates of $>96\%$ and complication rates of $<1\%$.[64,65]

Pilot trials have demonstrated a similar immediate success rate but a higher recurrence rate in those treated with cryoablation as compared with RF ablation in patients with AVNRT.[66] This particular pilot trial was underpowered to show increased safety profile with cryoablation, but the European Multicenter Study RF Versus Cryo in AVNRT with 500 anticipated enrollees with 6-month follow-up may be able to provide us with a more definitive answer as to its superiority.

Atrioventricular Re-entrant Tachycardia

The next most common type of SVT is AVRT.[53] About 30% of SVTs are due to AVRT. This is a re-entrant tachycardia utilizing the AV node and an accessory pathway (AP). These APs are remnants of conductive tissue from embryonic development that span the normally electrically inert tricuspid and mitral valve annulus and provide an independent path of conduction outside the AV node between the atria and the ventricles. The most common form of AVRT is part of the Wolff-Parkinson-White (WPW) syndrome of ventricular pre(mature)-excitation and symptomatic arrhythmias. The most common APs connect the atrium to the ventricle. Other APs may connect the atria or AV node to the His-Purkinje system. In sinus rhythm, antegrade conduction over the AP results in pre-excitation of the ventricles through conduction by other than the AV node, and is manifested by a short PR segment and slurring of the onset of the QRS, the delta wave. Absence of these findings does not exclude an AP, as the degree of pre-excitation may vary or conduction may only occur in the retrograde direction (~30% of APs).

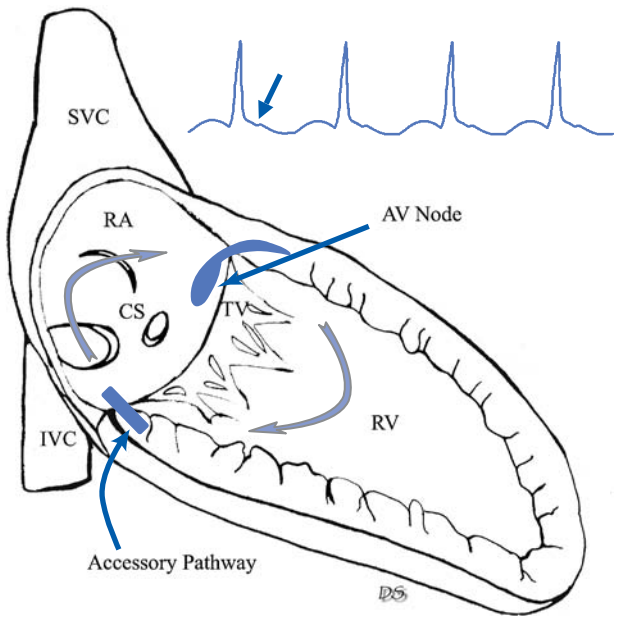
Patients with WPW typically present with palpitations due to rapid heart rate. This may be the result of AVRT or due to any SVT with resulting rapid AV conduction via the AP. Associated symptoms may be mild such as palpitations and shortness of breath, or as severe as syncope and sudden death.[67] Sudden death may be due to ventricular fibrillation resulting from the extremely rapid ventricular activation over the AP during atrial fibrillation in some patients.

Indications for ablation of APs include patients with symptomatic AVRT or those with atrial tachyarrhythmias with rapid ventricular conduction who fail or do not wish to undergo medical therapy. Relative indications for ablations include asymptomatic patients in high-risk professions, those with family history of sudden death, or those mentally distraught over their condition.[53]

In the typical or orthodromic form of AVRT, antegrade conduction from the atrium to the ventricle occurs over the AV node and retrograde conduction occurs over the AP. In this form of AVRT, the P wave in the tachycardia closely follows the preceding QRS complex with a long PR segment (Fig. 58-3). In the rare antidromic form of AVRT, antegrade conduction occurs over the AP with retrograde conduction over the AV node. This results in eccentric depolarization of the ventricle, producing a wide complex tachycardia with retrograde P waves that can be easily mistaken for ventricular tachycardia with one-to-one ventriculoatrial conduction.

Patients with highly symptomatic WPW syndrome or asymptomatic patients in high-risk professions who had failed medical therapy were the initial population to undergo surgical interruption of APs. Although this procedure evolved with success rates near 100% and mortality rates of 1%, it still involved a major surgical procedure.[68] Catheter-based ablation of accessory pathways has success rates approaching those of surgical ablation and have lower morbidity and mortality rates.

The first catheter ablation procedures were performed with DC energy in patients with posteroseptal accessory pathways.[69] With the development of RF energy for ablation, APs in all locations could be treated.



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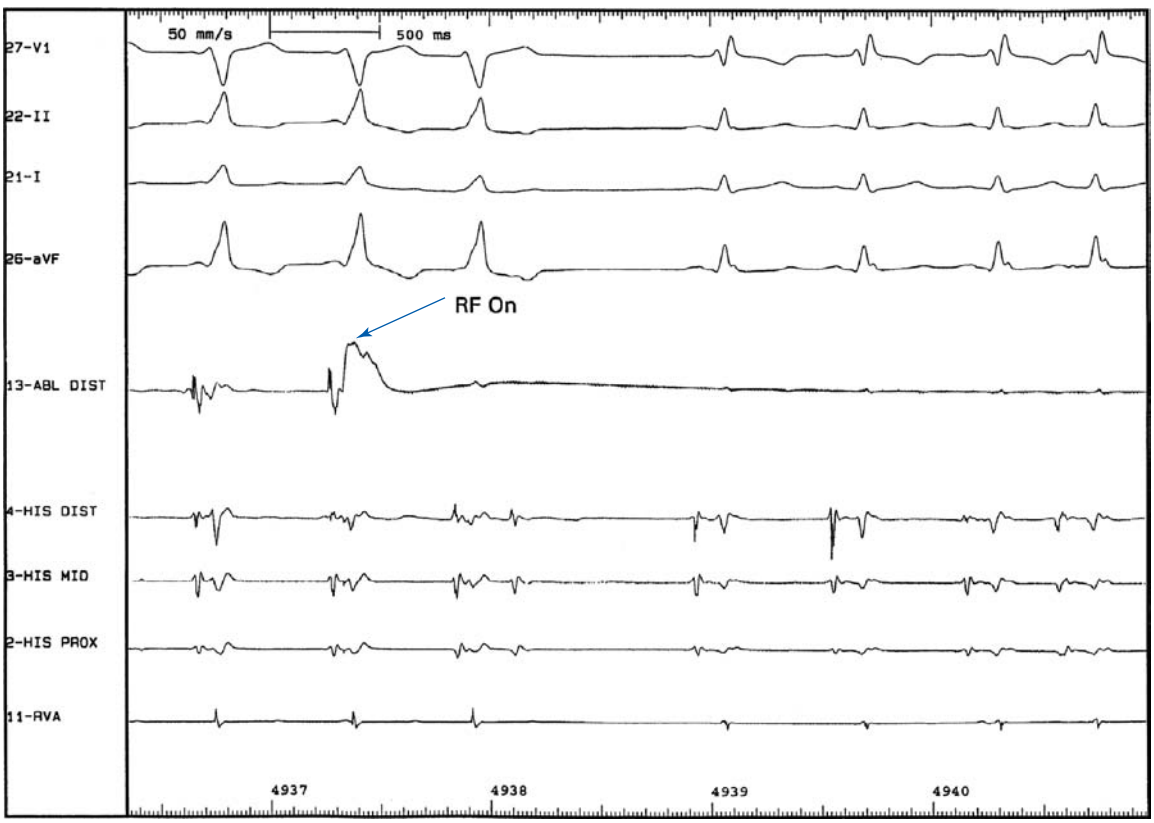

B

Figure 58-3. (A) Diagrammatic representation of atrioventricular re-entrant tachycardia. This macro re-entrant circuit (gray arrows) utilizes the AV node and an accessory pathway (AP), in this case a right lateral pathway. In orthodromic AVRT, antegrade conduction occurs over the AV node and retrograde conduction occurs over the AP. Because of the conduction delay from the His-Purkinje system through the ventricular myocardium to reach the AP, retrograde P waves are discernible after the QRS complexes (arrow). In antidromic AVRT, the re-entrant circuit is reversed and surface ECG shows P waves that closely precede the QRS complexes. CS = coronary sinus; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; SVC = superior vena cava; TV = tricuspid valve. (B) Intracardiac recording of atrioventricular re-entrant tachycardia with termination of eccentric conduction over the accessory pathway during RF ablation. The tracing at 50-mm-per-second speed shows four surface leads (VI, II, I, and aVF) and intracardiac recording from catheters: ablation (ABL); His distal, mid, and proximal; as well as right ventricular apex (RVA). The first three beats of the tracing show evidence of eccentric conduction over an accessory pathway: short PR segment and delta wave. With onset of RF energy (RF On) from the ablation catheter positioned in the region of shortest AV conduction, conduction becomes normal within two beats, with normalization of the PR segment and loss of the delta wave.

Ablation of a right-sided AP is performed by accessing the right heart via the femoral vein or occasionally via the antecubital, subclavian, or internal jugular veins. Left-sided APs are ablated via a transseptal approach or via a retrograde approach from the femoral artery. The initial procedures to ablate leftsided accessory pathways were via a retrograde aortic approach. While successful in more than 95% of patients, there was a small risk of aortic valve perforation or dissection of a coronary artery.[70] Most centers now perform ablation of left-sided accessory pathways via a transseptal approach.

Rarely, left-sided APs can be ablated from within the coronary sinus if they are on the epicardial surface, which is unusual. Due to the more sloping architecture of the tricuspid annulus, it is more difficult to achieve a stable catheter position for right-sided pathways. While the use of long curved vascular sheaths may be helpful, the success rates for right free wall APs may be lower than for other locations.

The major challenge that remains is the ablation of APs near the normal conduction system and those that are epicardial in location. Ablation of pathways that are anteroseptal and midseptal in location carries a high risk of causing complete heart block. It is hoped that newer ablative energy sources such as cryoablation, although found to be effective, may offer a safer alternative.[15] Recently, elimination of epicardial accessory pathways via a pericardial approach has been attempted.[71]

Unusual accessory pathways include atriofascicular (Mahaim) pathways. These show decremental conduction and the atrial insertion is typically located in the right free wall. These can often be successfully ablated via an endocardial catheter approach.[72] The 1998 NASPE prospective catheter ablation registry reported on 654 patients with a 94% success rate.[65] Success rates are lower (in the range of 84 to 88%) for septal and right free wall pathways. Other pathways have success rates in the range of 90 to 95%.[43,73,74]

Complications associated with ablation of accessory pathways include those associated with any ablation procedure. A specific complication associated with transseptal catheterization may be persistent intra-atrial shunt. Although acute shunt may be present in up to 50% of patients, long-term sequelae and persistence beyond 3 weeks are rare.[75,76] Mortality rates are less than 1% and nonfatal complications are about 4%.[65]

Atrial Tachycardia

Atrial tachycardias depend wholly on atrial tissue for initiation and maintenance of the tachycardia. Ectopic atrial tachycardia, sinoatrial nodal re-entrant tachycardia, inappropriate sinus tachycardia, atrial flutter, and atrial fibrillation can all be considered atrial tachycardias. Focal atrial tachycardias, a less common type of SVT, form about 10% of all SVTs referred for electrophysiologic studies.[53] Multifocal atrial tachycardia is due to multiple foci of abnormal automaticity or triggered activity and is not amenable to catheter ablation.[77]

Patients with atrial tachycardia present with palpitations and associated symptoms may include chest discomfort, shortness of breath, and dizziness. Symptoms most often are benign and not life-threatening. These arrhythmias are more common in patients with structural heart disease. Indications for ablation include failure or intolerance of medical therapy. Rarely, incessant tachycardias can lead to cardiomyopathy. With ablation and control of heart rate, myocardial dysfunction can be reversed, although there may be a delayed risk of sudden death that necessitates use of a defibrillator.[78–80]

Surface ECG features of atrial tachycardia include abnormal P-wave morphology or axes that are close to the following QRS complexes. Mapping and ablation of atrial tachycardias can be more difficult, as they can originate from anywhere within the right or left atrium. But there are specific anatomic regions that have a high incidence of foci and serve as primary targets. They include the crista terminalis, atrial appendages, valve annulus, and pulmonary ostia.[81] Intracardiac echocardiography has been used to localize these anatomic regions of interest.[82,83] Mapping can be facilitated by techniques previously mentioned and reviewed here.

Activation mapping by means of a roving mapping catheter is used to localize a region of earliest activation. Successful targets for ablation usually have intracardiac activation 30 ms or more prior to any surface P wave. Sometimes two catheters are used to triangulate a target by moving one catheter at a time toward sites of earlier activation. A caveat to this mapping technique is that an early right atrial activation site may in fact originate from the left atrium, as the posterior septum of the right atrium overlies the left atrium.[84] Other techniques that have aided focal ablation are the use of noncontact and electroanatomic mapping systems.[85,86] These newer mapping catheters have increased the success rate of ablation of focal tachycardias, especially in patients with altered atrial anatomy such as those with congenital anomalies and post–atrial surgery.[87–89]

Inappropriate sinus tachycardia and sinoatrial nodal re-entry tachycardias occur more infrequently and experience with catheter ablation of these tachycardias is more limited. Inappropriate sinus tachycardia is also difficult to ablate due to the variability and diffuse location of sinoatrial tissue.[90] Medical therapy is the preferred method of therapy and catheter ablation is attempted only after drug failure. Catheter ablation may result in complete loss of sinoatrial node function and resulting junctional rhythm, requiring insertion of a pacemaker. Even if the resting heart rate is reduced with nodal modification, symptoms may continue with episodes of tachycardia. Sinoatrial nodal re-entrant tachycardia is targeted for ablation using techniques similar to those used for other atrial tachycardias.

Success with ablation of atrial tachycardia is quite variable depending on the location of the arrhythmogenic foci and the experience of the operator. The 1998 NASPE survey showed a success rate of 80% for right-sided versus 72% for left-sided versus 52% for septal foci in 216 cases of atrial

tachycardia ablation.[65] Another large review examined the frequency of arrhythmias as a predictor of success. In 105 patients, the overall initial success rate was 77%, and 10% had recurrence over a 33-month follow-up period. There was an 88% success rate for the paroxysmal form versus 71% for permanent and 41% for repetitive forms of atrial tachycardia.[91]

Atrial Flutter

Atrial flutter is a type of atrial tachycardia that utilizes a macro re-entrant circuit contained within the atria. A variety of natural and surgical barriers to conduction can create a re-entrant circuit within the atria. Typical atrial flutter is due to a right atrial circuit, bound anteriorly by the tricuspid valve (TV) annulus. Posteriorly, it is confined by the superior vena cava, crista terminalis, inferior vena cava (IVC), eustachian ridge, and coronary sinus (CS)[92] (Fig. 58-4).

In the typical and more common form of atrial flutter, the circuit transverses the right atrium in a counterclockwise manner in the frontal plane. In the inferior leads, the P waves are negative and have a sawtooth appearance. In V_1, the P wave is usually upright and in V_6 it is inverted. Clockwise flutter utilizes the same circuit but in a reversed manner. The ECG also shows a reversed pattern. In the inferior leads the P waves are upright, with inverted P waves in V_1 and upright in V_6. This surface ECG morphology is suggestive of the circuit but needs intracardiac confirmation.[93] These two forms of atrial flutter have been termed "isthmus dependent" due to the use of the IVC-tricuspid annular isthmus. Other types of atrial flutter are called "atypical."

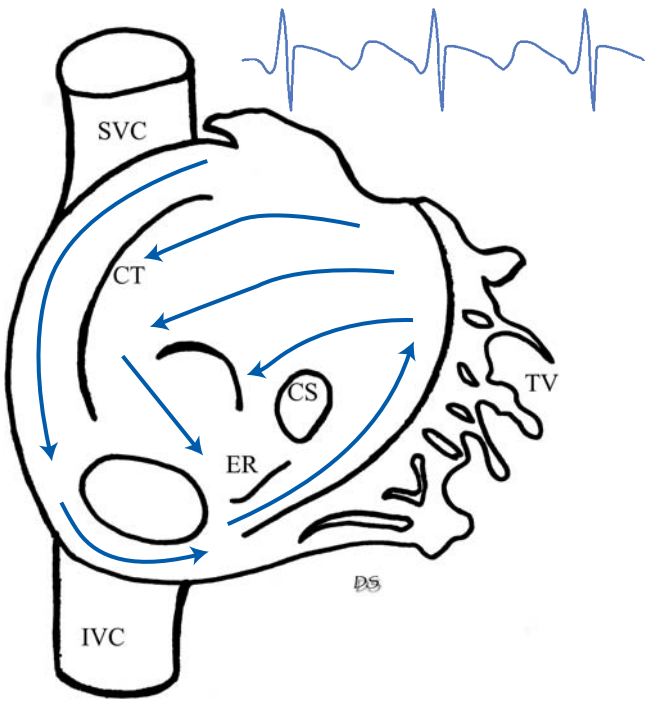

Figure 58-4. Diagrammatic representation of typical or counterclockwise right atrial flutter. Surface ECG shows large inverted P waves in the inferior leads. Lead III above shows 2:1 AV conduction with "sawtooth" flutter waves. The re-entrant circuit (gray arrows) is confined to the right atrium by the tricuspid valve annulus (TV) and barriers to conduction within the right atrium. These include the superior vena cava (SVC), crista terminalis (CT), inferior vena cava (IVC), eustachian ridge (ER), and coronary sinus (CS). The isthmus between the IVC and TV is the preferred target for ablation.

A macro re-entrant circuit can be cured by lesions that transect the circuit between two anatomic barriers. In the case of isthmus-dependent flutter, the target for ablation is the isthmus between the IVC and TV. This is a relatively narrow target and easily reachable by ablation catheters introduced from the IVC. Success rates for ablation of this form of atrial flutter are high. Initial success rates are up to 90% with recurrence rates of 10 to 15%.[94,95] Given these results, ablation has become the first line of therapy for recurrent isthmus-dependent atrial flutter.[53] In addition, studies have shown that the incidence of atrial fibrillation is markedly reduced in patients with atrial flutter treated with ablation as compared to medications.[96]

In some patients with atrial fibrillation, treatment with class IC antiarrhythmics or amiodarone results in the development of typical atrial flutter. A hybrid approach using ablation of the IVC-TV isthmus and continued use of the antiarrhythmic medication has been shown to be highly successful in reducing the incidence of atrial fibrillation.[97]

While the right atrial circuit described above is the most common, a variety of other circuits in the right and left atrium are possible. These are more common in patients with underlying heart disease. Although initially thought not to be amenable to ablative therapy, mapping and ablation of these arrhythmias are now routinely performed. However, the success rate is somewhat lower than that for typical isthmus-dependent atrial flutter. An electroanatomic map of a patient with left atrial flutter can be seen in Fig. 58-5. Ablation in the isthmus between these scars resulted in termination of the flutter.

Surgical Scar–Related Atrial Arrhythmias

Incisional scars from prior cardiac surgery can be the substrate for re-entrant atrial arrhythmias.[87–89] The most common is an atypical atrial flutter related to a lateral right atrial incision. Mapping demonstrates a circuit circling the incision. Ablation from the end of the incision to either the superior vena cava or more commonly the inferior vena cava is often curative.[98]

It had been thought that there was conduction block between the donor and recipient atria in patients who have undergone heart transplantation. Recent reports have demonstrated re-entrant arrhythmias due to donor-recipient atrial conduction. Mapping the connection between the atria can successfully ablate these arrhythmias.[99–101] Atrial arrhythmias have also been reported in a number of patients who have undergone the surgical Maze procedure for atrial fibrillation. These treatment failures are most often due to

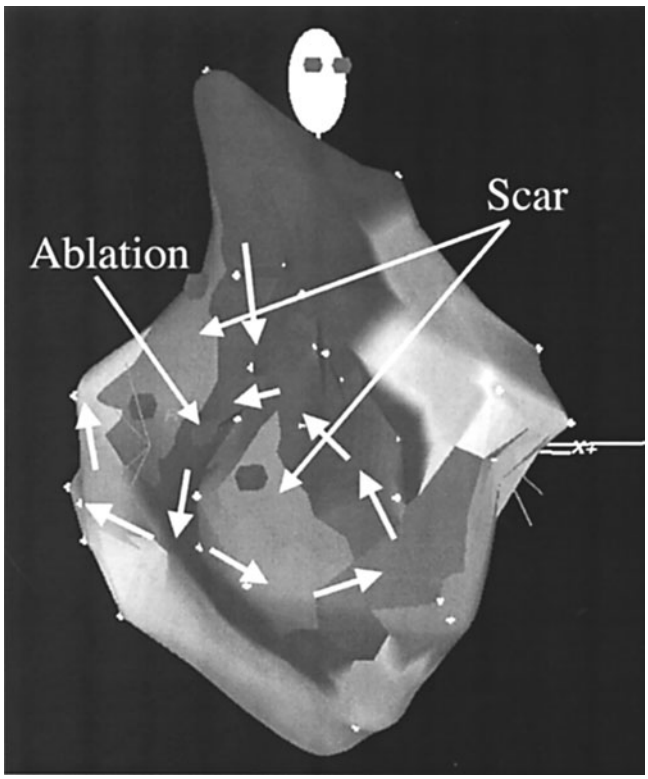

Figure 58-5. An electroanatomic map of a patient with left atrial flutter is shown in the right anterior oblique projection. Two large areas of scar can be seen in gray. Gradation in color shows activation sequence, with lighter being the earliest and darker being late in relation to a reference catheter, in this case positioned in the coronary sinus. The circulating wavefronts describe a figure-eight pattern around these two areas of scar but are confined by the narrow region (isthmus) between them. Ablation in the isthmus resulted in termination of the flutter.

re-entrant circuits involving gaps in the Maze lesion or through alternative pathways such as the musculature surrounding the coronary sinus.[102] These arrhythmias can now be successfully mapped and ablated. Mapping systems are useful in improving success of these ablations. The principle of interrupting these circuits by placing lesions to connect conduction barriers remains the same.[103]

Atrial Fibrillation

Atrial fibrillation is another difficult-to-treat atrial tachycardia with variable targets for ablation. Atrial fibrillation is often symptomatic for patients due to irregular and/or rapid ventricular rates. Patients can also be completely asymptomatic and present with stroke or be diagnosed on routine examination. Medical therapy for atrial fibrillation is of limited efficacy and pharmacologic control of atrial fibrillation may be associated with increased mortality in large trials.[104–106] In addition, sustained rapid ventricular rates can lead to a tachycardia-related cardiomyopathy.[80] When medical therapy aimed at maintaining sinus rhythm or blocking AV nodal conduction to slow ventricular response fails, ablation can be considered.[53]

In the past, AV nodal or His ablation, with placement of a permanent pacemaker, was considered in patients with difficult-to-control ventricular rates and symptomatic palpitations. The advantages of the approach are the relative ease and speed of the procedure. The downside is that it renders the patient pacemaker-dependent. Success rates of this procedure are nearly 100%.[53,107] Complications of this procedure include the same complications as those seen in other ablation procedures. A unique complication associated with creation of complete heart block is bradycardia-related ventricular tachycardia (torsades de pointes).[108] The incidence of this complication is reduced with high-rate atrial pacing at 80 to 90 bpm for up to a month following ablation. In highly symptomatic patients, this approach to the treatment of atrial fibrillation has been associated with improvement in quality of life and left ventricular function, and with a reduction in hospitalizations.[109] With up to 3 years of follow-up, no long-term sequelae have been noted.[110] Patients with congestive heart failure and atrial fibrillation may particularly benefit from this approach, and in some cases restoration of function will return as tachycardia slows; but in many cases it may be more beneficial to proceed directly with implantation of a cardiac resynchronization device.[111,112]

Surgical experience with the Maze procedure to create lines of conduction block in the atrium has led the way for catheter-based ablation procedures to treat atrial fibrillation. Studies have attempted to replicate the success of the surgical procedure using a catheter-based approach. Atrial fibrillation consists of multiple re-entrant circuits within the atrium; around the vena cava, pulmonary veins, and appendages; and around areas of functional block.[113] Creation of multiple lines of block between these nonconducting structures may prevent propagation of arrhythmic circuits.

A variety of catheter techniques have been employed including a "point-by-point" approach, a "drag" approach, and a multielectrode approach. Right atrial lesions alone were shown to be ineffective.[114] Attempts at left atrial or biatrial lesions have met with limited success due to the prolonged procedure times, high risk of complications, and limited efficacy.[115,116] There is also concern about reduced mechanical function of the atria following extensive ablation. This limits the hemodynamic benefit of the restored sinus rhythm. As understanding of the mechanism of atrial fibrillation has evolved, attempts to block propagation of atrial fibrillatory circuits have been abandoned in favor of attempted ablation of the fibrillatory triggers.

Data suggest that atrial fibrillation may in some cases be triggered by an organized SVT. About 12% of patients with AVNRT or AVRT will develop symptomatic atrial fibrillation in 1 year of follow-up.[117] Thus ablation of the initiating trigger arrhythmia may prevent atrial fibrillation. In a series of patients undergoing a left-sided catheter Maze procedure, it was discovered that rapidly firing premature atrial contractions arising from the musculature of the pulmonary veins were triggering atrial fibrillation.[118] Ablation of these foci eliminated atrial fibrillation in some patients. This procedure

has evolved to empiric electrical isolation of the pulmonary veins. One approach is the complete encircling of the pulmonary veins (i.e., wide area circumferential ablation).[119] Another approach is segmental isolation of each vein by mapping the location of the connecting fibers.[120] The encircling and nonencircling procedures have shown to be equally efficacious in 6-month follow-up. The advantage to the nonencircling method, whereby the focus is on pulmonary vein exit block, is the ability to avoid a posterior wall line. The placement of posterior wall lines is thought to be responsible for the finding of atrioesophageal fistula postoperatively. Electroanatomic mapping and intracardiac echocardiography have been employed to facilitate ablation.[121] Data on the long-term efficacy and complications of this procedure are limited and it is still considered to be a procedure in evolution. In one series of 251 patients, the short-term success over 10.4 months of follow-up was 80%. There was an 85% success rate in those with paroxysmal and 68% success in those with permanent atrial fibrillation. There was a continued need for antiarrhythmic medications in some patients.[122]

A major complication of ablation *within* the pulmonary veins was focal pulmonary vein stenosis. In 102 patients undergoing pulmonary vein focal ablation, 39% with right upper vein ablation and 23% with left vein ablation developed focal pulmonary vein stenosis by transesophageal echocardiography 3 days after the procedure.[123] In this series, only three patients experienced symptoms of dyspnea on exertion and only one had a mild increase in pulmonary pressure. Although most cases are asymptomatic, severe cases have been reported that progress to pulmonary hypertension and lung transplant. Changes to prevent this complication include limiting ablation to the vein ostia, limiting power, and using ultrasound imaging during ablation. Since its recognition as a possible adverse event, the occurrence postprocedurally should now be considered rare.

In some patients, triggering foci arise from outside the pulmonary veins. Reported sites have included the superior vena cava, ligament of Marshall, crista terminalis, posterior wall of the left atrium, tricuspid/mitral valve annulus, and limbus of the fossa ovalis. Pulmonary vein isolation failures in some cases may be due to the triggers from these alternative sites. In patients with persistent and/or chronic atrial fibrillation, there may be a combination of triggers and substrate responsible. Successful ablation may require elimination of triggers combined with modification of substrate.[22] The future of ablation for atrial fibrillation has been driving the future for electrophysiology.

Ventricular Tachycardia

Ablation techniques can also target ventricular tachycardia (VT). Over 90% of life-threatening ventricular arrhythmias originate from myocardium with structural abnormalities. Regions of scarred or aneurysmal myocardium create channels for re-entrant circuits. Initial successes with resection of ventricular arrhythmogenic foci and re-entrant circuits surgically have led to advancements in catheter-based ablation techniques. Beginning with DC ablation, techniques have advanced with the use of RF ablation catheters and electroanatomic mapping systems. Despite these advances, ablation for VT in patients with coronary artery disease has a secondary role. Given the life-threatening potential of VT in patients with structural heart disease, even a single recurrence can be disastrous. Therefore implantable cardiac defibrillators have become the primary therapy. Indications for ablation in this population are failure of antiarrhythmic medication to suppress symptomatic, sustained monomorphic VT, or more often frequent shocks from an implanted defibrillator despite optimal medical therapy.

There are several factors limiting the role of catheter ablation of ischemic VT. The hemodynamic instability of patients with coronary artery disease and depressed left ventricular function limits mapping during the tachycardia. A patient may have multiple re-entrant circuits, not all of which are clinically significant. The VT re-entrant circuits involve scarred myocardium or can be epicardial in locations that may be out of reach for RF energy to penetrate. Finally, short-term success may be eclipsed by development of new VTs with further myocardial injury.

Success of ischemic VT ablation is variable due to the heterogeneity of the population. Reported studies have shown efficacy in the range of 60 to 90% using the criteria of reduced defibrillator shocks and decreased need for antiarrhythmic medications. The recurrence rate is as high as 40%. Recently, success has been reported with an approach employing "substrate mapping." This technique defines the potential arrhythmic substrate using electroanatomic voltage maps. Ablation is targeted to eliminate potential re-entrant circuits. Complications are in the range of 2%, with concern for perforation and cardiac tamponade due to the thin, scarred ventricles that are the substrates for ablation and thromboembolic events in those undergoing extensive ablation.[124–126] One reason for failure of ischemic VT ablation is the deep or epicardial location of circuits. Catheter ablation has been directed at these epicardial circuits using a pericardial approach with some success.[127]

In patients with dilated cardiomyopathy and His-Purkinje system disease, sustained monomorphic VT can occur due to a macro re-entrant circuit using the bundle branches. Patients typically present with syncope or sudden death or can present with palpitations. The most common circuit is down the right bundle branch and up the left bundle branch resulting in a wide complex tachycardia with a left bundle-branch block pattern. Treatment involves ablation of one of the fascicles involved in the re-entrant circuit. The right bundle is most commonly targeted to interrupt the re-entrant circuit. Long-term success is good for prevention of recurrent bundle branch re-entry. Due to intrinsic conduction disease, patients may develop heart block. Patients may also develop other VTs due to other structural abnormalities, requiring further ablation, antiarrhythmic therapy, or defibrillator implantation.[128,129]

Other cardiac disorders can be associated with VT and are potential candidates for catheter ablation. These include right ventricular dysplasia,[130] infiltrative disorders (sarcoid), and tumors. As in patients with atrial arrhythmias due to surgical incisions, patients with prior ventricular surgery can develop incision-related VT. This has occurred most often in patients who have undergone repair of congenital abnormalities such as tetralogy of Fallot.

Ventricular tachycardia that presents in patients with no structural heart disease is termed idiopathic and represents up to 10% of all VTs that present to tertiary referral centers. Patients may be asymptomatic or present with palpitations, dizziness, or syncope. Idiopathic VT may be focal or a micro–re-entrant circuit utilizing the Purkinje fibers.

Focal VT can originate from either the right or left ventricle. Right ventricular tachycardia typically originates from the outflow tract, on the septal or free wall sites. It has typical left bundle-branch morphology with leftward, inferior axis. This occurs more often in women than men, and patients typically present in their 30s to 50s. Idiopathic left ventricular tachycardia typically originates from the left posterior fascicle. It has a right bundle-branch morphology with rightward, superior axis, and may be verapamil sensitive. It occurs more often in men. These VTs are localized by activation or pace mapping. Ablation is facilitated by the lack of other cardiac pathology and the presence of only one VT. Success rates for idiopathic VT are in the range of 70 to 90% with recurrence rates in the range of 15%. Complication rates are consistent with those of other ablative procedures.[131,132]

Cost-Effectiveness

Several studies have shown the cost-effectiveness of catheter ablation compared to medical therapy and surgical ablation. Catheter ablation has lower procedural costs than surgical ablation and reduces the need for further medical care and emergency department visits in comparison to drug therapy. Studies from both the United States and from Australia have shown both cost savings and improvement in quality of life for those undergoing catheter-based ablation compared to medical management.[133–135]

FUTURE DIRECTIONS

After the advent of steerable catheters, newer imaging techniques have been the most useful in directing the positioning of catheters to specific areas of interest within the heart. The techniques of nonfluoroscopic mapping discussed above have extended the efficacy of catheter-based ablation. Newer imaging techniques are in development that will continue to push the field of electrophysiology. The Niobe system (Steroetaxis, Inc., St. Louis, Mo) is a magnetic navigation system that uses two externally located magnets to create a steerable field that can be used to affect the magnetically active catheter tip. For advancing and retracting, the unit can be completely controlled remotely through a small motor. The entire system can be controlled from a shielded room by joystick and touch-screen monitors to allow for catheter manipulation through hands-free robotic catheter control. The ability to perform an entire ablative procedure with the primary operator behind a glass in a lead-lined room may be the next step in development of electrophysiologic treatment. One novel technology in development is the use of magnetic resonance imaging that would allow high-resolution three-dimensional mapping of the heart and localization of catheters in three-dimensional space in real time without radiation.[136] Magnetic resonance imaging would also allow for the visualization of any tissue injury due to attempted ablation in real time.

CONCLUSION

The past 35 years have seen the development of intracardiac recording, programmed stimulation, and catheter ablation. The field of interventional electrophysiology is relatively young. Over the past two decades, great advances have been seen in the interventional management of atrial and VTs. Where the surgeons have gone with their scalpels, electrophysiologists have followed with their catheters. Transvenous RF ablation, once the standard of care for the treatment of many arrhythmias, may be phased out in preference of alternative energy sources. These procedures have been proven to be safe and efficacious. Improved treatments for arrhythmias such as atrial fibrillation and VT will come with further understanding of the mechanisms underlying these arrhythmias. Future advances in catheter design, energy delivery, and imaging techniques will continue to advance the field of electrophysiology.

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CHAPTER 59

Surgical Treatment of Atrial Fibrillation

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ATRIAL FIBRILLATION

Atrial fibrillation (AF) is present in up to 2% of the general population and in approximately 10% of patients over the age 60, making it the most common form of sustained cardiac arrhythmia.[1–5] The actual incidence and prevalence of AF may be substantially higher, due to undetected asymptomatic AF and undersampling in patients with paroxysmal AF. With the increasing age of the population in North America, there is no question that the prevalence will continue to rise.[6] Health care costs related to AF have increased significantly. Admissions for inpatient care in which AF was a factor tripled between 1985 and 1999 in the United States, rising from 787,750 to almost 2.3 million.[7] Similarly, inpatient hospitalizations with the primary diagnosis of AF increased from 154,086 to 376,487 during the same period.[7] At this rate, experts predict that the number of AF-related hospitalizations will increase to over 3.3 million by 2025 in the United States.[7] It is not an exaggeration to state that AF is a growing epidemic in this country.[8]

AF is undoubtedly a costly public health issue. Unfortunately, the actual numeric data on the economic burden of AF are sparse compared to those on other significant cardiac disease states such as stroke and congestive heart failure. A recent study in the United Kingdom, however, estimated a 50% increase in health care expenditures on AF from 1995 to 2000.[9] Stewart and associates further stated that AF consumes around 1% of all health care expenditures and indirectly contributes to an additional 2% of the health care costs in the UK.[9]

Although AF is often considered to be an innocuous arrhythmia, it is associated with serious morbidity and mortality due to its three detrimental sequelae: (1) palpitations, resulting in patient discomfort and anxiety; (2) loss of synchronous atrioventricular (AV) contraction, which compromises cardiac hemodynamics, resulting in varying degrees of ventricular dysfunction or congestive heart failure; and (3) stasis of blood flow in the left atrium, which increases the risk of thromboembolism and stroke.[10–14] It has been estimated that AF results in a three- to fivefold increase in a patient's risk of stroke.[15] Twenty to 30% of all acute stroke patients are found to be in AF.[16–18] AF has been the attributed cause of stroke in one-quarter of patients over 80 years of age.[19] AF also independently increases mortality rates. Using the data from the Framingham Heart Study, Benjamin and associates established the risk factor–adjusted odds ratio for death in men and women with AF as 1.5 and 1.9, respectively.[20]

Unfortunately, the results with medical therapy for AF have been disappointing. Antiarrhythmic drugs have limited long-term efficacy in converting AF to normal sinus rhythm and have significant and sometimes fatal side effects.[21–26] The goal of pharmacotherapy is therefore often shifted from the ideal *rhythm* control to *rate* control (i.e., slowing the ventricular response rate to AF and avoiding the development of rate-related cardiomyopathy due to prolonged rapid ventricular response). The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study[27,28] showed that management with rhythm control did not have any survival benefit over a rate control strategy in anticoagulated patients with AF.[29,30] Furthermore, a rate control strategy may potentially have advantages over rhythm control, such as lower risk for adverse side effects that can be seen with aggressive rhythm control.[29]

Despite the results from the AFFIRM trial supporting no difference in long-term outcome between rhythm control versus rate control in anticoagulated patients with AF, some patients may have clinically meaningful advantages from being in normal sinus rhythm. These advantages include increased exercise tolerance, decreased palpitations, and prevention of atrial remodeling.[28,31] Most importantly, in the AFFIRM trial, the presence of sinus rhythm was associated with a significantly decreased risk of death (hazard ratio = 0.53, $p < .0001$).[32] The conclusion to be drawn from the

AFFIRM study is that antiarrhythmic drugs are detrimental, but normal sinus rhythm is beneficial in this patient population.

Rate control alone clearly has its disadvantages. Although the ventricular response rate can often be controlled pharmacologically with rate control, the atria are still in fibrillation. With persistent AF, three of the detrimental sequelae associated with AF persist. In patients with baseline cardiac dysfunction, the absence of atrial "kick" often can result in worsening symptoms of congestive heart failure. Most importantly, patients with chronic AF are at a risk for developing thromboembolism, requiring indefinite anticoagulation with warfarin. The use of warfarin itself is associated with significant morbidity, with a major complication rate of approximately 2% per year.[33–35]

PHYSIOLOGIC BASIS

AF is characterized by the irregular activation of the atria and an irregular ventricular response. Activation of the atria during AF exhibits two different patterns. One pattern is a stable source, focal or small reentrant circuit, with fibrillatory conduction away from the source. The other pattern is characterized by multiple changing sources or reentrant circuits. These sources can be stable for short periods of time, spawning one or more sources, that then assume dominance. For either pattern of activation there are four substrates that determine whether or not AF is initiated and sustained. They are: (1) a trigger, usually a premature depolarization or runs of focal ectopic depolarizations; (2) refractory period, both the magnitude and spatial distribution; (3) conduction velocity, including the magnitude and anisotropic spread; and (4) geometry or anatomy, both macroscopic and microscopic. Whatever the pathology, whether it be valvular disease, heart failure, ischemia, tachycardia, pericarditis, or inflammation, the changes that occur in the atrial myocardial structure and physiology affect one or more of these four factors.[36]

The surgical treatment of AF is directed at altering the geometry and anatomy needed to support AF. Non-reentrant mechanisms, such as abnormal automaticity or triggered activity, are important for the generation of premature beats, which act as a trigger for reentry, but may also be involved in maintaining AF. The premature beats interact with the underlying distribution of refractory periods. As the distribution becomes more inhomogeneous, unidirectional block can occur. This is a necessary condition for the initiation of reentry. When unidirectional block occurs, reentrant arrhythmia will occur only if a critical mass of tissue is present. The critical mass is the interaction of the tissue geometry, the magnitude of refractory periods, and the magnitude of conduction velocity. As the atrial size increases, or the conduction velocity is slowed, or the refractory period is decreased, the probability of initiating and sustaining AF increases. Although numerous nonpharmacologic approaches to treating AF have involved altering one of these substrates, like isolating triggers, it must be remembered that the other substrates can be affected, too. Incisions or ablations affect conduction, alter the geometry, and can denervate regions of the atria, altering refractory periods.

There are several systems of classifying AF. These include the historic paroxysmal and chronic AF. The classification system published jointly by the American Heart Association, American College of Cardiology, and the Heart Rhythm Society is the most widely used.[37] This system defines AF as either paroxysmal, persistent, or permanent. When a patient has had two or more episodes, AF is considered recurrent. If recurrent AF terminates by itself, it is designated paroxysmal; but if it does not, it is termed persistent. Termination by pharmacologic therapy or electrical cardioversion before expected spontaneous termination does not change the designation of paroxysmal. Permanent AF includes cases of long-standing AF (>1 year), in which cardioversion has not been indicated or has failed to convert the arrhythmia. This terminology applies to episodes of AF that last more than 30 seconds and that are unrelated to a reversible cause. Recently, Cox has offered a new system, defining intermittent and continuous AF.[38–40] In this system, the patient is either in AF all the time (continuous) or not (intermittent). This has not been widely accepted by professional organizations.

Recently, there has been a great deal of emphasis placed on the role of the pulmonary veins (PVs) in AF. Paroxysmal AF often originates in the PVs.[41] In humans, the anatomy of the PVs is variable, with electrically excitable cardiac muscle extending 1 to 4 cm beyond the ostium of the veins.[42] The cardiac muscle is insulated from the smooth muscle of the veins by connective tissue. The muscle fiber orientation is complex, spiraling perpendicularly around the vein with other fibers running parallel to the vein. There is an increase in connective tissue going from the proximal to the distal end of that portion of the vein composed of cardiac muscle.[43] Developmental biology data suggest that pacemaker tissue may be present in the PVs. During the development of human embryos, HNK-1 antigen, a specific marker of the developing specialized conduction system, is seen not only in the sinus and AV node regions, but also in the regions superior and inferior to the sinoatrial (SA) node, the coronary sinus, the lower septum, and the PVs.[44]

In studies in the guinea pig, normal and abnormal automaticity have been observed in the PVs.[45] However, no pacemaker tissue has been found within the veins of humans or animals. Another potential mechanism of focal activation is afterdepolarizations. Studies in animal models have also shown that these can be evoked from the PVs in animal models.[45] Intraoperative mapping studies in humans have shown ectopic atrial beats originating from the region of the PVs.[36] Biatrial mapping studies by Schmitt and colleagues have shown that the premature beats that trigger AF were located in the PVs 53% of the time.[46]

Arora and coworkers have shown in the canine atria that action potential durations are longer but more inhomogeneous in the PVs than adjacent muscle.[47] Recent studies by

Cha and associates, also in the dog, show exactly the opposite data with shorter action potential duration in the PVs than the body of the left atrium.[48] However, in atria that have remodeled as a result of a fast rate, the PVs no longer have a shorter refractory period than the surrounding tissue. In this model, removal of the PVs did not prevent the initiation or maintenance of AF. Jais and colleagues have shown in humans that refractory periods are longer in the PVs than adjacent muscle.[49]

Conduction velocities within the PVs are 0.3 m/s compared to surrounding left atrial tissue with velocities of 0.9 m/s.[47] The complex fiber orientation and the lack of Cx40 in the veins, a major determinant of conduction velocity in the atria, probably contribute to this slower conduction.[43] The slow conduction properties are particularly manifested during premature depolarizations that occur in the veins. Mapping studies in animal models have shown conduction to be decremental and highly anisotropic.[47] Arora and colleagues have demonstrated reentry within the veins with a circuit size of 1 to 2 cm.[47] Without adequate spatial resolution, such small circuits would appear focal. Most intraoperative and catheter mapping systems do not have the spatial resolution within the PVs to separate reentrant from non-reentrant mechanisms. So even though "focal" fibrillation may be reported, it is important to realize that this does not rule out reentry as a mechanism underlying the arrhythmia.

What is the significance of these data to the diagnosis and treatment of AF in patients? First, the mapping studies of Schmitt and associates suggest that the trigger for initiating AF is in the PVs slightly over 50% of the time.[46] Likewise, if the triggers were outside the PVs, but the other substrates were within the veins, the AF would be prevented. This logic assumes that there is only one driver of the AF. As shown by the low success of curing AF by isolating a single vein, this is not true for most patients. Nitta and coworkers have also observed concurrent drivers of AF by using intraoperative mapping in patients with mitral valve disease.[50] In our experience, the driver of AF moved during the short period in which we intraoperatively map (~10 minutes) in about 50% of patients. These data suggest that many patients have multiple potential drivers of AF. Furthermore, caution should be taken in interpreting various interventional studies, whether catheter ablation or surgery, about the underlying mechanisms involved in a patient's AF. In very few studies are only the PVs isolated. In some studies, all the PVs, adjacent atrial muscle, and the muscle in the oblique sinus between the veins are isolated. This represents about one-third of the left atrium. Some ablation devices extend beyond the PVs, further increasing the amount of left atrium that is isolated. This substantially reduces the critical mass needed to sustain AF and may incorporate other non-PV substrates.

It should be pointed out that the definitions of paroxysmal, continuous, persistent, chronic, and permanent AF do not imply a specific mechanism. Even though some data would suggest that in paroxysmal AF patients PV isolation is effective 70 to 80% of the time, it is clear that 20 to 30% of the time the PVs are not involved. Likewise, in persistent AF, where PV isolation alone has a much lower success rate, the definition of AF does not implicate a mechanistic substrate. The PVs have the substrates needed to initiate and maintain AF in some patients; however, they are not the only regions within the atria that can initiate and maintain AF, and present diagnostic technologies rarely allow for a preoperative delineation of mechanism.

HISTORICAL ASPECTS

Because of the inadequacy of medical therapy for AF, there has been strong interest in the nonpharmacologic treatment of AF, which led to the development of various catheter-based and surgical techniques in the 1980s and 1990s. Unfortunately, many of them were not successful in addressing all of the detrimental sequelae associated with AF. Nevertheless, they helped physicians gain fundamental knowledge regarding the mechanism of AF and laid a foundation for the development of the Cox-Maze procedure. The Cox-Maze procedure today is recognized as the gold standard for surgically curing AF. The next section of this chapter will briefly describe these various surgical procedures developed in an attempt to cure AF.

The Left Atrial Isolation Procedure

In 1980, Williams and colleagues developed the *left atrial isolation procedure*, which was successful in confining AF to the left atrium and restoring the remainder of the heart to normal sinus rhythm.[51] This procedure was important because it restored normal ventricular rhythm without requiring a permanent pacemaker. Since the sinoatrial node, AV node, and internodal conduction pathways are located in the right atrium and interatrial septum, the left atrial isolation procedure did not interfere with normal AV conduction.

Electrically isolating the left atrium also unexpectedly restored normal cardiac hemodynamics. This occurred because the right atrium and the right ventricle contracted in synchrony following the procedure, providing a normal right-sided cardiac output that was then delivered to the left side of the heart. Although the left atrium was isolated, the left ventricle adapted immediately to the normal right-sided cardiac output and delivered a normal forward cardiac output.

By confining AF to the left atrium only, the left atrial isolation procedure eliminated two of the three detrimental sequelae of AF: irregular heartbeat and compromised cardiac hemodynamics. However, since the electrically isolated left atrium remained in AF, this procedure did not eliminate the risk of thromboembolism.

Catheter Ablation of the Atrioventricular Node-His Bundle Complex

In 1982, Scheinman and associates described the *catheter fulguration of the His bundle*, which controlled the irregular

cardiac rhythm associated with AF and other refractory supraventricular arrhythmias.[52] Similar to the left atrial isolation procedure, this procedure electrically isolated the arrhythmia to the atria. However, ablating the His bundle necessitated the implantation of a permanent ventricular pacemaker to restore normal ventricular rhythm.

Unfortunately, His bundle ablation only eliminated the irregular heartbeat. Both atria still remained in fibrillation, and the vulnerability to thromboembolism was unaffected. AV contraction remained desynchronized, compromising cardiac hemodynamics. Despite its drawbacks, this remains a common current treatment of medically refractory AF.

The Corridor Procedure

In 1985, Guiraudon and coworkers introduced the *corridor procedure* for the treatment of AF.[53] This was an operation that isolated a strip of atrial septum harboring both the SA node and the AV node, thereby allowing the SA node to drive the ventricles. This procedure corrected the irregular heartbeat associated with AF, but both atria either remained in fibrillation or developed their own asynchronous intrinsic rhythm because they were isolated from the septal "corridor." In addition, the atria were also isolated from their respective ventricles, thereby precluding the possibility of AV synchrony. The corridor procedure was soon abandoned because neither the hemodynamic compromise nor the risk of thromboembolism associated with AF was addressed.

The Atrial Transection Procedure

All three surgical procedures developed in the early 1980s described above had attempted to isolate and confine AF to a certain region of the atria, stopping it from propagating its effects on the ventricles. None of the aforementioned procedures were targeted to cure the AF itself.

In 1985, Cox's group described for the first time a series of experiments that attempted to cure AF in a canine model.[54] After a number of experiments, it was found that a single long incision across both atria and down into the septum cured AF (Fig. 59-1). This "atrial transection" procedure prevented the induction and maintenance of AF or atrial flutter in every canine receiving the procedure.[55]

Unfortunately, this procedure was effective but not curative in its clinical application. It soon became apparent that the surgical cure of AF would require a more complete understanding of the fundamental electrophysiologic mechanisms of AF.

DEVELOPMENT OF THE COX-MAZE PROCEDURE

Extensive experimental investigation at Washington University in St. Louis under the leadership of James L. Cox led to the introduction of the Maze procedure in 1987.[55–57] The

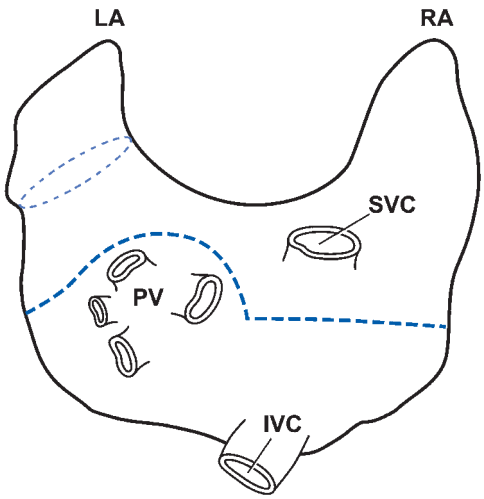

Figure 59-1. A single long incision across both atria down into the septum cured AF. IVC = inferior vena cava; LA = left atrium; PV = pulmonary vein; RA = right atrium; SVC = superior vena cava. (*Reprinted with permission from Cox et al.*[55])

Cox-Maze procedure was designed to interrupt any and all macro-reentrant circuits that might potentially develop in the atria, thereby precluding the ability of the atrium to flutter or fibrillate (Fig. 59-2). In contrast to the previous procedures, the Maze procedure successfully restored both AV synchrony and a regular heartbeat, thus significantly decreasing the risk of thromboembolism and stroke.[58] The operation involved creating a myriad of incisions across both the right and left atria. The surgical incisions were placed so that the SA node could "direct" the propagation of the sinus impulse throughout both atria. It also allowed

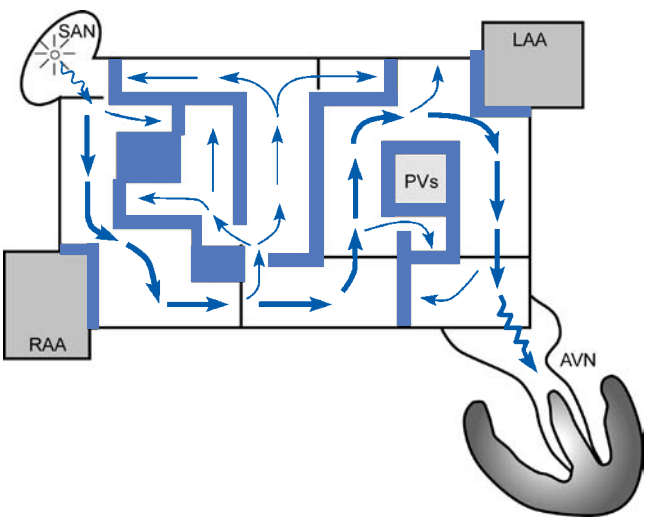

Figure 59-2. By creating a myriad of surgical incisions in the atria, the Maze procedure is designed to preclude the ability of the atria to fibrillate. AVN = atrioventricular node; LAA = left atrial appendage; PVs = pulmonary veins; RAA = right atrial appendage; SAN = sinoatrial node. (*Reprinted with permission from Cox et al.*[55])

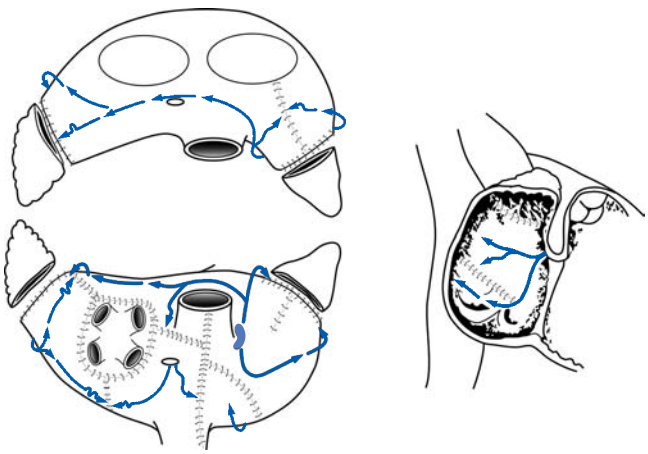

Figure 59-3. The traditional cut-and-sew Cox-Maze III procedure. (*Reprinted with permission from Cox et al.*[55])

all of the atrial myocardium to be activated, resulting in preservation of atrial transport function in most patients.[59]

The original technique, the Maze-I procedure, was introduced in 1991, only to be soon modified to become the Maze-II procedure because of late chronotropic incompetence and a high incidence of pacemaker implantations. The Maze-II procedure, however, proved to be extremely technically difficult to perform. It was therefore modified again to become the Maze-III procedure, also known as the Cox-Maze III procedure today[60,61] (Fig. 59-3).

Over the last decade, the Cox-Maze procedure has become the gold standard for the surgical treatment of AF. In a long-term study of patients who had the Cox-Maze procedure, 97% of the patients at late follow-up were free of AF.[62] These superb results have been reproduced by other institutions around the world.[63–65]

NEW SURGICAL ABLATION TECHNOLOGY

Despite its proven efficacy, the Cox-Maze III procedure did not gain widespread acceptance. Few cardiac surgeons were willing to add the procedure to a coronary revascularization or valve procedure due to its complexity and technical difficulty. In an attempt to simplify the operation and make it more accessible to the average surgeon, groups around the world have replaced the incisions of the traditional cut-and-sew Cox-Maze III procedure with linear lines of ablation.[66] These linear lines of ablation are created using a variety of energy sources, including radiofrequency energy, microwave, cryoablation, laser, and high-frequency ultrasound.

The development of these new ablation technologies has revolutionized the surgical treatment of AF by taking a technically difficult and time-consuming operation and making it easy for all cardiac surgeons to perform. Today, most patients undergoing open heart surgery who have chronic AF are offered concomitant AF surgery. Another advantage of ablation technologies is the promise for the development of less-invasive procedures for AF performed via a small incision or port. A beating heart procedure with high efficacy is the ultimate goal of these efforts. With the availability of easy-to-use ablation devices, numerous groups around the world have also introduced a variety of new procedures for AF involving more limited sets of atrial lesions. Some groups are currently performing only the left atrial lesions, while others are advocating PV isolation alone. Results with these new procedures will be discussed in a later section.

For ablation technology to reliably replace the incision in AF surgery, it must meet several important criteria. First, it must reliably produce bidirectional conduction block. This is the mechanism by which incisions prevent AF, by either blocking macro- or micro-reentrant circuits or by isolating trigger foci. In order to do this with certainty, an ablation device must have the capability to reliably make transmural lesions on the arrested heart from either the epicardial or endocardial surface.

The second crucial characteristic of the ablation device is its safety. This requires a precise definition of dose-response curves to limit excessive or inadequate ablation. The surgeon also must have knowledge of the effect of the specific ablation technology on surrounding vital cardiac structures, such as the coronary sinus, coronary arteries, and valves.

Third, a device should make AF surgery simpler and require less time to perform. This would require features such as rapidity of lesion formation, simplicity of use, and adequate length and flexibility.

Finally, the device ideally would have to be adaptable to a minimally invasive approach. This would require the ability to insert the device through minimal access incisions or ports. It would also require the device to be capable of creating epicardial transmural lesions on the beating heart. The following sections will briefly introduce the current ablation technologies, with their potential advantages and disadvantages.

Cryoablation

There are currently two commercially available sources of cryothermal energy that are being used in cardiac surgery. The older technology utilizes nitrous oxide and is manufactured by Cooper Surgical (Trumbull, Conn). The nitrous oxide devices use rigid reusable electrodes. More recently, CryoCath Technologies (Montreal, Quebec, Canada) has developed a device using argon. This device uses a disposable flexible catheter that has a 6-cm ablation electrode. At 1 atmosphere of pressure, nitrous oxide is capable of cooling tissue to –89.5°C, while argon has a minimum temperature of –185.7°C.

The size and depth of cryolesions are determined by numerous factors, including probe temperature, tissue temperature, probe size, the duration and number of ablations, and the particular liquid used as the cooling agent.[67] With

conventional nitrous oxide, 2- to 3-minute ablations have been shown to reliably create transmural lesions on both the right and left atrium. Because of the heat sink provided by circulating endocardial blood, epicardial cryolesions on the beating heart made with nitrous oxide have not been transmural.

There are few data available regarding dose-response curves or efficacy for cryoablation with argon. There has been one published study on epicardial cryoablation using the argon device in a sheep model.[68] In the animal study, they examined epicardial cryoablation for 2 minutes at –160°C on the beating heart. They were able to create transmural lesions 62% of the time around the PVs. Five of six lesions on the right atrial appendage were transmural, but only two of eight (25%) on the left atrial appendage were transmural. Thus, this device appears to be capable of creating transmural epicardial lesions, but not in a reliable fashion.

Cryoablation has the benefit of preserving the fibrous skeleton of the heart and thus is one of the safest of the technologies available. Nitrous oxide cryoablation has extensive clinical use and has an excellent safety profile. While cryothermal energy appears to have no permanent effects on valvular tissue or the coronary sinus, experimental studies have shown late minimal hyperplasia of coronary arteries and these structures should be avoided.[69–72] In the report by Doll and colleagues, they were able to create mild esophageal lesions in seven of the eight cases with epicardial cryoablation.[68]

In summary, cryoablation is unique among the currently available ablation technologies in that it destroys tissue by freezing rather than heating. The important advantage is its ability to preserve tissue architecture. The nitrous oxide technology has a well-defined efficacy and safety profile and is generally safe except around the coronary arteries. The potential disadvantages of cryoablation technology include the relatively long time necessary to create a lesion (1 to 3 minutes). There is also difficulty in creating lesions on the beating heart due to the "heat sink" of the circulating blood volume. Furthermore, if blood is frozen during epicardial ablation on the beating heart, it coagulates, creating a potential thromboembolism risk.

Radiofrequency Energy

Radiofrequency (RF) energy has been used for cardiac ablation for many years in the electrophysiology laboratory.[73] It was one of the first energy sources to be used in the operating room for AF ablation. RF energy can be delivered by either unipolar or bipolar electrodes, and the electrodes can be either dry or irrigated.

There are numerous unipolar RF devices available for ablation. Boston Scientific (Natick, Mass) has marketed the Cobra catheter, a dry unipolar catheter that is a segmented, flexible device with variable lesion lengths of 10 to 95 mm. It has seven electrodes, which can be individually selected and temperature controlled. The more recent Cobra Cooled surgical probe is the same size, but has an irrigated tip that allows for better heat transfer. Medtronic (Minneapolis, Minn) has developed a unipolar RF device, the Cardioblate catheter. This is an irrigated unipolar RF catheter used to make point-by-point ablations by dragging it across tissue to make a linear lesion.

Bipolar RF is similar to unipolar energy except that two electrodes, instead of one, are used to focus the path of energy. This allows for faster ablation (usually less than 10 seconds), while limiting destruction to tissue that is in close proximity to the electrodes. For bipolar RF, the electrodes are clamped over the targeted atrial tissue. The first bipolar RF device was introduced by AtriCure, Inc.(Cincinnati, Ohio). The Isolator was a specially designed clamp with 1-mm wide, 5-cm long electrodes embedded in the jaws. The device was unique in that it had an online measurement of lesion transmurality. The conductance between the electrodes was measured during ablation. When the conductance dropped to a stable minimum level, this correlated well both experimentally and clinically to histologically transmural lesions.[74–76] Two other bipolar ablation devices have since been released by Medtronic and Boston Scientific.[77,78] The Medtronic bipolar device, the Cardioblate BP, has an irrigated, flexible jaw along with an articulating head, with 5 cm-long electrodes.

RF energy uses an alternating current in the range of 100 to 1000 KHz. This frequency is high enough to prevent rapid myocardial depolarization and the induction of ventricular fibrillation, yet low enough to prevent tissue vaporization and perforation. Resistive heating occurs only within a narrow rim of tissue in direct contact with the electrode, usually less than 1 mm. The deeper tissue heating occurs via passive conduction. With unipolar catheters, the energy is dispersed between the electrode tip and an indifferent electrode, usually the grounding pad applied to the patient. In the bipolar clamp devices, alternating current is generated between two closely approximated electrodes. This results in a focused ablation. The lesion size depends on electrode-tissue contact area, the interface temperature, the current and voltage (power), and the duration of delivery. The depth of the lesion can be limited by char formation and the tissue-electrode interface. To resolve this problem, irrigated catheters were developed; this reduced char formation by keeping temperatures cooler at the tissue interface. These irrigated catheters have been shown to create larger-volume lesions than dry RF devices.[79,80]

Dose-response curves for unipolar RF have been described.[81–83] Although unipolar RF has been shown to create transmural lesions on the arrested heart in animals with sufficiently long ablation times (60 to 120 seconds), there have been problems in humans. After 2-minute endocardial ablations during mitral valve surgery, only 20% of the in vivo lesions were transmural.[82] Epicardial ablation has been even more difficult. Animal studies have consistently shown that unipolar RF is incapable of creating epicardial transmural lesions on the beating heart.[83,84] A recent clinical study has confirmed this problem. Epicardial RF ablation in humans resulted in only 7% of lesions being transmural despite

electrode temperatures of up to 90°C.[85] Bipolar RF ablation, on the other hand, has been shown to be capable of creating transmural lesions on the beating heart both in animals and humans with average ablation times between 5 and 10 seconds.[74,75,86]

Because RF ablation is a well-developed technology, much is known about its safety profile. A number of clinical complications of unipolar RF devices have been described, including coronary artery injuries, cerebrovascular accidents, and the devastating creation of esophageal perforation leading to atrioesophageal fistula.[87–90] Use of the bipolar RF devices has eliminated most of the collateral damage that is created with the unipolar devices, and there have been no injuries described with these devices.

Unipolar RF ablation has been shown to be able to create endocardial transmural lesions most of the time, but is incapable of creating epicardial transmural lesions on the beating heart. As with all unipolar energy sources, it radiates unfocused heat, and this can cause collateral injury if not used carefully. On the other hand, bipolar RF ablation has the advantage of focused and discrete lesions that can be made in a fraction of the time of unipolar ablation. Furthermore, by using a conductance algorithm, bipolar RF ablation is capable of creating reliable transmural lesions. However, bipolar RF ablation has the disadvantage that it can only ablate tissue that can be clamped and is difficult to use in proximity to valve tissue.

Microwave Energy

Microwave ablation uses dielectric heating created by electromagnetic waves emitted from an antenna. The field that is created causes oscillation of molecular dipoles, generating heat and an area of ablated tissue. This technology produces efficient and uniform penetration without overheating and does not cause char formation.[91,92]

Guidant Corporation, Inc. (Indianapolis, Ind) has developed the only microwave catheters available in the United States, the Flex 4 and Flex 10. The former has a flexible 4-cm long sheath and is able to ablate in increments of 2 cm; the latter device is 20 cm long and also ablates in 2-cm increments. Both probes consist of a flexible and malleable sheath containing a 2-cm microwave antenna that emits microwave radiation at 2450 Hz. The Flex 10 design allows for placement of the sheath around the heart and then positioning of the antenna within the sheath in 2-cm increments to create a continuous linear lesion up to 20 cm in length. Minimally invasive techniques with the Flex 10 catheter have been described.[93,94]

Microwave energy encompasses electromagnetic waves between 30 and 3000 MHz; 915 MHz or 2450 MHz is used in ablation catheters. Microwave devices radiate an electromagnetic field into the surrounding tissue. The energy is independent of current flow from ablation catheter to tissue. As a result, catheter contact pressure, orientation, and tissue desiccation do not limit lesion formation. In vitro as well as in vivo studies of the bovine heart show that lesion size depends on the power, duration of delivery, and antenna length and width. The depth is dependent on power and duration.[91,95]

Dose-response curves for microwave ablation have been developed on the arrested heart.[91,92] In our laboratory, both the Flex 4 and Flex 10 devices created uniformly transmural lesions on cardioplegic-arrested porcine atrial tissue after 90 seconds of ablation.[92] Thus, this energy source appears capable of creating endocardial transmural lesions on the arrested heart. However, there is controversy regarding its ability to create transmural lesions on the beating heart.

In a recent canine study, the Flex 10 device was evaluated. The histology showed full circumferential lesions after 1 to 3 weeks; however, they were not fully transmural.[96] In our laboratory, the Flex 10 device has been incapable of creating reliable transmural lesions on the beating heart in an acute porcine model.[92]

Microwave technology ablates tissue using heat, and is therefore potentially susceptible to complications of collateral damage. There are reports of coronary artery stenosis after microwave ablation.[97] Concern for esophageal injury exists, although there are no published reports of such injury from this modality. Reports of over 600 patients from several clinical trials have not mentioned complications attributable to the microwave device, lending confidence in its safe use.[98]

Microwave ablation has an advantage over RF ablation in that the device is less likely to create char formation, and is less sensitive to electrode positioning. Microwave ablation can reliably create endocardial lesions, but there is some question of whether it is capable of creating epicardial lesions on the beating heart. Microwaves are still an unfocused source of heat energy with the potential to cause collateral injury. A disadvantage of this technology is that there is no way to judge the transmurality of ablation during surgery.

Laser Energy

A laser energy device consists of a power source, a laser medium (usually crystal or gas), and two mirrors, one at each end of the medium; one is fully and the other is partially reflective. Lasers boost the energy state of the medium to a higher level, and then the device allows energy to be emitted when the medium drops back to its lower state. This mechanism allows controlled direction of energy output. Lasers produce narrow, deep lesions in a short amount of time, making this an attractive power source for ablation.[99]

Edwards Lifesciences (Irvine, Calif) has developed the Optiwave 980, an endocardial device with a malleable shaft and a 5-cm diffuser that allows creation of linear ablation lines. Two forms of light are carried from the source via fiber-optics to the treatment site: visible red light to allow targeting of tissue, and invisible 980-nm–wavelength laser energy that induces the destruction of tissue. The light is scattered within the tip and a diffuser disperses the infrared laser energy perpendicular to the shaft.

The lesion created is a direct result of tissue heating, termed photocoagulation. Laser beam power decreases within tissue in an exponential decay manner, and absorption is tissue-dependent. Because adipose tissue and cardiac muscle each has its own specific extinction coefficient (the amount of scattering and absorption), the infrared laser is able to penetrate myocardial tissue independent of overlying fat.

Laser energy produces no surface charring, and direct heating of the tissue by the laser is accompanied by conductive heating that allows penetration. The lesion size depends on the amount of energy delivered, the level of tissue heating, and the amount of scatter, transmission, reflection, and absorption.

The ability of laser to create transmural lesions in atrial tissue has been investigated in a small number of studies.[99–104] Keane and Ruskin demonstrated the ability of the diode laser to create transmural, linear, continuous atrial lesions in a goat model.[101] In a study by Thomas and associates, narrow, transmural lesions were successfully created in the myocardium using a laser catheter.[99] Reddy and colleagues used laser ablation for PV isolation in a goat model, demonstrating successful creation of transmural lesions.[100] Lemery and coworkers showed similar results in a pig model.[103] Linear transmural lesions in canine myocardium were successfully created using laser radiation by Fried and colleagues as well.[102,104] Clinical trials with humans have been encouraging, but results are few.[105]

Laser ablation is a promising technology that may have some advantages over other energy sources. The energy is focused, unaffected by overlying fat, and may have enhanced penetration. A disadvantage of this technology is that the energy delivery is unconfined and thus could cause collateral damage. Another problem is that at present, there is no way to judge transmurality of the ablation during procedures.

High-Intensity Focused Ultrasound

Although the interaction between ultrasound energy and biologic tissue has been a subject of interest for decades, its application with cardiac tissue has only been recently studied.[106–112] Ablation using ultrasound in the surgical treatment of AF is currently the newest modality being tested clinically. Ultrasound effectively ablates tissue via mechanical hyperthermia.[113] When ultrasound waves are emitted from the transducer, the resulting wave travels through the tissue causing compression, refraction, and particle movement. This translates into kinetic energy and ultimately thermal coagulative tissue necrosis.

Ultrasound can either be utilized in a focused (HIFU; high-intensity focused ultrasound) or nonfocused form. HIFU produces rapid, high-concentration energy in a focused area, and is able to create transmural epicardial lesions through epicardial fat in less than 2 seconds.[114] Nonfocused ultrasound, although it has a simpler transducer system and more flexibility, requires more time to create transmural lesions.

Over recent years, HIFU has become an increasingly attractive possible modality for cardiac ablation for several reasons. HIFU is unique in its ability to create noninvasive, non-contact focal ablation in three-dimensional volume without affecting intervening and surrounding tissue. HIFU utilizes ultrasound beams in the frequency range of 1 to 5 MHz or higher, creating focused lesions quickly by rapidly raising the temperature of the targeted tissue to above 80°C, effectively killing the cells.[115] There is a steep temperature gradient between the focus and collateral tissue, demonstrated by the sharp demarcation seen between the volume of necrotic tissue and normal surrounding cells on histology.[116] By using focused ultrasound waves, HIFU is able to create targeted thermal coagulation of tissue at a very well-defined focus without harming intervening tissue with very limited collateral damage.

Another advantage of HIFU is its mechanism of thermal ablation. Most other energy sources heat or cool tissue by thermal conduction, thereby creating a graded response depending on the distance from the energy source. Since the mechanism of thermal conduction in these energy sources is relatively slow, they may be particularly susceptible to cooling near blood vessels or "heat sink."[117,118] HIFU, on the other hand, ablates tissue by directly heating the tissue in the acoustic focal volume and is affected much less by the "heat sink."[119]

Since ultrasound can be collimated through fluid media, it is ideal for application with a balloon delivery system. Saliba and associates evaluated the use of an 8-MHz HIFU transducer mounted in a saline-filled balloon designed for pulmonary vein isolation (PVI) for the treatment of AF. Unfortunately, only 30% of 33 patients who underwent PVI were cured of AF in late follow-up. The variability of the PV anatomy was the main reason for the poor results, often requiring several applications to achieve PVI during the procedure.[109,110]

Because of its ability to focus the target of ablation at specific depths, epicardial surgical ablation using HIFU has recently gained interest. In a recent study by Ninet and colleagues, 103 patients with AF underwent beating-heart PV isolation procedures with concomitant cardiac procedures.[120] At 6-months' follow-up, the freedom from AF was 85%.[120] Epicardial approaches using HIFU for the ablation of AF allow for the possible development of minimally invasive techniques.

In summary, each ablation technology has its own advantages and disadvantages. In the future, it will be imperative to develop a more complete understanding of the effects of each surgical ablation technology on atrial hemodynamics, function, and electrophysiology.

ELECTROPHYSIOLOGIC EVALUATION

Initial experimental electrophysiologic studies showed that AF was much more complex than other arrhythmias previously treated with surgery.[57] The traditional algorithm of

obtaining pre- and postoperative mapping data and applying this information to guide the specific surgical technique, as was done with arrhythmias such as Wolff-Parkinson-White and ventricular tachycardia, was not feasible. AF is complex and requires a high density of closely placed electrodes as well as a sophisticated mapping and signal processing system to define the particular mechanism in each individual patient.

Although it was previously thought that AF was maintained by multiple macro-reentrant circuits, there is evidence that focal triggers can be responsible for the initiation of paroxysmal AF.[41,121] Therefore, preoperative mapping data may allow surgeons to identify the particular triggers of AF in individual patients. Unfortunately, the analysis of multiple atrial electrograms over long periods of time has been difficult. Thus, it usually is not possible to locate the precise focal point of origin responsible for the initiation or maintenance of AF in the majority of patients.

For the reasons mentioned above, preoperative mapping is not routinely performed on patients prior to undergoing the Cox-Maze procedure. Furthermore, the traditional activation sequence is difficult and time-consuming and is not suitable to provide useful real-time information during the procedure. Improvements in technology and further experimentation may provide the means for faster data analysis and a map-directed approach may be feasible in the future. Recent studies have shown the possibilities of determining the location that has the highest frequency of activation from multiple sites in the left or right atrium. This may allow for designing a more directed and limited set of lesions. Although still investigational, these new techniques may eventually allow us to customize the incision set to the specific underlying mechanism.[50,122,123]

SURGICAL INDICATIONS

Lone Atrial Fibrillation

The main indication for the surgical treatment of AF is intolerance of the arrhythmia in patients who have failed medical therapy. Patients with paroxysmal atrial flutter or fibrillation are usually more symptomatic than those with continuous or permanent AF. Major symptoms include dyspnea on exertion, easy fatigability, lethargy, malaise, and a general sense of uneasiness. Patients with lone AF should receive a trial of medical therapy prior to surgery. A significant number of patients with AF are referred to surgery because of significant side effects or intolerance to antiarrhythmic drugs.

The development of tachycardia-induced cardiomyopathy (TIC) in patients with AF is another important indication for surgery. TIC is a condition characterized by atrial or ventricular dysfunction resulting directly from increased heart rates in an otherwise structurally normal heart.[124] Untreated TIC can lead to heart failure. It is extremely important to recognize this condition in patients with uncontrolled AF, since TIC is reversible if normal sinus rhythm is restored surgically.[125]

Another important indication for surgery is in patients who develop a contraindication to long-term anticoagulation, such as patients who have suffered intracranial hemorrhage while on warfarin. Up to one-third of patients screened for participation in prior clinical trials of the use of warfarin in AF were deemed ineligible for chronic anticoagulation, primarily because of a high perceived risk for bleeding.[126,127] Patients taking warfarin have twice the rate of intracerebral hemorrhage mortality in a dose-dependent manner.[128] In a recent study, the annual rate for major bleeding in anticoagulated patients with AF was 2.3% per year, and the rate for intracranial hemorrhage was 0.9% per year.[127]

In addition, patients with chronic AF who suffer from cerebrovascular accidents despite adequate anticoagulation should be considered for surgical treatment. Anticoagulation with warfarin reduces the risk of ischemic and hemorrhagic stroke by over 60% in patients with AF, but does not eliminate this dreaded complication.[18,129] Approximately 20% of patients who underwent the Cox-Maze III procedure at our institution had experienced at last one episode of cerebral thromboembolism that resulted in a significant temporary or permanent neurologic deficit prior to having the procedure.[62]

Concomitant Atrial Fibrillation

Virtually all patients with AF who undergo elective cardiac surgery (i.e., coronary artery bypass grafting or valve repair or replacement) should be strongly considered for a concomitant Cox-Maze procedure. Recent studies have shown that adding a Maze procedure can decrease the late risk of cardiac- and stroke-related deaths in these patients.[130,131] The only contraindication to the Maze procedure would be in high-risk patients who have tolerated their AF well and have not had problems with anticoagulation.

SURGICAL TECHNIQUE: THE COX-MAZE IV PROCEDURE

The final version of the standard cut-and-sew technique to cure AF was the Cox-Maze III procedure.[55,123,132,133] However, only a handful of cardiac surgeons still perform this operation. At most centers, many of the surgical incisions have been replaced with linear lines of ablation using different energy sources. At Washington University, bipolar RF energy has been used successfully to replace most of the surgical incisions of the Cox-Maze III procedure. Our current procedure incorporates the identical lesions as the Cox-Maze III procedure and has been named the Cox-Maze IV[134] (Fig. 59-4). Our clinical data have shown that this modified operation has significantly shortened the operative time while maintaining the high success rate of the traditional cut-and-sew Cox-Maze III procedure.[135]

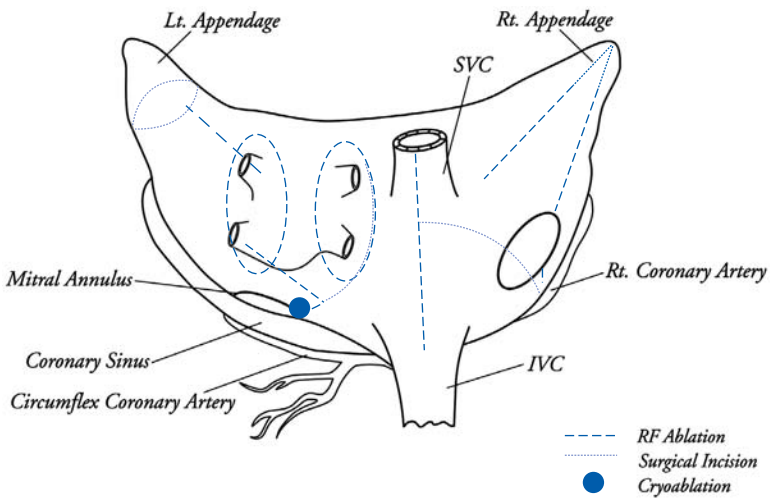

Figure 59-4. The Cox-Maze IV lesion sets. IVC = inferior vena cava; RF = radiofrequency; SVC = superior vena cava. (*Adapted with permission from Gaynor et al.*[86])

Bipolar RF ablation was chosen for the Cox-Maze IV procedure over other potential energy sources for several reasons. First, the device allows for the online determination of lesion transmurality by measuring the conductance between the two electrodes. Second, the bipolar RF device has extremely short ablation times, with 5- to 6-cm long transmural ablations performed in 5 to 15 seconds. Third, the lesions are narrow (2 to 3 mm in width) and tissue injury is confined to within the clamp. This virtually eliminates the possibility of unwanted collateral injury.[88,136–138]

The Cox-Maze IV procedure is performed with the patient on cardiopulmonary bypass using bicaval cannulation. Initially, the heart is perfused at normothermia to maintain sinus rhythm and allow for accurate determination of pacing thresholds. The right and left PVs are bluntly dissected. If the patient is in AF, an intravenous bolus of amiodarone is given and the patient is cardioverted. The ablations are performed on the cuff of atrial tissue surrounding the right and left PVs (Fig. 59-5). Proof of electrical isolation is confirmed after ablation by pacing from both the superior and inferior PVs.

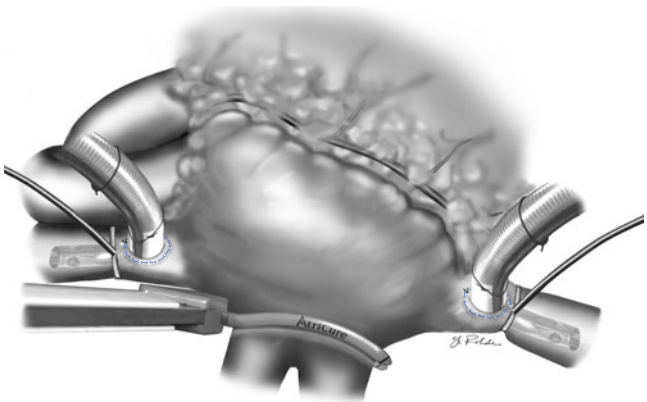

Figure 59-5. The right and left PVs are isolated using the bipolar RF device. (*Reprinted with permission from Damiano et al.*[134])

The right atrial lesions are performed with the heart beating. A small, 1-cm atriotomy is created in the right atrial appendage (Fig. 59-6). The bipolar device is placed through this incision to create the right atrial free wall lesion. A 2-cm gap is left between this ablation and a vertical atriotomy that extends from the crista terminalis to the AV groove approximately at the acute margin of the right ventricle. After bluntly dissecting the AV groove fat pad, the bipolar RF device is placed across the anterior tricuspid annulus and extended slightly onto the valvular tissue at approximately the 10 o'clock position. Occasionally, a cryolesion is needed to complete this ablation line so that it extends onto the valvular tissue. A similar lesion is created to the posterior tricuspid valve annulus at the 2 o'clock position. To complete the right-sided lesions, the RF clamp is placed up to the

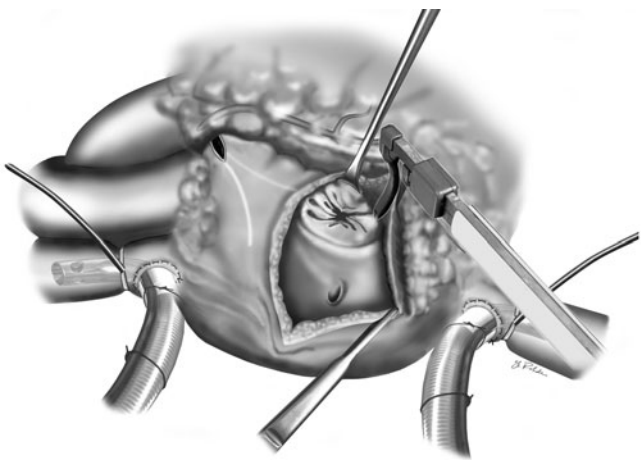

Figure 59-6. The right vertical atriotomy is created down to the tricuspid valve annulus. The bipolar RF clamp is advanced with one arm inside the right atrium and the other outside the atrium down to the tricuspid annulus. An ablation is performed with care being taken to ensure that the jaws of the clamp extend onto the tricuspid valve. (*Reprinted with permission from Damiano et al.*[134])

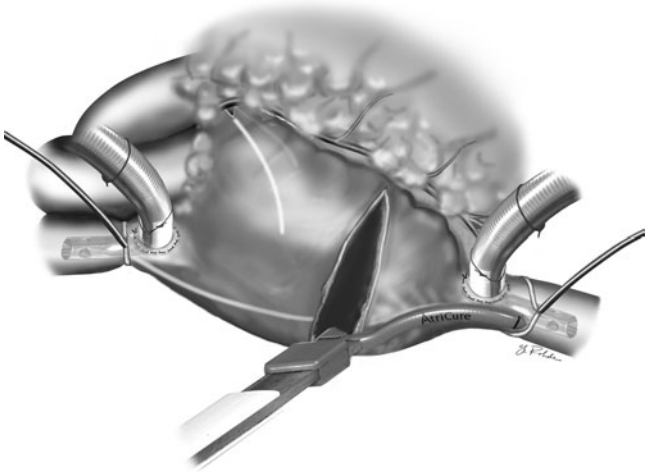

Figure 59-7. From the inferior aspect of the vertical right atriotomy, the bipolar RF clamp is placed up to the superior vena cava, extending the ablation onto caval tissue. The clamp is then rotated 180° and extended in a similar fashion onto the inferior vena cava to create the ablation. (*Reprinted with permission from Damiano et al.*[134])

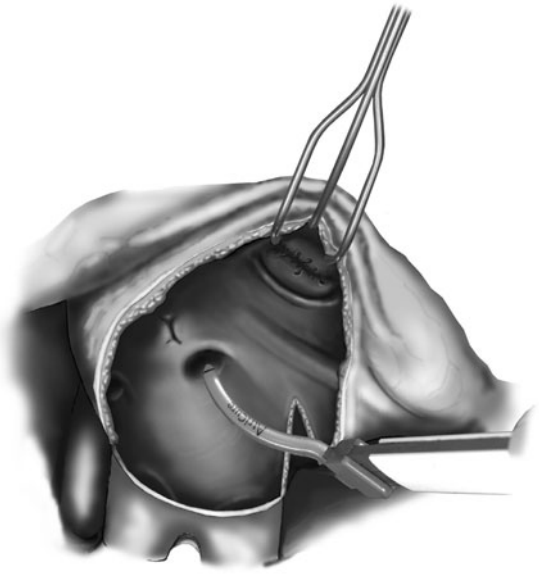

Figure 59-9. A standard left atriotomy is performed below the interatrial groove and extended inferiorly around the right inferior PV. The bipolar RF clamp is used to create a lesion connecting the left atrial incision inferiorly to the ablation line encircling the left PVs. (*Adapted with permission from Damiano et al.*[134])

superior vena cava and then rotated 180° and extended down onto the inferior vena cava (Fig. 59-7).

The left-sided lesions are performed through a standard left atriotomy with the heart arrested (Fig. 59-8). This incision is extended inferiorly around the right inferior PV and superiorly onto the dome of the left atrium. The incision is made such that it connects to the right PV ablation lesion. A lesion is made with the bipolar RF device connecting the left atrial incision inferiorly to the ablation line encircling the left PVs (Fig. 59-9). If the left atrium is greater than 5 cm in size, another lesion is performed from the superior aspect of the left atriotomy, across the dome of the left atrium and into the left superior PV. A lesion is then created up to the mitral valve annulus, usually with the bipolar RF device. This lesion is performed from the inferior aspect of the left atrial incision across the posterior left atrium, AV groove, and the coronary sinus. The ablation is performed in the space between the circumflex and right coronary artery circulation in order to avoid damage to the coronary arteries. If the patient has a left dominant circulation, this lesion is usually created surgically in order to identify and spare the circumflex artery. A cryolesion is placed at the mitral valve annulus using a 15-mm bell cryoprobe cooled to –60°C for 2 to 3 minutes. The left atrial appendage is amputated and a final ablation is performed through the amputated left atrial appendage onto the left superior PV (Fig. 59-10). The left atrial appendage is oversewn, the aorta is unclamped, and the right atrial incision is closed during the rewarming period.

In patients undergoing a mitral valve replacement, it is recommended to amputate the left atrial appendage prior to performing the other left atrial lesions to avoid excessive traction. Pacing wires are left in place for control of postoperative arrhythmias.

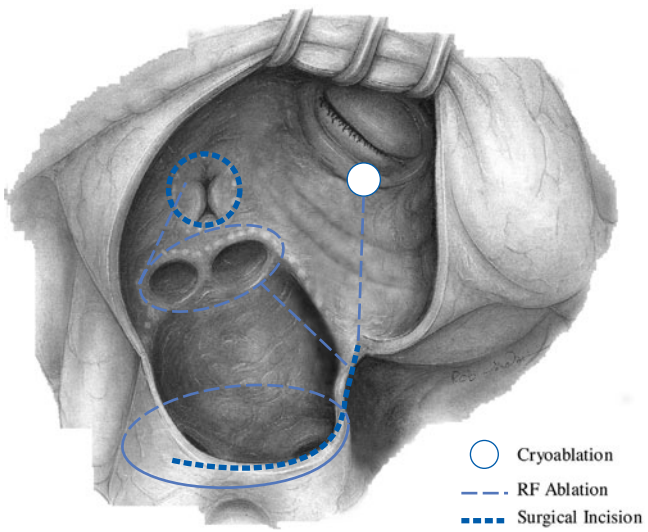

Figure 59-8. Left atrium with left-sided Cox-Maze IV lesions. (*Adapted with permission from Gaynor et al.*[86])

SURGICAL TECHNIQUE: OTHER ATRIAL FIBRILLATION PROCEDURES

There have been a number of new surgical procedures introduced in an attempt to cure AF. This plethora of procedures

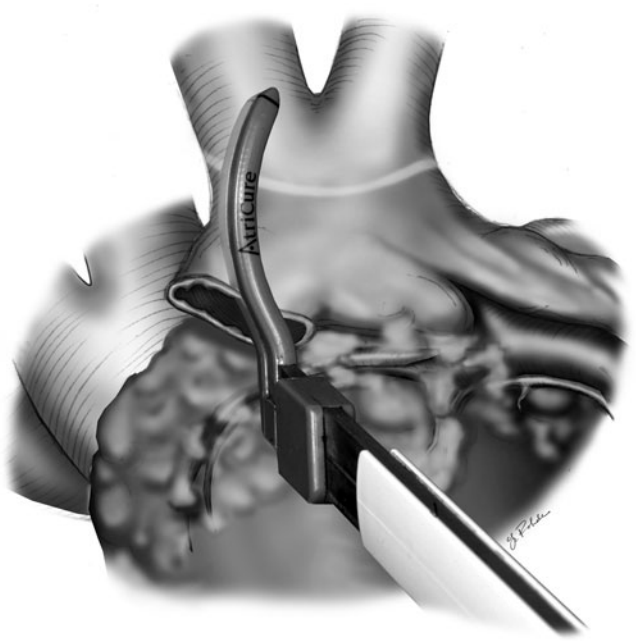

Figure 59-10. The bipolar RF clamp is placed through the amputated appendage down into the left superior PV with one jaw inside and the other outside the atrium. This ablation should overlap the previously performed encircling ablation of the left PVs. (*Reprinted with permission from Damiano et al.*[134])

can be divided into two groups. The first group comprises operations including only left atrial lesions to cure AF. These procedures typically involve isolating the PVs, either as a box or separately with a connecting lesion. Most surgeons also advocate creating a lesion to the mitral annulus from the PV isolation and amputation of the left atrial appendage.[87,139–147]

The second group includes those who advocate only isolating the PVs for curing AF.[94,148,149] These procedures involve either isolating the PVs as a box, or separately (Fig. 59-11). Different devices have been developed to create these lesions, including laser, microwave energy, and high-frequency ultrasound.

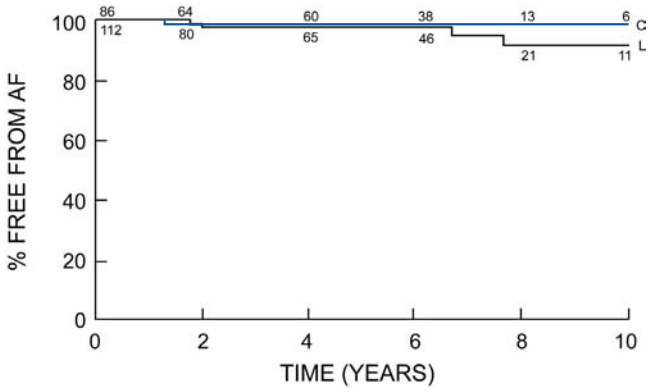

Figure 59-12. Kaplan-Meier survival analysis of freedom from recurrent AF. The numbers on each line indicate the number of patients at risk. There was no difference in the long-term estimate of freedom from AF between the lone Cox-Maze group (L) and the concomitant group (C; $p = 0.64$). (*Reprinted with permission from Prasad et al.*[62])

SURGICAL RESULTS: THE COX-MAZE PROCEDURE

The Cox-Maze III procedure has excellent long-term results. In our series at Washington University, of 198 consecutive patients undergoing the procedure, 97% of all patients at a mean follow-up of 5.4 years were in sinus rhythm (Fig. 59-12). There was no statistical difference in cure rates between patients undergoing a lone Cox-Maze procedure and those also undergoing concomitant procedures. The cure rate off all antiarrhythmic medications was 80% and 73%, respectively, in patients undergoing lone and concomitant Cox-Maze procedures at late follow-up.[62] Similar results have been obtained from other centers around the world (Table 59-1) with the traditional cut-and-sew technique (Cox-Maze III).[63,65,150]

Early results from patients who underwent the Cox-Maze IV procedure have been encouraging as well. In a prospective, single-center trial from our institution, 91% of patients at 6 months' follow-up were free from AF. The new procedure was also safe, as its operative mortality in this

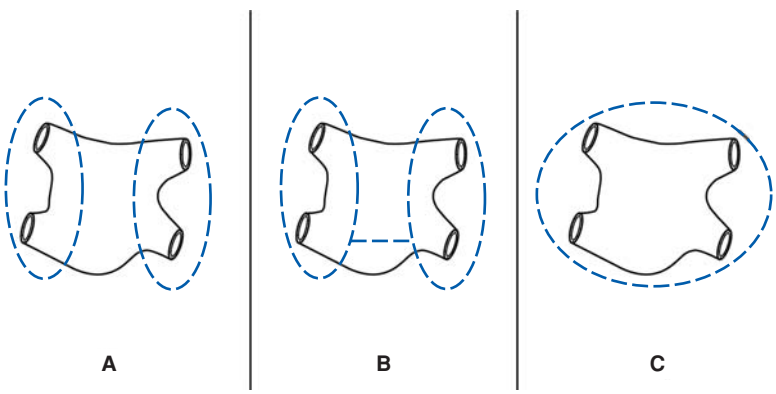

Figure 59-11. Pulmonary vein isolation is performed either separately or as a box. (A) illustrates pulmonary vein isolation separately. (B) illustrates pulmonary vein isolation separately plus an ablation line connecting the inferior aspect of the two isolated islands. (C) illustrates the isolation of all four pulmonary veins as a box.

Table 59–1.

Results of the Cut-and-Sew Cox-Maze III Procedure

Study	No. of patients	Mean follow-up in years	Overall freedom from AF (%)	Drug-free freedom from AF (%)
Prasad et al[62]	198	5.4 ± 2.9	97	80
Schaff et al[65]	221	2	85–90	N/A
McCarthy et al[63]	100	3	91	N/A
Arcidi et al[150]	99	N/A	97	N/A

AF = atrial fibrillation.

series was 0%.[86] A multicenter trial of the Cox-Maze IV procedure had similar results.[135] In this study, 96% of patients were free of AF at 6 months, and there was no operative mortality in this group of 30 patients.[58]

The Cox-Maze IV procedure has significantly shortened the mean cross-clamp times for a lone Cox-Maze from 93 ± 34 minutes for the Cox-Maze III procedure to 54 ± 27 minutes for the Cox-Maze IV ($p < .001$), and from 123 ± 36 minutes for the Cox-Maze III procedure alone to 99 ± 30 minutes ($p < .005$) in those undergoing the Cox-Maze III procedure concomitantly with another cardiac operation.[86]

The Cox-Maze III procedure also has been effective at decreasing the risk of late stroke in this high-risk patient population.[151] In Cox's experience in over 300 patients, there were only two perioperative strokes (0.7%) and only one minor stroke during long-term follow-up (11.5 years; mean 3.9 ± 2.7 years). The long-term stroke rate after the Cox-Maze III procedure was 0.1% per year, despite the fact that the vast majority of patients were off all anticoagulation at last follow-up.[58]

In a series from Japan that examined the effect of mitral valve replacement on stroke rates, the Cox-Maze procedure was found to significantly decrease the incidence of late stroke, even in those patients already receiving anticoagulation for mechanical mitral valves. Patients who underwent a concomitant Cox-Maze procedure with their mitral valve replacement were 99% stroke-free at 8-years of follow-up, while the group with lone mitral valve replacement only had an 89% stroke-free rate.[152]

While the efficacy of the Cox-Maze procedure has been established, there are only a few studies examining the benefit of adding the operation during concomitant cardiac surgery in patients with chronic AF. Bando and associates[131] reported on 363 patients with nonischemic, noncardiomyopathy mitral regurgitation with preoperative AF undergoing either mitral valve repair alone or mitral valve repair with a concomitant Cox-Maze procedure. At late follow-up, adding a Cox-Maze procedure significantly improved the freedom from cardiovascular-related death (97% versus 82%; $p < .001$) and freedom from stroke (98% versus 83%; $p < .001$). Adding a Cox-Maze procedure also improved late left ventricular function as measured by left ventricular end-systolic dimension.[131]

SURGICAL RESULTS: OTHER ATRIAL FIBRILLATION PROCEDURES

A number of centers around the world have suggested performing ablation only in the left atrium to successfully cure AF. This concept is supported by the fact that the majority of paroxysmal AF appears to originate around the PVs and the posterior left atrium. The success rates from these procedures have varied between 58% and 95% at different follow-up periods[87,139,143,146,147,153–165] (Table 59-2). One of the complications from performing surgery only on the left atrial lesions is postoperative atrial flutter. In a series by Golovchiner and associates from Tel Aviv that evaluated a group of 50 patients who underwent left atrial ablation, 13% of patients developed atrial flutter at a 15-month follow-up. Left atrial flutter was present in four of the six patients.[165] In a similar series from Japan, 21% (5 of 24) patients developed recurrent atrial flutter or tachycardia during follow-up (36.9 ± 14.1 months) after left atrial ablation.[146]

Other surgeons have proposed only isolating the PVs. These procedures have had mixed results. In studies evaluating patients undergoing concomitant procedures (particularly mitral valve surgery), the outcomes have been poor. At Washington University, 23 patients with AF (12 with paroxysmal AF and 11 with permanent AF) underwent PVI only during concomitant mitral valve surgery or coronary revascularization. The average duration of AF in 12 patients was 6.7 ± 14.2 years. At a mean follow-up of 57 ± 37 months, only 50% of patients were free from AF.

In a larger series, Gaita and colleagues[139] evaluated 105 patients who underwent AF and valve surgery by assigning them randomly to three groups. Two groups included patients who underwent left atrial ablation using two different patterns. The third group was composed of patients who

Table 59–2.

Results Of Left Atrial Lesions Only

Study	No. of patients	Energy source	Removal of LAA	Mean follow-up in months	Overall freedom from AF
Gaita et al[139]	70	Cryoablation	No	41 ± 17	90% (at 24 mo)
Benussi et al[143]	132	RF ablation	Yes*	16.9 ± 14.2	77% (at 36 mo)
Benussi et al[153]	40	RF ablation	Yes	11.6 ± 4.7	77%
Sueda et al[154]	36	Cryoablation	Yes	18	78% (at 6 mo)
Imai et al[146]	32	Cryoablation	Yes	36.9 ± 14.1	74% (at 36 mo)
Usui et al[155]	41	Cryoablation	Yes	N/A	74%
Kondo et al[147]	31	Cryoablation†	No	37.7 ± 15.0	79% (at 28 mo)
Kottkamp et al[87]	70	RF ablation	No	18 ± 7	95% (at 12 mo)
Guden et al[156]	57	RF ablation	Yes	10.9 ± 5.6	76%
Williams et al[157]	40	RF ablation	Yes	4.2 ± 2.8	79%
Pasic et al[158]	48	RF ablation	No	4	92% (at 6 mo)
Mohr et al[159]	234	RF ablation	No	N/A	73% (at 12 mo)
Halkos et al[160]	42	RF ablation	Yes	8.7	77%
Starck et al[161]	100	RF ablation	Yes	7.3	80%
Melo et al[162]	43	RF ablation	Yes	>3	64%
Knaut et al[163]	105	Microwave	No	N/A	58% (at 12 mo)
Knaut et al[164]	202	Microwave	No	N/A	62% (at 12 mo)
Golovchiner et al[165]	100	RF ablation	Yes	15 ± 7	72%

**LAA was preserved in 13 patients.*
†Cryoablation in 30/31 patients, RF ablation in 1/30 patients.
AF = atrial fibrillation; LAA = left atrial appendage; RF = radiofrequency.

had PVI-alone. Only 29% of patients in the PVI-only group were free from AF at last follow-up. In contrast, 76% of patients who had more extensive left atrial lesions were free from AF.[139]

In another series, Isobe and coworkers evaluated a group of 101 patients who underwent PVI with cryoablation concomitantly with mitral valve surgery. In this series, 53% of patients were free from AF at last follow-up.[166] Without antiarrhythmics, only 24% of the patients were free from AF.

Finally, in another study from Japan, 66 patients with mitral valve disease and chronic AF underwent pulmonary vein cryoablation. At late follow-up, 61% of patients were free from AF, but only 17% of patients were free from AF without antiarrhythmics.[148] Compared to the 97% rate of freedom from AF at late follow-up seen in mitral valve patients undergoing the Cox-Maze III procedure at Washington University, these results compare very unfavorably.[62]

Some groups around the world have suggested performing endoscopic or limited-access beating-heart PVI in patients with lone AF. Although there have been some promising early results, the series are too small with too short of a follow-up to evaluate their efficacy.[93,94,167,168] In a series by Wolf and associates, 27 patients underwent video-assisted bilateral PVI and left atrial appendage exclusion for AF.

Bipolar RF energy was used and patients underwent bilateral thoracotomies. Ninety-one percent of patients were free from AF without antiarrhythmics postoperatively.[168] However, the average postoperative follow-up was only 6 months. Similarly, Salenger and associates published a series of 14 patients who underwent completely thoracoscopic PVI and amputation of the left atrial appendage. Microwave energy was used for epicardial ablation. Only 67% of patients were free from AF at 12 months follow-up.[94]

In summary, there have been exciting recent advances in the surgical treatment of AF. The use of ablation devices has widely expanded the number of patients undergoing arrhythmia surgery. At present, virtually all patients undergoing concomitant cardiac surgery with chronic AF should undergo a curative procedure for their AF. Ablation technology has also simplified the operation to the point that minimal access procedures are a reality for the treatment of lone AF. In the coming years, it is likely that there will be continuing progress in this area, and that a beating-heart, limited-access procedure with high efficacy will be developed.

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CHAPTER 60

Surgical Implantation of Pacemakers and Automatic Defibrillators

Henry M. Spotnitz • George H. Humphreys, II

Pacemaker and defibrillator management is increasingly complex and is the subject of comprehensive reviews.[1–3] In 2760 procedures in the authors' experience at New York Presbyterian Hospital, 23% of pacemaker recipients and 5% of implantable cardioverter defibrillator (ICD) recipients were octogenarians. The 80- to 90-year-old age group accounted for 22% of pacemaker generator replacements and 5% of ICD generator replacements. The incidence of pacemaker insertion in patients older than 75 was 2.6% in a recent survey of noninstitutionalized adults. The high pacemaker efficacy and cost-effectiveness in late middle-aged and younger elderly patients are widely accepted,[4] but the appropriate role for ICD insertion in much older patients is still in evolution. Application of pacemaker and ICD technology is now feasible across the entire span of human age, and the technology continues to expand into pacing for heart failure and prophylaxis against lethal arrhythmias. Arrhythmia control devices are increasingly becoming part of the purview of the electrophysiologist. Thoracic surgeons are being progressively excluded from ICD insertion and endocardial biventricular pacemaker insertion due to lack of interest, as well as referral patterns and recommendations of cardiology groups. However, because some aspects of pacemaker/ICD insertion still require thoracotomy, it is likely that thoracic surgeons will continue to play an important role both as implanters and consultants for complex or complicated cases. This chapter presents an overview of practical information related to pacemaker and ICD insertion and management.

PACEMAKERS

History

The early history of cardiac surgery was complicated by iatrogenic heart block, which was lethal. Transthoracic pacing was implemented with Zoll cutaneous electrodes.[5] Percutaneous endocardial pacing was described in 1959.[6] A "permanent" pacemaker using epicardial electrodes was described in 1960.[7] Pacemakers and implantation techniques have progressed rapidly since the 1960s, reflecting advances in bioengineering and technology. Persistent problems include lead durability, chronic inflammatory responses to pacemaker materials, infection, device size, programmer compatibility, and expense.

Anatomy of Surgical Heart Block

The conduction system is vulnerable to injury during heart surgery. Complete heart block can occur as a result of suture placement during aortic, mitral, or tricuspid valve surgery, or during closure of septal defects or during myotomy for idiopathic hypertrophic subaortic stenosis. The sites of these lesions are indicated schematically in Fig. 60-1. Occlusion of the blood supply to the conduction system or incomplete myocardial protection can also result in surgical heart block.

Device Description

A permanent pacemaker consists of pacing leads[8] and a pacemaker generator. The generator contains a battery, a telemetry antenna, and integrated circuits. The power source is generally lithium iodide, but rechargeable and nuclear batteries have been used. The integrated circuits include programmable microprocessors, oscillators, amplifiers, and sensing circuits.[9] The integrated circuits employ CMOS (complementary metal-oxide semiconductor) technology, which is subject to damage by ionizing radiation.[10] Current pacemakers can store and monitor their internal status, the condition of their external connections, their programmed settings, recent activity, and notable arrhythmias. Unfortunately, each device responds only to the programmer of its manufacturer.

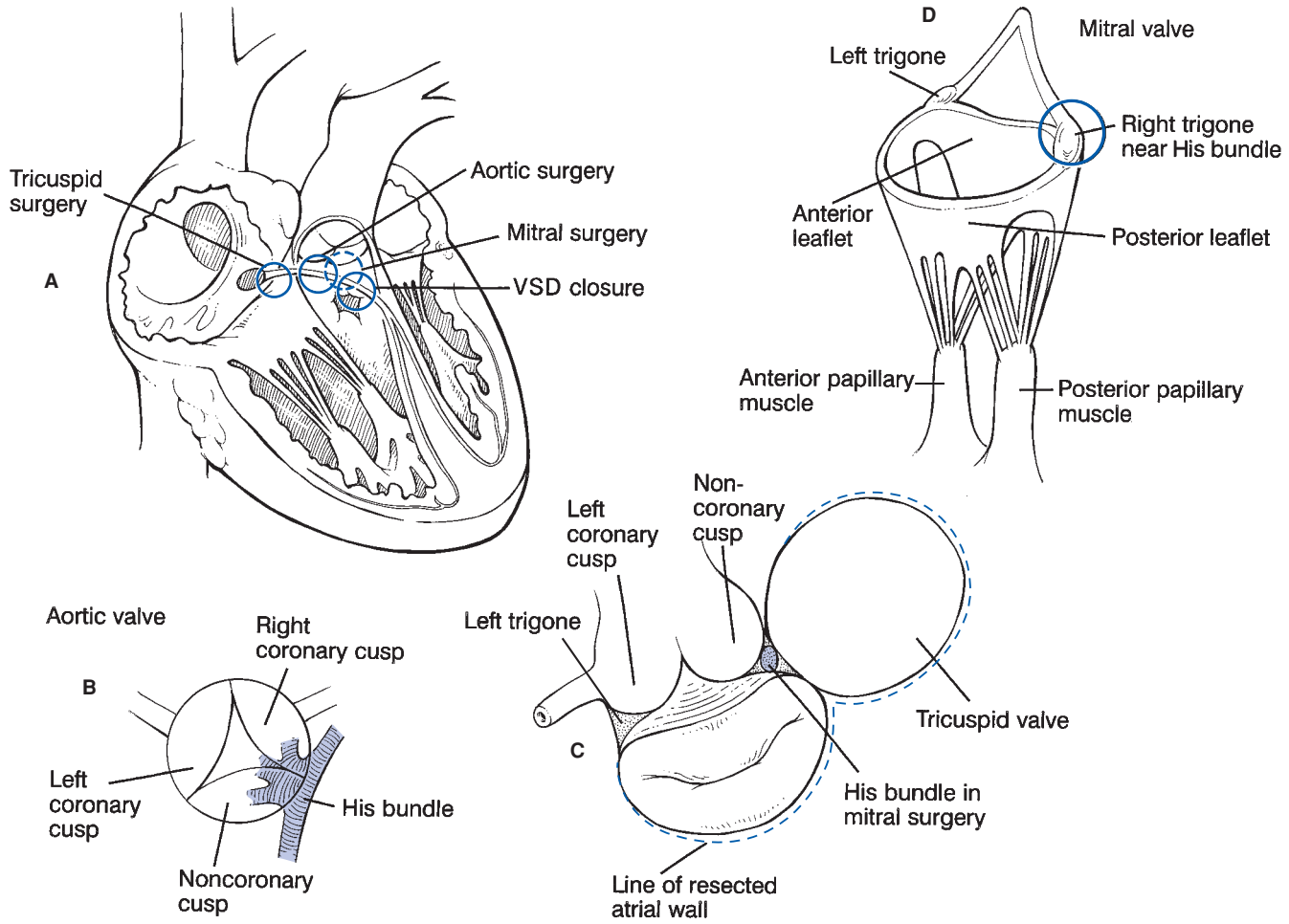


Figure 60-1. Anatomy of iatrogenic complete heart block. (A) The His bundle and nearby cardiac structures are illustrated. Common sites of injury are indicated. (B) The His bundle lies within the ventricular septum, just below the commissure between the noncoronary and right coronary aortic cusps. (C) During mitral valve surgery, the His bundle is on the ventricular septum anteromedial to the posterior commissure and right fibrous trigone (D). VSD = ventricular septal defect.

International Pacemaker Code

A five-letter code describes pacemaker function.[11] Three letters are in common usage (Table 60-1). The first letter is the chamber paced and the second is the chamber sensed. The third letter describes the algorithm used to integrate pacing and sensing functions. Thus, fixed-rate ventricular and atrial pacemakers are VOO and AOO, respectively. Demand (rate-inhibited) pacers for the same chambers would be VVI and AAI. VDD refers to a pacemaker that paces the ventricle only, but senses both the atrium and the ventricle.[12] DVI involves atrial and the ventricular pacing, but only ventricular sensing. DDD is the most flexible of current designs. The suffix R added to the three-letter code indicates rate responsiveness, discussed below.

Cellular Electrophysiology

Cellular membrane depolarization and repolarization provide a mechanism for automaticity of the cardiac chambers and the conduction system. In the resting state, the outer surface of the cell is positive, and the interior of the cell is negative. Applying a negative current to the outside of the cell theoretically produces a greater potential difference and would be expected to be more successful in depolarizing the cell than a positive current. Empirically, this is correct—unipolar pacing thresholds are lowest when the negative terminal (cathode) of a pacing system is connected to the heart and the positive terminal (anode) is connected to ground.[13] Electrogram amplitude is not substantially affected by polarity.

Rhythm Disorders

Indications for pacemaker insertion

Concern about indiscriminant referral for pacemaker insertion led to Medicare guidelines (Table 60-2). Supporting documentation may be required for billing. There are three categories: accepted, controversial, and not warranted.

Table 60–1.

International Pacemaker Code

I chamber paced	II chamber sensed	III pacing algorithm
A	A	T
V	V	I
D	D	D
O	O	O
S	S	—

A = Atrium; D = Dual (both triggered and inhibited); I = Inhibited; O = None; S = Single; T = Triggered; V = Ventricle.

Table 60–2.

Medicare Guidelines for Cardiac Pacemaker Implantation (Pre-2002)

Accepted, in symptomatic patients with chronic conditions
- Atrioventricular block
  - Complete (third-degree)
  - Incomplete (second-degree)
    - Mobitz I
    - Mobitz II
  - Incomplete with 2:1 or 3:1 block
- Sinus node dysfunction (symptomatic)
  - Sinus bradycardia, sinoatrial block, sinus arrest
  - Bradycardia-tachycardia syndrome

Controversial
- In symptomatic patients
  - Bifascicular/trifascicular intraventricular block
  - Hypersensitive carotid sinus syndrome
- In asymptomatic patients
  - Third-degree block
  - Mobitz II
  - Mobitz II atrioventricular block following myocardial infarction
  - Congenital atrioventricular block
  - Sinus bradycardia <40 bpm with long-term necessary drug therapy
  - Overdrive pacing for ventricular tachycardia

Not warranted
- Syncope of undetermined cause
- In asymptomatic patients
  - Sinus bradycardia, sinoatrial block, or sinus arrest
  - Bundle-branch blocks
    - Mobitz I

Source: Modified from AMA Council on Scientific Affairs: The use of cardiac pacemakers in medical practice. Excerpts from the report of the Advisory Panel. JAMA 1985; 254: 1952; superseded by Gregoratos et al.[15]

Symptomatic third- or second-degree heart block or profound sinus bradycardia is an accepted indication for pacemaker insertion if adequately documented. Sinus bradycardia may justify pacemaker insertion if symptoms can be causally related to the underlying bradyarrhythmia. Documentation often requires Holter monitoring. Pacemakers may be allowed for bradycardia <40 bpm in support of long-term necessary drug therapy for medical conditions such as supraventricular arrhythmias, ventricular tachycardia, hypertension, and angina. While novel indications for pacemaker therapy may be supported by clinical research, recognition of such advances by the Food and Drug Administration and insurance carriers is often slow. Electrophysiology studies are often helpful in defining proper treatment.[14] In 2002, an American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology (ACC/AHA/NASPE) task force released revised recommendations for pacemaker and ICD insertion that expand and detail the indications for device insertion. Any practitioner who implants arrhythmia control devices should be familiar with these guidelines.[15]

Atrioventricular block

First-degree block refers to prolongation of the P-R interval beyond 200 ms. First-degree block, at a low atrial rate, may progress to Wenckebach as the atrial rate is increased. Second-degree block involves incomplete dissociation of the atria and ventricles, which results in either progressive P-R prolongation and dropped beats (Wenckebach and Mobitz I, usually atrioventricular nodal block), or frequently dropped beats without prior progression of the P-R interval (Mobitz II, usually in the His-Purkinje system[16]). Third-degree block is complete atrioventricular (AV) dissociation, the atrial rate usually exceeding the ventricular rate. Left and right bundle-branch blocks and left anterior and posterior hemiblocks are partial conduction system blocks recognizable by electrocardiogram. The etiology of AV block includes ischemic heart disease, idiopathic fibrosis, cardiomyopathy, iatrogenic damage, AV node ablation, Lyme disease, bacterial endocarditis, systemic lupus erythematosus, and congenital heart disease.

Sinus node dysfunction

Whether sinus node dysfunction warrants pacemaker insertion depends on whether it is symptomatic and whether symptomatic bradycardia is caused by administration of drugs required for treatment of ancillary conditions. Causes of sinus node dysfunction include coronary artery disease, cardiomyopathy, and reflex influences.

Reflex problems include carotid sinus hypersensitivity, vasovagal syncope, and oddities like micturition-induced and deglutition syncope.[17] Both cardioinhibitory (asystole >3 s) and vasodepressor (marked fall in blood pressure despite adequate heart rate) components of reflex-mediated syncope are recognized. Whether pacemaker insertion is indicated is determined by symptoms and clinical judgment based on the duration of asystole. Tilt table testing provides objective data. Current trends favor pacemaker insertion for asystolic intervals >3 s medical therapy is favored for vasodepressor syncope even with substantial sinus bradycardia.[18] Dual-chamber (DDD or VDD) pacing is favored for this population because of beneficial effects of AV synchrony on stroke volume and symptomatology.

Features of Permanent Pacing

Dual-chamber pacing and atrioventricular synchrony

AV synchrony is important for maintenance of ventricular filling and stroke volume. In the normal heart, stroke volume is augmented 5 to 15% by AV synchrony versus the asynchronous state.[19,20] Left ventricular hypertrophy, decreased diastolic compliance, and heart failure increase the quantitative importance of AV synchrony.[21] Apical pacing of the right ventricle disrupts the normal sequence of activation, because depolarization spreads slowly and progressively over the ventricular walls rather than spreading rapidly and symmetrically through the conduction system.

The hypothesis that abnormalities of the sequence of activation can impair mechanical performance of the left ventricle has been established experimentally, and recent experience has demonstrated clinical relevance. Thus, disruption of the activation sequence is believed to explain why the ventricular-aortic gradient in idiopathic hypertrophic subaortic stenosis can be reduced in some patients by DDD pacing.[22–24] Furthermore, right ventricular outflow tract pacing may improve stroke volume when compared to apical pacing because of favorable effects on activation sequence.[25] Biventricular pacing via the right ventricular apex and coronary sinus in patients with advanced cardiomyopathy and an intraventricular conduction defect improves left ventricular function by restoring simultaneous contraction of the septum and free wall, "ventricular resynchronization."[26,27] Single-site, epicardial left ventricular pacing may provide similar benefits in some patients. For temporary epicardial DDD pacing in postoperative heart block, biventricular pacing is superior to right ventricular pacing[27] and may prove useful for treatment of left ventricular dysfunction after cardiac surgery.

Dual-chamber pacing algorithm

DDD pacemaker programming includes the lower rate, the upper rate, and the AV delay.[28] When the intrinsic atrial rate is between the upper and lower rate limits, the pacemaker tracks the atrium to maintain a 1:1 response between the right atrium and right ventricle. If the atrial rate falls to the lower rate limit, the pacemaker adds atrial pacing at the lower rate limit. If the atrial rate exceeds the upper rate limit, the ventricle is paced at the upper rate limit with loss of AV synchrony, resembling a Wenckebach effect.

The programmable AV delay defines the allowable interval between atrial and ventricular contraction. Timing starts with the atrial electrogram or pacing stimulus and continues until the allowed AV delay has elapsed. If no ventricular depolarization is detected during the delay, the ventricle is then paced. When the atrium is being paced because of low intrinsic rate, the actual P wave may be delayed 100 ms or more after the atrial pacing artifact. Thus, a longer AV delay is needed during atrial pacing than during atrial tracking, so these delays are programmable to different values.

Rate response to increased metabolic demand

During high metabolic demand, cardiac output is potentiated physiologically by increases in ventricular contractility, venous return, and heart rate. In patients with heart block and a normal sinus node response to exercise, dual-chamber pacing restores both AV synchrony and a physiologic rate response. However, with sinus node incompetence (no atrial rate increase with exercise) or with single-chamber ventricular (VVI) pacing, alternate methods of increasing heart rate with exercise are needed. Pacemakers with this capability are identified by the letter "R" (for "rate responsive") added to the three-letter pacemaker code. When the response of the sensor indicates increased metabolic demand, the lower rate of the pacemaker increases within a programmed range. Body vibration[29] or respiratory rate[30] is commonly employed to estimate demand in these pacemakers. Other indicators under evaluation include body temperature,[31] venous oxygen saturation,[32] QT interval,[33] right ventricular systolic pressure,[34] and right ventricular stroke volume.[35] All proposed and implemented indicators can produce aberrant increases in heart rate.[36] For example, a pacemaker that senses body vibration may cause tachycardia during a bumpy car ride. Elderly patients with sedentary life styles are not likely to benefit substantially from rate responsive pacing, and adverse effects can result from elevated heart rates in patients with evolving coronary disease.

Choice of pacing technique

Dual-chamber pacing has become a standard, with the exception of chronic atrial fibrillation. Paroxysmal atrial fibrillation is usually well handled by mode switching, and sinus rhythm apparently is better maintained by atrial than ventricular pacing.[37] Benefits of dual-chamber pacing in reflex-mediated syncope with cardioinhibitory features have been reported.[18] Whether the additional complexity of dual-chamber pacing is warranted in elderly patients who do not suffer from pacemaker syndrome is debatable. VVI or VVIR pacing is most appropriate for patients with bradycardia in chronic atrial fibrillation. AAIR is appropriate for cardiac allograft recipients with sinus arrest or sinus bradycardia.[38]

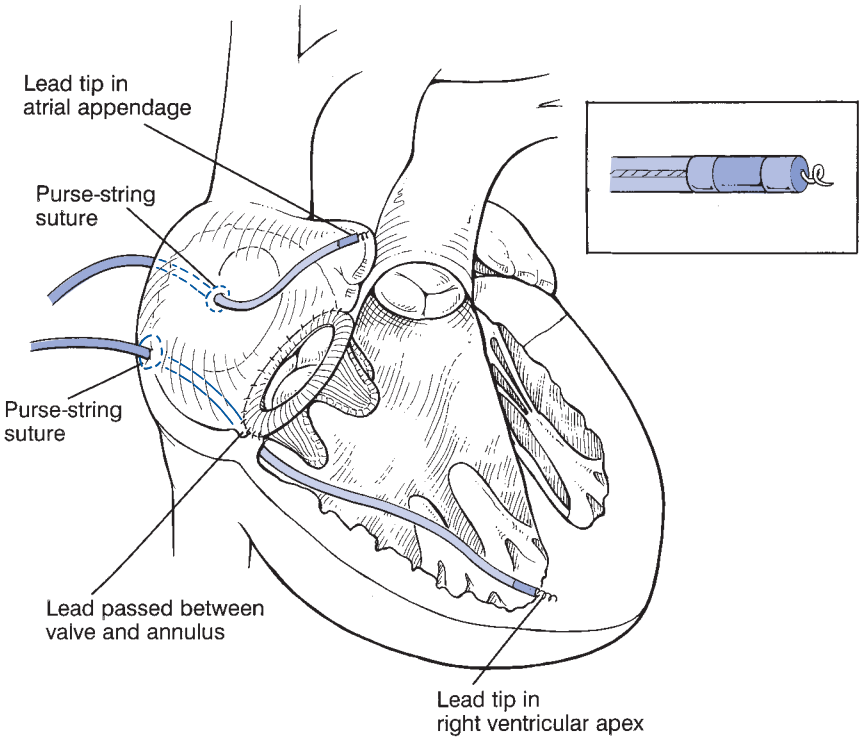


Figure 60-2. Endocardial pacing from an epicardial approach during cardiac surgery. Purse-string sutures in the atrium provide access; leads are advanced and screwed into position with the aid of introducers or by manual palpation. The ventricular lead is shown traversing the tricuspid plane between the valve prosthesis and the annulus. The inset shows the tip of the endocardial screw-in lead.

Biventricular pacing using an endocardial coronary sinus lead is recommended for symptomatic heart failure in patients with an ejection fraction below 36%, and QRS prolongation beyond 120 ms.[39]

Pacemaker Technology

Epicardial versus endocardial leads

Epicardial leads are generally inferior to endocardial leads in electrical characteristics and stress-related fractures.[40,41] Steroid-eluting tips and low-threshold designs with small contact surfaces have recently been developed for epicardial leads.[8] Fibrosis and trauma make epicardial pacing more difficult at reoperative cardiac surgery. Infected epicardial leads require a thoracotomy for lead removal. The epicardial approach is thus best reserved for congenital heart disease, tricuspid obstruction by mechanical valves, or venous thrombosis/occlusion. At thoracotomy, the option of inserting endocardial leads through an atrial purse-string is useful.[42] Left ventricular pacing is more easily achieved with epicardial than coronary sinus leads. A technical failure rate of 5 to 10% for coronary sinus lead insertion is stimulating development of minimal access approaches to biventricular pacing. Epicardial pacing avoids problems with coronary sinus entry and lead security while allowing many lead locations to be tested for efficacy.[43]

A preferred approach to DDD pacemaker insertion during open-heart surgery is indicated in Fig. 60-2. Endocardial atrial and ventricular fixed-screw, positive fixation leads are introduced into the heart through small atrial punctures and passed to the cardiac chambers. They are fixed into position by axial rotation, tested, and secured with purse-string sutures. When a tricuspid prosthesis or ring is being inserted, an option is to pass the right ventricular lead between the sutures securing the prosthetic ring and the valve annulus. A method for epicardial atrial application of endocardial pacing leads is illustrated in Fig. 60-3. Additional approaches to the patient with limited venous access are described below.

Unipolar versus bipolar

Bipolar leads include two conductors electrically separated by insulation. In unipolar systems, the patient's body is the

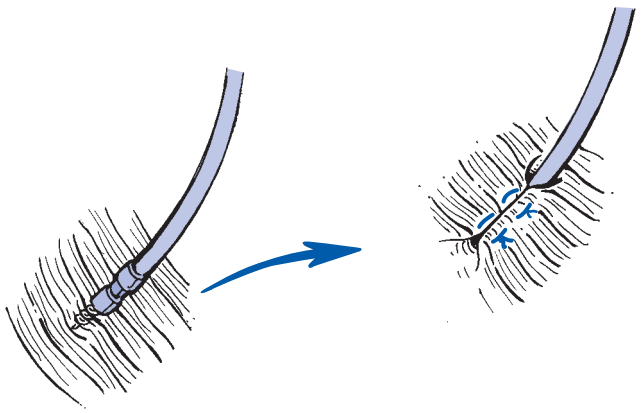


Figure 60-3. Permanent epicardial atrial pacing with an endocardial screw-in lead. The tip is screwed into the atrial myocardium, and atrial myocardium is then overlapped over the electrode with 6-0 monofilament suture.

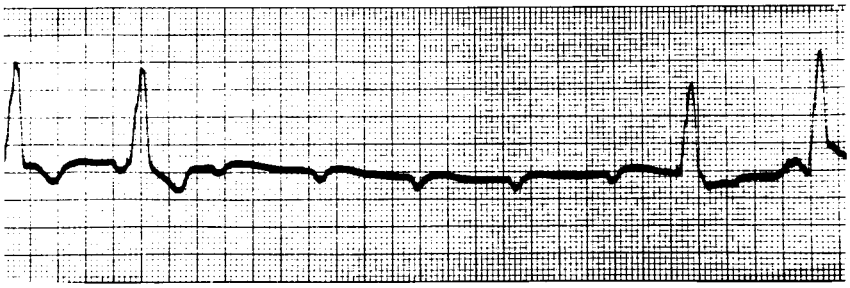


Figure 60-4. Telemetry from a patient with presyncopal episodes, third-degree heart block, poor escape rhythm, and a bipolar VVI pacemaker. The differential diagnosis of oversensing versus failure to capture was resolved when programming to VOO mode eliminated pauses. The patient underwent successful lead replacement and was discharged the next day. This is a life-threatening effect of oversensing. This older model pacemaker was not capable of monitoring electrograms to confirm the diagnosis.

second (anodal) conductor; a single conductor in the lead carries the negative current to the heart. Bipolar pacing systems reduce electrical noise (oversensing) and adventitious pacing of the diaphragm or chest wall. These advantages are offset by increased engineering complexity. Bipolar leads historically were prone to breakdowns of insulation or conductors. This could severely compromise sensing, pacing, or both[8,44] (Fig. 60-4). Early bipolar leads were thicker, stiffer, and less maneuverable than unipolar leads. Flexibility facilitates J bends and loops (Fig. 60-5) and reduces the chance of perforation through the right ventricular apex. Recent bipolar leads are much improved and similar in dimensions and handling to unipolar leads (Fig. 60-6). Short-term durability is improved, but durability of these leads beyond 10 years of service remains to be confirmed. The choice of endocardial leads for infants and small children is presently rather limited, but this is likely to improve in parallel with new technology for coronary sinus leads.

Lead fixation

We prefer positive fixation techniques, particularly in locations with sparse trabeculation. A small wire spiral or screw holds the lead in place (see Fig. 60-6G). In designs with extended screws, a soluble coating on the tip promotes venous passage. In retractable screw designs (Bisping), extension/retraction is accomplished by rotation of the pin at the lead tip. Axial clockwise rotation of these screw-in leads during fixation provides tactile feedback on the firmness and security of the attachment. Lead impedance provides feedback on the adequacy of tip extension in retractable screw designs.

Tined leads use miniature anchors in a variety of shapes and sizes to secure the lead tip between myocardial trabeculae (see Fig. 60-6A). Tined leads require a larger introducer than screw-in leads and are not as secure in smooth-walled (i.e., atria or ventricles in corrected transposition of the great vessels) or dilated chambers. Nevertheless, many physicians report excellent results with these leads.[45,46]

Temporary Pacing

Acute bradycardia can be treated with transthoracic pacing, temporary endocardial pacing, or chronotropic drugs including atropine, dobutamine, or isoproterenol. Right ventricular perforation has become less prevalent with current temporary endocardial leads but must be borne in mind if hypotension develops acutely after removal of temporary wires.

Bradycardia after cardiac surgery is commonly treated with pacing via temporary atrial and ventricular epicardial wires. Problems may include unfavorable evolution of right atrial or right ventricular thresholds and right atrial sensing. Atrial undersensing and pacemaker competition can precipitate atrial fibrillation or atrial flutter. If atrial sensing is not adequate, overdriving the atrium faster than the intrinsic

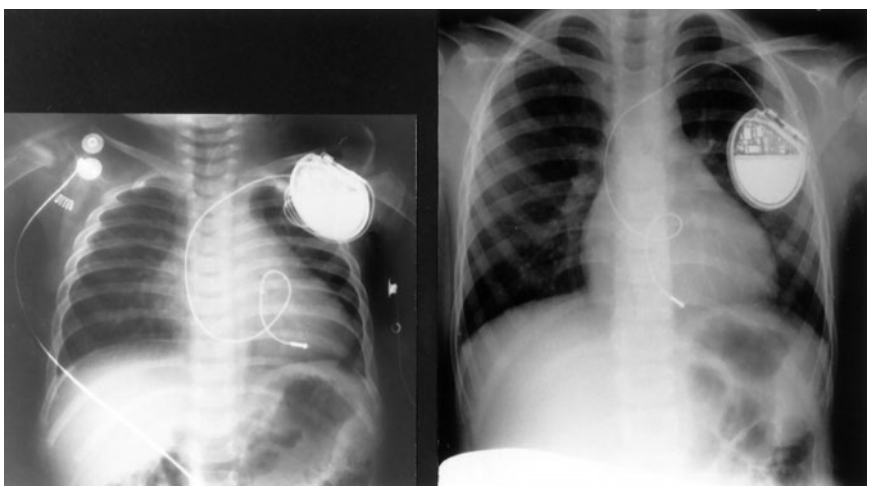
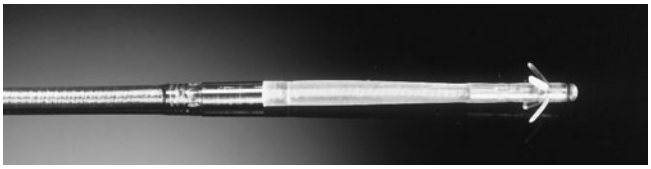


Figure 60-5. Excellent fixation and flexibility of small-diameter, positive fixation leads is illustrated in these x-rays, demonstrating the stability of a transvenous pacing lead with an intracardiac lead loop over 4 years of growth in a patient from age 1 (left) to age 5 years (right).



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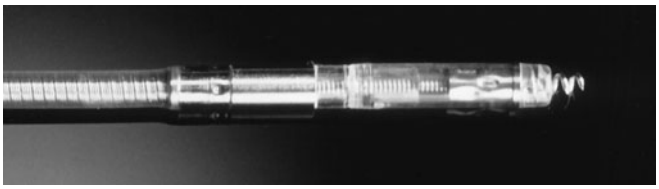

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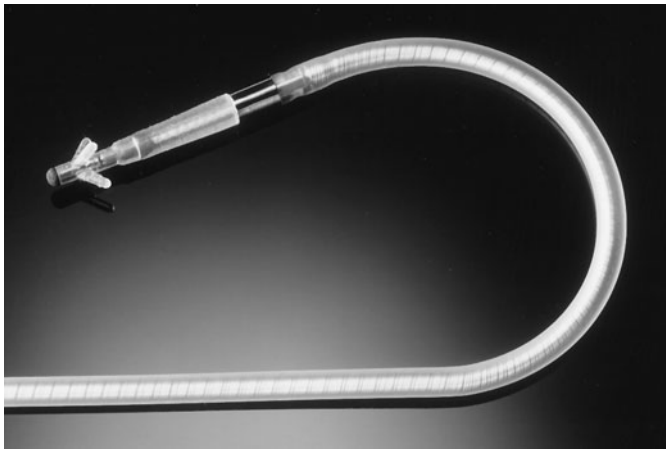

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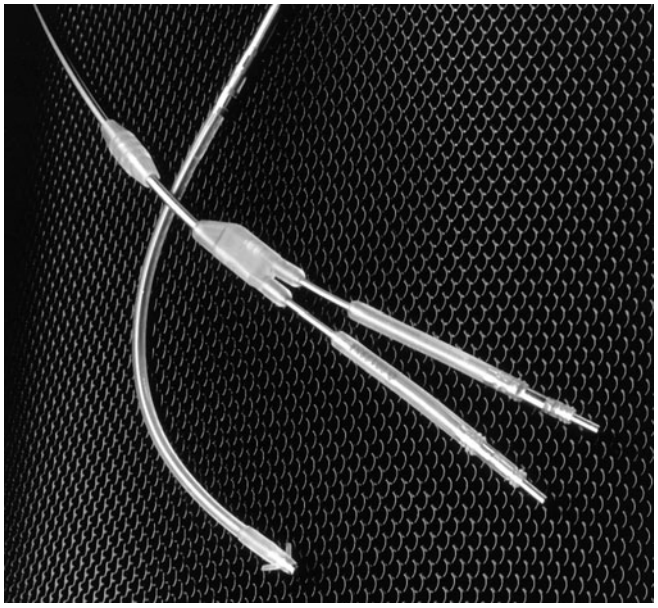

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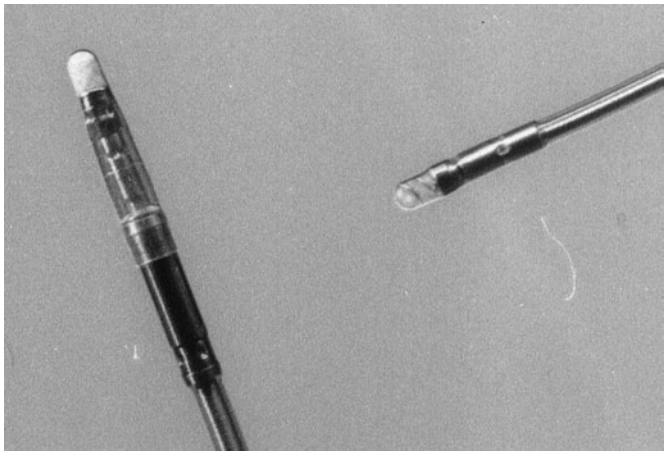

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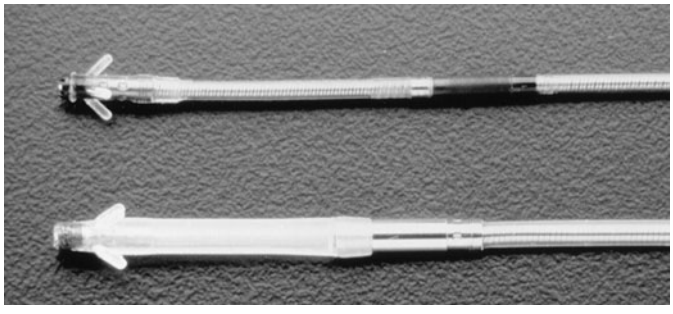

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Figure 60-6. (A) Straight bipolar tined ventricular pacing lead with steroid-eluting tip. (B) J-shaped, bipolar tined atrial pacing lead with steroid-eluting tip. (C) Bisping bipolar ventricular pacing lead with retractable, screw-in tip. (D) Bipolar (left) and unipolar (right) pacing leads with fixed-screw tips. A soluble coating over the tip, which dissolves in blood, reduces snagging during insertion. These leads can be used in the atrium or ventricle. The lead on the right was used by the author extensively for both atrial and ventricular transvenous pacing. (E) Single-pass lead for VDD pacing. (F) Current technology leads demonstrating progress in reduction of bipolar lead diameter. (G) Fixed-screw bipolar 7F lead with steroid-eluting white collar at lead tip. (*A, B, and C: Courtesy of Medtronic, Inc., Minneapolis, Minn; D, E, and F: Courtesy of Intermedics, Inc., Bellaire, Tex; G: Courtesy of Guidant Corp., Indianapolis, Ind.*)

rate can prevent competition. Reversing polarity or inserting an independent ground wire in the skin under local anesthesia may alleviate problems with pacing threshold. The output of the external generator in volts or milliamps should be left at least twice as high as the threshold, and be measured daily. Ventricular undersensing in critically ill patients is hazardous, as pacing during the vulnerable period can precipitate ventricular tachycardia or fibrillation.

Cardiac output and pacing rate

For patients with hemodynamic compromise following cardiac surgery, pacing rate and AV delay can affect hemodynamics. Mechanisms include effects on valve leaks or fixed stroke volume. Mean arterial pressure can be used to estimate cardiac output, if systemic resistance is constant. Rate and timing adjustments should be assessed over intervals of less than 20 s to minimize reflex effects. The settings producing the highest sustained mean arterial pressure should also produce the highest cardiac output.

Pacemaker Insertion

Environment and anesthesia

Pacemaker and ICD surgery is increasingly performed in electrophysiology (EP) laboratories.[47] Whether in the operating room or EP lab, properly functioning equipment is essential. Infection control is critical;[48] operating room standards for air quality should be enforced. Pacemakers can be inserted in an EP laboratory by one skilled surgeon and one skilled circulating nurse. This is satisfactory until a problem like angina, transient ischemic attack, patient disorientation, or lidocaine toxicity arises. Also, certain patients are simply too unstable because of dementia, myocardial ischemia, heart failure, anxiety, or ventricular tachycardia to undergo pacemaker insertion without an anesthesiologist. Vancomycin reactions (red man syndrome), pacing-induced ventricular fibrillation, air embolism, and Stokes-Adams attacks are rare emergencies that are less problematic if considered in advance. Intraoperative death can occur due to hemorrhage, tamponade, or myocardial infarction. Good clinical judgment about when an anesthesiologist is essential is important. If English is not the patient's first language, a translator is helpful.

Monitoring

R-wave detection by an electrocardiogram (ECG) monitor is inadequate for pacemaker insertion, because pacing artifacts that fail to capture may not be distinguished from those that do. Thus, subthreshold pacing can elicit regular beeping from the monitor in an asystolic patient. Oxygen saturation monitors are preferable, as they beep only during blood flow. Pulse oximeters should not be placed on the same extremity as a blood pressure cuff. When monitors are unreliable, palpation by an anesthesiologist or nurse of the temporal, facial, or radial artery pulse can detect asystole.

Venous access strategy

Choices include which side will be employed and whether a cutdown or percutaneous venipuncture will be used. Cutdown approaches to the cephalic, subclavian, external jugular, and internal jugular system have been described.[49] Subclavian vein anatomy has been analyzed[44,50] in an effort to reduce the frequency of subclavian crush (Fig. 60-7). Subclavian puncture is associated with an apparently unavoidable but low incidence of pneumothorax, hemothorax, and major venous injury. Ultrasonic vessel locators may further reduce the frequency of injury during deep vein puncture.

Venous access is effectively impossible in superior vena cava syndrome or subclavian/innominate vein obstruction or thrombosis (e.g., with chronic dialysis, mediastinal tracheostomy, or multiple pacemaker leads). Access from below

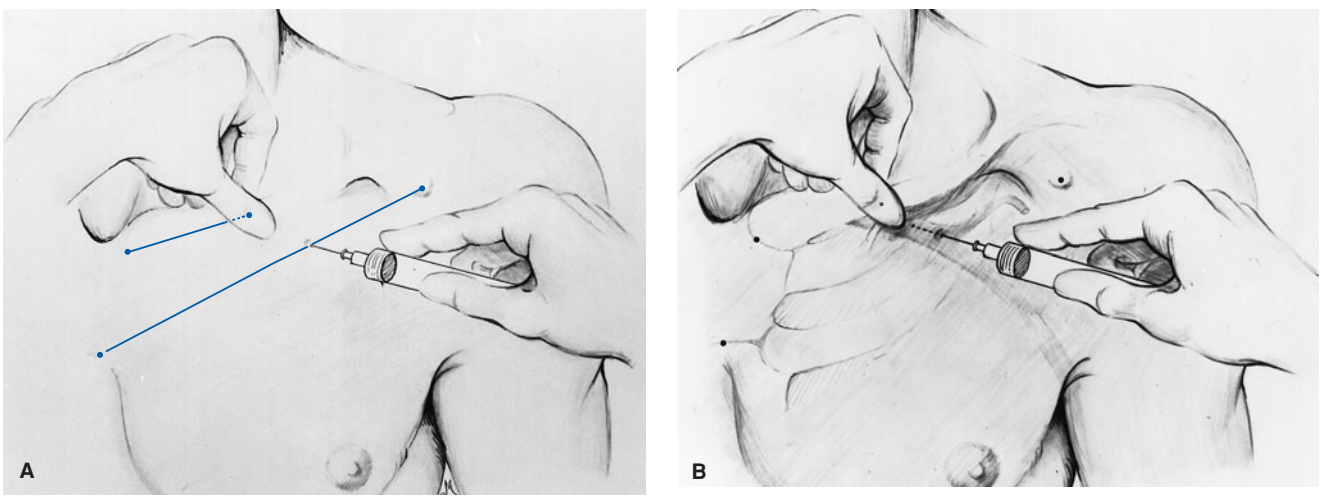


Figure 60-7. Landmarks for subclavian vein puncture. Potential complications of this procedure include pneumothorax, hemothorax, and lead damage due to subclavian crush injury. (*Reproduced with permission from Magney et al.*[44])

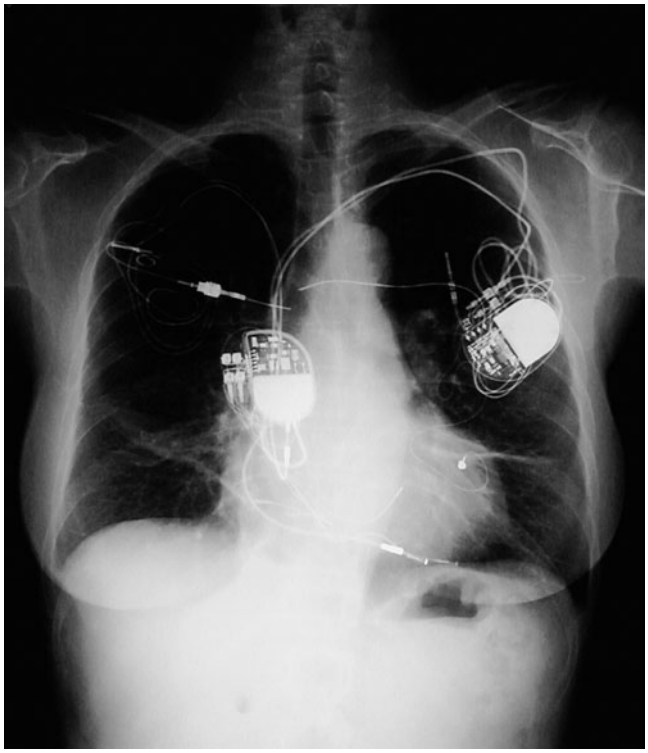


Figure 60-8. X-ray of a patient with very poor escape rhythm, bilateral venous obstruction, and severe exit block. A new pacing system was inserted through the right atrial appendage via right parasternal mediastinotomy. Her old pacemaker was programmed to back-up mode and scheduled for removal at a later date.

or even transhepatically is possible,[49,51] but the potential for bleeding, venous thrombosis, and pulmonary embolism are concerns. Right parasternal mediastinotomy exposure of the right atrium and a Seldinger approach with small introducers and atrial purse-string sutures can be useful in difficult cases[42] (Fig. 60-8).

Antibiotic prophylaxis

Antibiotic prophylaxis is indicated before insertion of a prosthetic device.[48] We prefer 1 g of intravenous cefazolin. We also irrigate the operative field with a portion of a solution of 1 g of cefazolin in a liter of warm saline. Patients who have a valve prosthesis or who have a penicillin or cefazolin allergy receive vancomycin (500 mg) and gentamycin (1 mg/kg).

Pacing systems analyzer

Pacing thresholds and electrogram amplitudes are measured with a pacing systems analyzer. Electrogram characteristics and slew rate can be examined with many current analyzers, and electrogram telemetry is available from most current pacemakers. The analyzer must function properly, and should be serviced and tested periodically. The batteries must be checked and replaced when depleted. Any discrepancies between measurements by the analyzer and the pacemaker should be noted and related functions of the analyzer rechecked.

A skilled operator is needed to run the analyzer and record the results. Alternatively, the analyzer can be placed in a sterile bag and operated from the surgical field. Manufacturer's representatives, an increasing presence in the operating room and EP lab, are skilled in operation of these analyzers.

Cables

The cables connecting the analyzer to the leads are the patient's lifeline. Even with excellent quality control, cables with open or reversed connections may be delivered to the surgical field. Errors can also occur in connecting the cables to the analyzer. A routine for testing the cables and the integrity of their connections is therefore recommended. After passing the cables from the operating table, pacing is initiated from the analyzer at 5-V output. The alligator connectors are then briefly touched to the subcutaneous tissue, with caution to minimize inhibition of the permanent pacemaker. The current measured in the analyzer should rise to 300 to 1000 ohms. If impedance is more than 5000 ohms, the circuit is faulty. The operation should not proceed until the problem is corrected, as the analyzer-cable circuit is defective. Connections to the analyzer should also be checked, since inadvertent reversal of polarity can make measured pacing thresholds inappropriately high. Even disposable leads with polarized connectors can be manufactured with the connectors reversed.

Fluoroscopy

Fluoroscopy is essential for transvenous device implantation, and operating room personnel need to be familiar with the equipment. Distracting problems with image orientation, rebooting, timers, brakes, and locks can be avoided by a knowledgeable team. Sudden failure of fluoroscopy at a critical point happens to every pacemaker surgeon with a large enough clinical volume. If a back-up unit is not available, the options include "blind" endocardial lead insertion, epicardial insertion, or postponement of the procedure. Overheating is an issue when fluoroscopy is prolonged, as may occur during biventricular pacemaker insertion. The use of low-dose and pulsed image options is desirable when prolonged use of the fluoroscope is planned.

Surgical approach

We approach the patient from the left when feasible. The fluoroscope, on the patient's right, is positioned carefully to allow visualization of the apex, right atrium, and deltopectoral groove. The right arm is extended to the right on an arm board. The drapes are suspended from IV poles. One pole is caudad to the arm board. Careful positioning allows the left clavicular region to be exposed while leaving the patient adequate light and air. After skin preparation, towels are aligned with the deltopectoral groove and clavicle to define the essential landmarks. The region of the incision and generator is infiltrated with 1% lidocaine to produce a field block. A 5- to 6-cm horizontal incision is created 4 cm beneath the clavicle, the lateral extent of the incision just reaching the deltopectoral

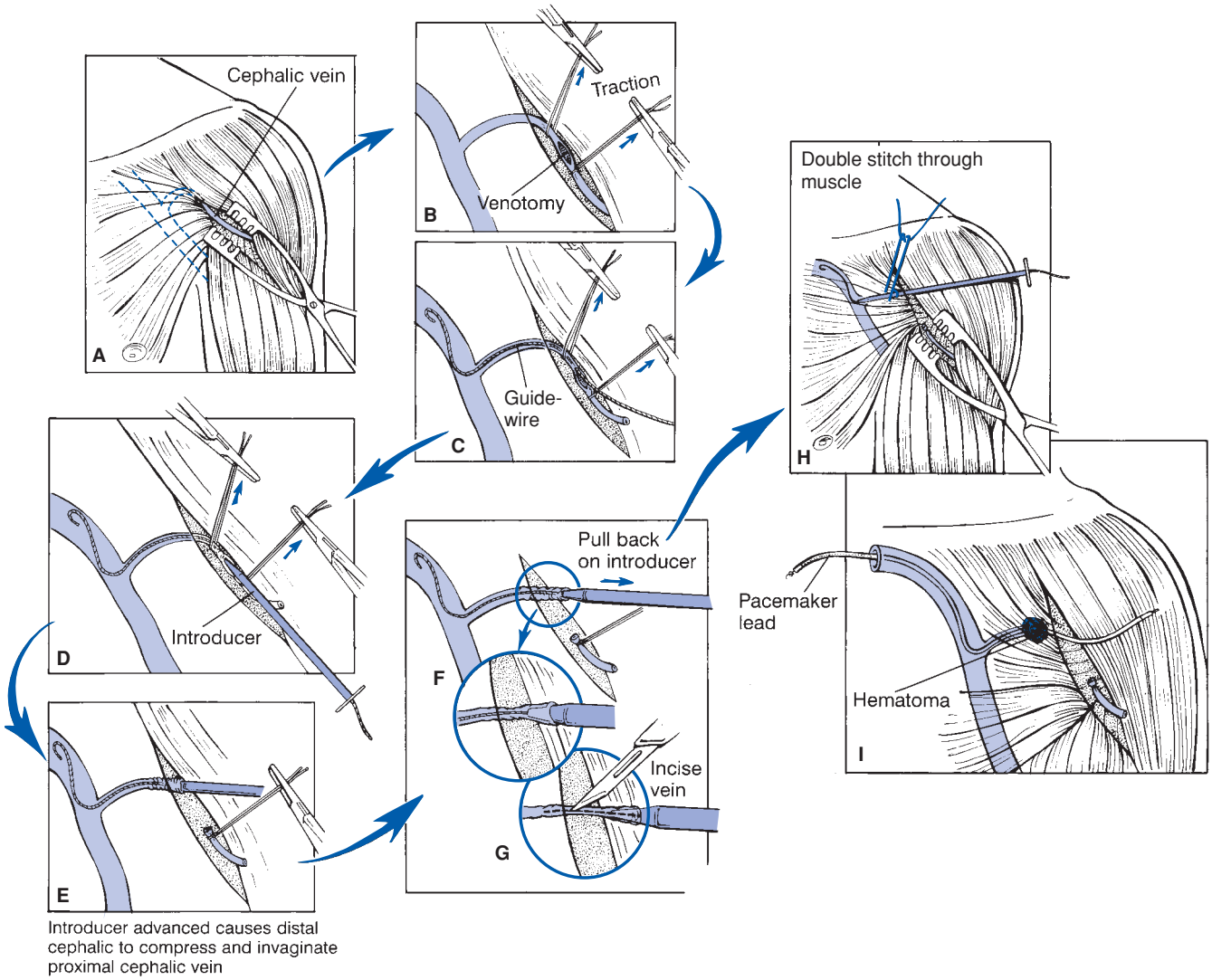


Figure 60-9. Cephalic cutdown approach to small veins that pass a guidewire, but not an introducer, to the central veins. Resistance results from entrapment of the introducer tip and inversion of the vein; the introducer advances by turning the vein outside-in. Fortunately, this entrapment can be put to good use. After the guidewire is advanced (C), a no. 18 Angiocath is passed over the guidewire to dilate the vein (not shown). This allows the introducer tip to enter the vein (D), but if the vein does not split, the introducer cannot be advanced (E). The impaled vein is exposed by gently withdrawing the introducer (F). The adherent, exposed segment of vein is then split longitudinally with a no. 11 blade (G). The procedure can be repeated, if necessary, to advance the introducer centrally. A purse-string suture approximates soft tissue around the path of the introducer to achieve hemostasis (H, I).

groove. This allows the generator to be positioned away from the deltopectoral groove and axilla, avoiding interference with motion of the left arm at the shoulder. An alternate incision directly over the deltopectoral groove facilitates exposure of the cephalic vein; this is particularly valuable in obese patients or elderly patients with atretic veins.

Venous access

When the deltopectoral groove has been exposed, additional anesthesia is infiltrated into the lateral margin of the pectoralis and laterally into the deltoid. The dissection proceeds into the deltopectoral groove, following the lateral edge of the pectoralis, until the cephalic vein or another venous branch is exposed. Failure to find a vein may mean the incision is too far cephalad or caudad or not lateral enough. The incision can be deepened into the subpectoral fat if necessary. If the vein is too small to pass a pacemaker lead, the curved end of the guidewire for a 7F introducer is passed centrally. The ability to manually stiffen and extend the curve by central manipulation of the tension in the guidewire is an important technical aid in tortuous veins. The method illustrated in Fig. 60-9 can be used to dilate the vein. If the guidewire will not pass centrally, a no. 18 Angiocath is advanced over the guidewire and used to inject a small amount of iodinated contrast to visualize the venous system fluoroscopically. If the cutdown approach must be

abandoned, precise localization of the subclavian vein by venogram reduces the risk of injury during subclavian puncture. If dual-chamber pacing is planned, the guidewire should be reinserted through the introducer before the introducer is stripped away. This provides venous access for the duration of the procedure.[52,53] A purse-string suture in the muscle usually provides adequate control of bleeding and allows stabilization of the lead(s).[54,55] Ultrasonic localizers may be useful at this stage, with appropriate sterile precautions.

Right ventricular lead insertion

From the patient's left, a gentle spiral in the distal 10 cm of the stylet will guide the lead toward the tricuspid valve, right ventricle, and pulmonary artery. Advancing the lead into the pulmonary artery outside the cardiac silhouette confirms that the lead is not in the coronary sinus. For fixed-screw positive fixation leads, withdrawing the stylet 3 to 5 cm minimizes the risk of apical perforation while screwing the lead tip into the myocardium with axial clockwise rotation. Reverse torque that develops as the lead is rotated should be noted; this torque is a guide to the security and safety of fixation. We fix the lead with three consecutive 360° clockwise rotations of the lead shaft and then release the torque. This fixation sequence is repeated as many times as is necessary, until the lead is secure, with substantial reverse torque after the first 360° rotation. No more than three complete axial rotations are employed in any sequence. A rare problem that can develop with screw-in leads is undetected ventricular perforation. The lead tip should be watched during the fixation process to look for sudden extra-anatomic movement, with the lead tip following the cardiac silhouette around the apex and then cephalad. If this happens, the lead should be withdrawn and repositioned. An echocardiogram should be obtained and the patient carefully monitored for tamponade.

When the lead tip has been properly positioned, the stylet should be withdrawn and thresholds tested. The patient is asked to hyperventilate and cough to confirm fixation. The ventricular pacing threshold should be less than 0.7 V, and R-wave amplitude should be more than 5 mV. For unipolar leads, impedance should be 400 to 1000 ohms, depending on lead design. There should be no diaphragmatic pacing at an output of 10 V.

If the lead is dislodged by hyperventilation and coughing, or if thresholds are not adequate, the lead should be repositioned. A positive fixation lead can be unscrewed by counterclockwise axial rotation until it floats free. Positive fixation leads can be secured almost anywhere along the margins of the right ventricular silhouette (Fig. 60-10), including the right ventricular outflow tract (Fig. 60-11[56]). In difficult cases, we have relocated leads as many as 15 times. The geographic center of the right ventricular silhouette is not a desirable location, as it can lead to entanglement of the lead in the chordae tendineae (see Fig. 60-10).

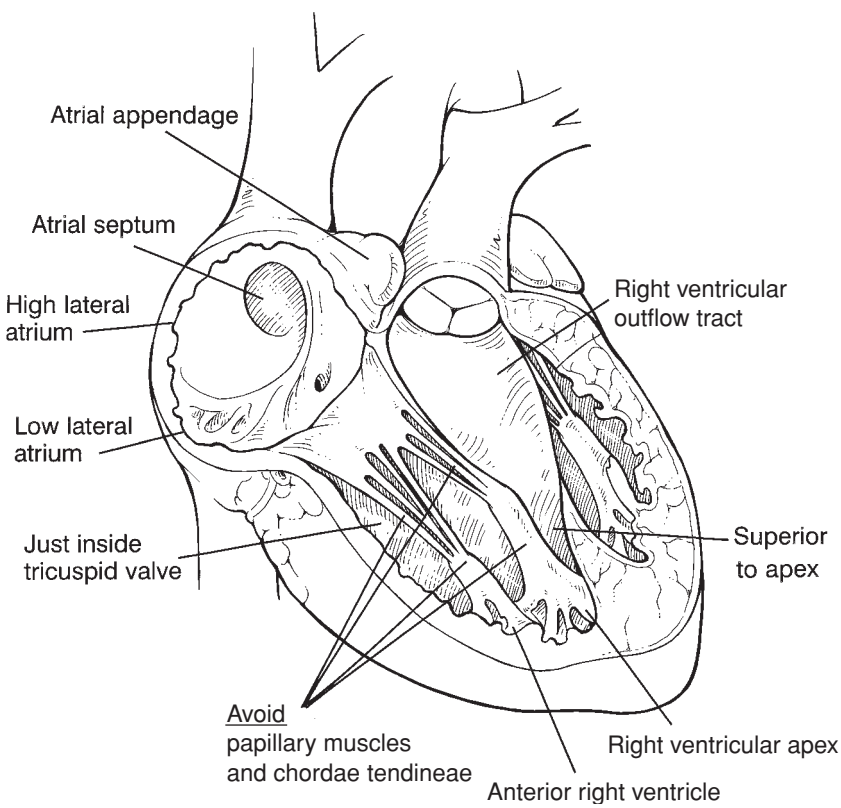


Figure 60-10. Useful sites for transvenous atrial and ventricular pacing using fixed-screw unipolar leads. The geographic center of the right ventricle (RV) should be avoided; screwing leads into this location can result in lead entrapment in the chordae tendineae, which may necessitate lead abandonment.

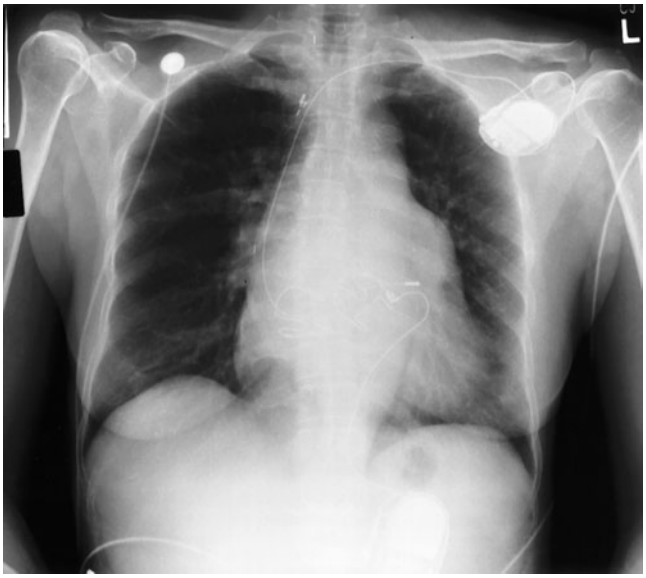


Figure 60-11. Screw-in lead in the right ventricular outflow tract of a patient with complete heart block after tricuspid valve replacement for Ebstein anomaly.

Coronary sinus lead insertion

Left ventricular pacing via the coronary sinus (CS) is a desirable skill as a result of the MIRACLE trial and subsequent studies indicating that biventricular pacing can improve the symptoms of heart failure and also may reduce the mortality of dilated cardiomyopathy.[26,27,39] Electrophysiologists are familiar with CS entry for arrhythmia mapping, with steerable mapping catheters and biplane fluoroscopy being important tools. However, most clinical trials of biventricular pacing for heart failure indicate a technical failure rate of CS lead insertion of 5 to 10%.[26,39] The CS is a posterior structure near the caudal aspect of the tricuspid valve (Fig. 60-12). Locating the os in heart failure patients is difficult because the CS is angulated and distorted by enlargement of the right ventricle and right atrium. Transesophageal echocardiography and venography can be helpful in locating the os. Biventricular pacing candidates are prone to ventricular arrhythmias, making rapid defibrillation capability desirable. Even experienced operators may require hours to insert a CS lead with present methods, although technology for both endocardial and epicardial left ventricular lead placement is improving. Over-the-wire lead designs are the most successful. We prefer to do the CS lead first via the cephalic approach, with right atrial and right ventricular leads following via subclavian puncture. Lead insertion involves insertion of an angled catheter into the CS, CS venography, and lead insertion through the cannula into a lateral branch of the CS. The CS cannula must then be removed and stripped off without dislodging the lead. Positive fixation leads are not available. The large selection of angled CS cannulas, steerable probes, and lead designs testifies to the technical challenge. The difficulty of CS lead insertion in heart failure patients should not be underestimated; special training by an experienced preceptor is definitely worthwhile.

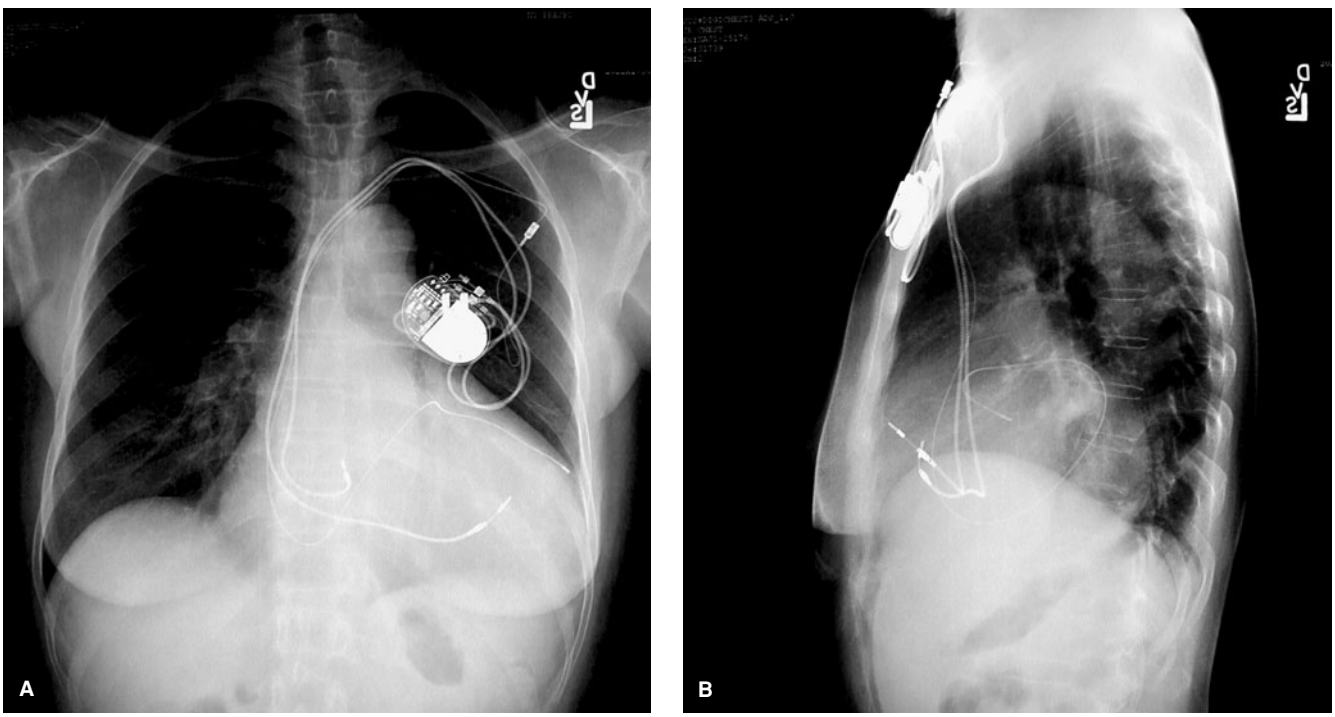


Figure 60-12. (A) Biventricular, dual-chamber pacemaker with endocardial leads in the right atrium, right ventricle, and lateral branch of the coronary sinus (left ventricle). This patient was relieved of dobutamine dependence by addition of the left ventricular lead. (B) Lateral x-ray of the same patient. The posterior course of the coronary sinus is apparent.

Length adjustment

Lead length must be adjusted between "too short," in which a deep breath results in lead displacement, and "too long," in which a cough results in formation of a loop that effectively shortens the lead, also causing displacement. Maximal inspiration and expiration under fluoroscopy helps judge length. Vigorous coughing tests the security of lead tip fixation. This valuable feedback is lost if the patient is heavily sedated or cannot cooperate. Pacemaker syndrome also can be detected immediately during VVI pacing in conscious patients.

Atrial lead insertion

For dual-chamber pacing, the atrial lead is introduced last. A "J" or "S" stylet shape is best for finding the atrial appendage from the left side.[55] The "S" shape is also useful for passing a positive fixation lead to the right margin of the atrium near the junction of the right atrium and inferior vena cava (Fig. 60-13). P-wave amplitude is often best in this location. The atrial pacing threshold should be less than 2 V. In the presence of complete heart block, it may be difficult to confirm atrial capture from the surface ECG. Pacing the atrium at 150 bpm results in rapid oscillation of the lead tip. If this is apparent fluoroscopically, lead oscillation can be used to determine the atrial pacing threshold. This technique should only be used if the high atrial rate is not conducted to the ventricle. High-output atrial pacing can inhibit whatever temporary VVI pacing is supporting the patient, resulting in asystole.

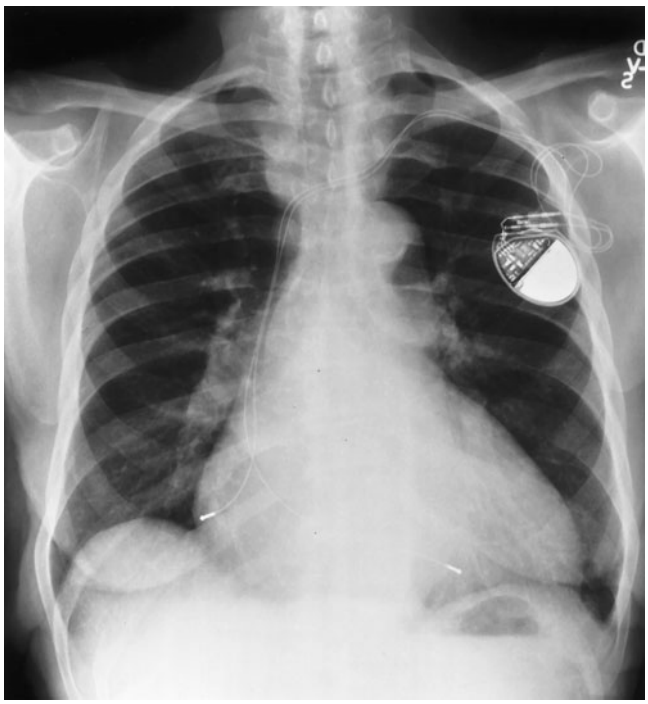


Figure 60-13. Dual-chamber pacemaker illustrates low, right lateral atrial lead placement. This location, particularly advantageous after obliteration of the atrial appendage at heart surgery, requires a positive fixation lead. P-wave amplitude in this location is often acceptable when other sites fail. If phrenic nerve stimulation is observed with 10-V stimulation, however, the lead tip should be repositioned.

The P-wave electrogram is the Achilles heel of dual-chamber pacing. If atrial sensing is not satisfactory, a DDD pacemaker will not function properly. The P-wave amplitude should ideally be greater than 2 mV. Measurement of P-wave amplitude with unipolar leads can be confusing. Crosstalk or far-field sensing of ventricular depolarization from the atrial lead can occur, so that the signal measured through a pacemaker analyzer is not the P wave but the QRS complex. Simultaneous measurement and display of atrial and ventricular electrograms as well as the surface ECG can resolve this. An alternate solution involves programming the generator as a P-wave detector: The lower rate is set below the patient's intrinsic atrial rate, the AV delay is set shorter than the patient's PR interval, and atrial sensitivity is set at 2 mV. When the generator is connected to the atrial and ventricular leads, every P wave will be followed immediately by a ventricular pacing spike if P-wave amplitude is greater than 2 mV. The pacemaker must be reprogrammed to clinically appropriate settings at the conclusion of surgery.

Telemetry of atrial and ventricular electrograms by pacemakers is a valuable source of EP data. For example, inability to pace the atrium or to measure atrial electrograms in the operating room may indicate low-amplitude atrial fibrillation or supraventricular tachycardia; this may be invisible on the surface ECG but may be detectable as electrogram activity. Electrogram telemetry provides valuable confirmation of proper DDD pacing (Fig. 60-14).

Generator location

We utilize a watertight, three-layer skin closure for primary implants, three layers in generator replacements. Cosmetic appearance is important to many patients, and in others technique is critical to optimize healing. Past injury to the chest wall or surgery/radiotherapy for breast cancer can present formidable technical problems. The use of bipolar systems facilitates generator placement behind the pectoralis or inside the rectus sheath. Diminutive generators are available, but battery life is reduced. Innovative locations for pacemaker generators include axillary, retromammary, intrathoracic, and preperitoneal sites. These approaches are rarely indicated with present generator designs.

Length of Stay After Pacemaker Implantation

Ambulatory surgery

Same-day hospital discharge after pacemaker insertion is feasible in patients who have an adequate escape rhythm. Positive fixation leads are preferred. After monitoring and recovery from sedation, patients are ambulated and instructed in range of motion exercises for the shoulder. A chest x-ray is obtained to document lead position and rule out hemothorax or pneumothorax or pericardial enlargement.

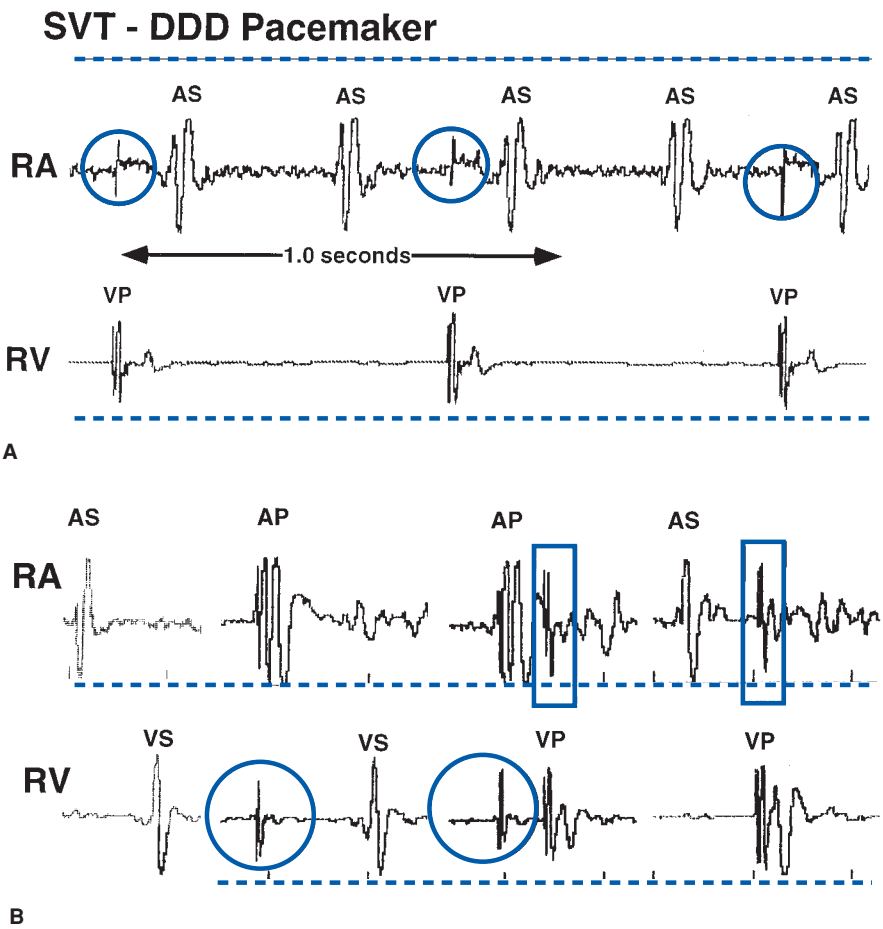


Figure 60-14. Right atrial (RA) and right ventricular (RV) electrograms from a unipolar DDD pacemaker during supraventricular tachycardia (SVT). Regular atrial depolarizations appear (AS) at a rate of 160 bpm. The pacemaker paces the ventricle (VP) at 80 bpm, because alternate P waves fall inside the postventricular atrial refractory period and are not detected. The circles illustrate far-field sensing of the RV pacing artifact in the RA lead. The SVT was not detected preoperatively. Once this recording was obtained, overdrive atrial pacing from the pacemaker converted the SVT to normal sinus rhythm, and normal pacemaker function returned.

Pacemaker-dependent patients

Lead displacement can be result from technical error, to struggling of demented patients, and other factors. Since a small percentage of lead displacement is probably unavoidable,[45,46,57,58] patients who might suffer death or injury in the event of abrupt pacemaker failure should be observed in the hospital overnight on telemetry. However, lead displacement in our experience in ambulatory patients has not been more frequent than in hospitalized patients.

Pacemaker Generator Replacement

Planning

Fifteen percent of functioning pacemakers were replacements in a recent survey.[59] Complications of pacemaker generator replacement include infection, lead damage, connector problems, and asystole during the transition from the old generator to the new. Relative pacemaker independence at the time of initial pacemaker implant may progress to severe pacemaker dependence by the time of generator replacement. Ambulatory surgery is common. As a practical matter, we no longer reverse warfarin for pacemaker generator replacement unless lead replacement is expected.[60] Patients with leads more than 10 years old should be carefully evaluated for pacemaker dysfunction prior to generator replacement; a Holter monitor should be obtained if lead dysfunction is suspected. Rising pacing threshold may indicate impending lead failure. The possibility of unexpected lead replacement should be discussed with the patient in advance.

Back-up pacing

Some practitioners insert a temporary transvenous pacing wire during pacemaker generator replacement, but this is rarely necessary. The output of the replacement unit must be high enough to match the pacing threshold of a chronically implanted lead. This can be problematic if the generator is an older type with a fixed output of 5.4 V. Lack of programmability prevents preoperative threshold testing, and the 5.4-V output is considerably higher than nominal for most current generators. The standard approach with newer generators is to test the pacing threshold with a pacemaker analyzer and program the replacement to appropriate output before connecting it. Before disconnecting the old generator, be sure that the pacemaker analyzer, cables, and connections are intact and that personnel in the operating room are aware of where the cables run. Some place the analyzer in a sterile bag on the operative field. With many generators, an Allen wrench placed in the header establishes electrical continuity with the

ventricular lead; the pacing threshold can then be established before disconnecting the old generator. The old generator should be kept within reach as a back-up in case of trouble with the new generator, the analyzer, or the connectors.

Lead sizes

The three common sizes of lead connector for permanent pacing are 6 mm, 5 mm, and 3.5 mm (VS-1 or IS-1). The new generator should be an exact match for the patient's lead size, but a selection of step-up and step-down adapters can be helpful. The contacts do not always line up correctly across VS-1 and IS-1 connectors, even though the connector diameter is the same. It is important to determine in advance whether connections can safely be made across the VS-1/IS-1 interface.

Postoperative Care

Wound care

Patients are instructed to keep implant wounds dry until an office visit 7 to 10 days postoperatively. Any wound drainage at the postoperative visit is cultured, and prophylactic antibiotics are started until culture results are available. We have abandoned aspiration of the rare postoperative hematoma in favor of close observation, unless infection is an issue or spontaneous drainage occurs or appears imminent.

Antibiotic prophylaxis

Routine use of prophylactic antibiotics before dental work and other invasive procedures in pacemaker or ICD recipients is not recommended under AHA/ACC guidelines. We recommend prophylaxis for 3 months after device insertion, allowing time for the pacing leads to become endothelialized.

Testing and Follow-Up

Office/clinic versus telephone

Pacemakers require periodic testing to confirm sensing and pacing function and detect battery depletion. Current standards involve testing these functions at 1- to 3-month intervals. Whether follow-up should be done by transtelephonic monitoring or clinic or office visits is in dispute.[61–63] Transtelephonic monitoring alleviates transportation issues for elderly patients, but some are too anxious or debilitated to manage the process. In addition to reducing patient travel and strain on office resources, many commercial services provide emergency monitoring on a 24-hour basis, an important advantage in managing apprehensive or incapacitated patients.

Pacemaker programming

Programming can be done in an office setting by trained, experienced personnel. In some situations, a manufacturer's representative may provide valuable help. Transtelephonic programming is not currently available.

DDD pacemaker programming allows adjustment of electrogram sensitivity as well as pacing stimulus amplitude/pulse width for both the atrium and ventricle. Lower rate, upper rate, atrioventricular delay, and refractory periods for atrial and ventricular sensing are programmable. Rate responsiveness, unipolar/bipolar configuration, and many other options are also adjustable noninvasively.

We initially program newly inserted pacemakers to stimulation amplitude and pulse width higher than nominal. At the initial office visit, pacing thresholds are retested and amplitude and pulse width are adjusted to nominal levels if pacing thresholds are low. The use of high initial output is less important with steroid-eluting leads. Details of pacemaker programming have been described elsewhere.[63,64] Some current pacemakers are capable of automated threshold adjustment.

Programming allows most problems detected by transtelephonic or Holter monitoring to be corrected. The etiology of symptoms can often be elicited from real-time electrograms or stored data. Adjustments may include not only sensitivity or pacing output but also pacing mode for new-onset atrial fibrillation[65] (Fig. 60-15A) or sinus node incompetence related to medication changes (Fig. 60-15B). Problems that may require reoperation include lead displacement, lead fracture (Fig. 60-16), insulation degradation (see Fig. 60-4), and exit block[57,58] (Fig. 60-17).

Pacemaker interrogation should begin with a printout of the initial settings, which is an invaluable reference after involved programming. Telemetry should be examined to determine time-related variation in heart rate, percentage of beats sensed and paced, the quality of the electrograms, lead impedance, and battery voltage.

The pacing amplitude and pulse width are finely tuned at the 1-year follow-up visit. We generally provide at least 100% safety margin on pulse width threshold. Pacing mode, rates, refractory periods, rate response, and delays are adjusted to optimize patient comfort and battery life. For example, some pacemakers allow programmed reduction of a lower rate at night, eliminating unnecessary pacing during sleep. A very long atrioventricular delay can eliminate ventricular pacing in some patients with first-degree block, but a reduction in the upper rate limit to 105 bpm may be necessary to achieve this.

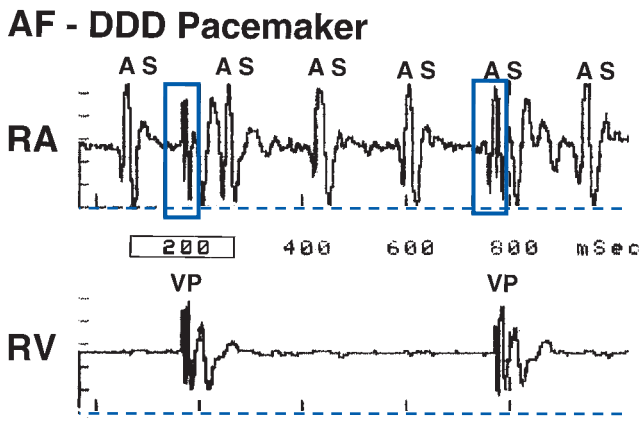
Complications of Pacemaker Insertion

Mortality

Death is a rare complication of pacemaker implantation.[57,58,66] Lethal problems can include lead displacement, venous or cardiac perforation, air embolism, and ventricular tachycardia or fibrillation.[57,58] A review of 650 pacemaker insertions by the author between January 1984 and April 1993 revealed one perioperative death due to heart failure induced by general anesthesia in a child with congenital heart disease (Table 60-3).

Incidence of complications

The incidence of early complications in one recent published series was 6.7%, with 4.9% requiring reoperation.[57] For



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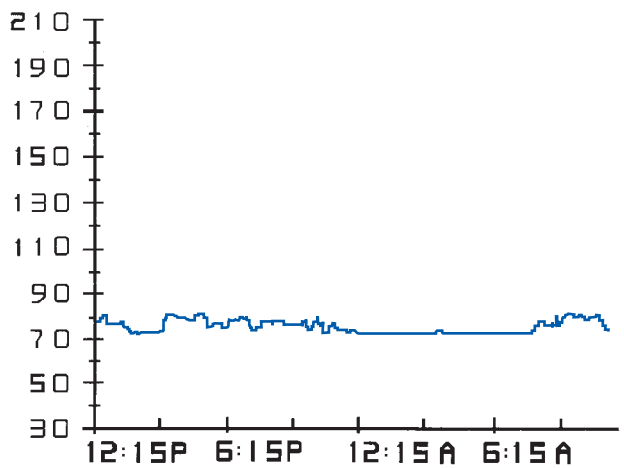

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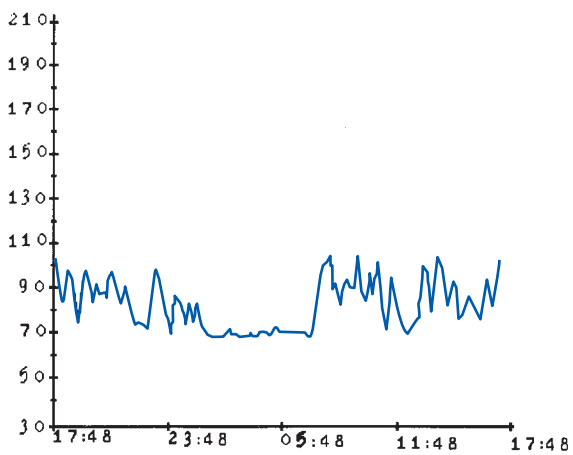


C

Figure 60-15. (A) Atrial (upper, RA) and ventricular (lower, RV) electrograms from a unipolar DDD pacemaker during atrial fibrillation (AF). The AF appears as rapid atrial depolarizations (AS). The upper rate limit and postventricular atrial refractory period of the pacemaker determine the rate at which the pacemaker stimulates the ventricle (VP). (B and C) Average heart rate over 24 hours recorded by memory circuits in a DDD pacemaker. The initial tracing (B) reveals sinus node incompetence, which developed during amiodarone therapy for paroxysmal atrial fibrillation. More normal rate variation resulted from activation of the rate-responsive feature of the generator (C), and the patient reported improved exercise tolerance.

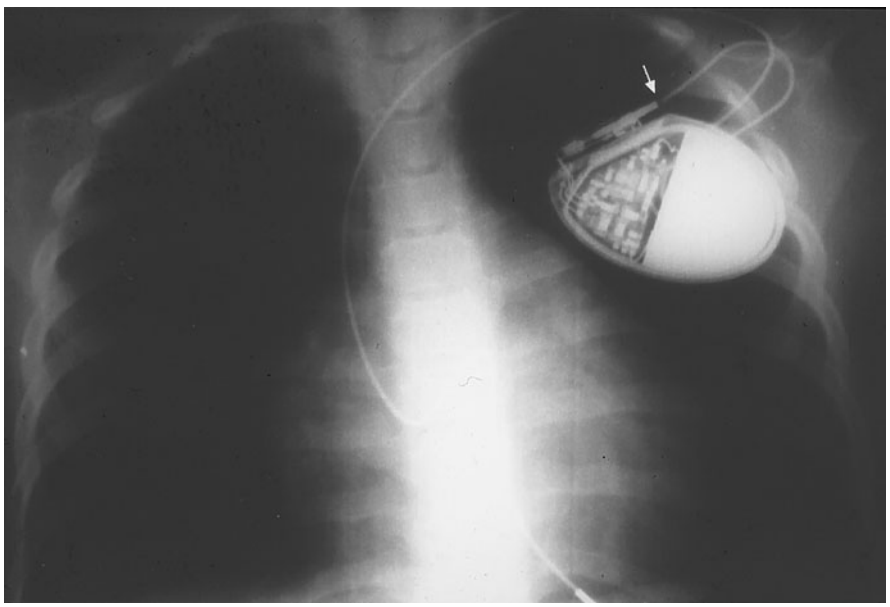


Figure 60-16. Unipolar lead fracture in a 3-year-old with complete heart block as revealed by x-ray. The patient underwent successful lead replacement.

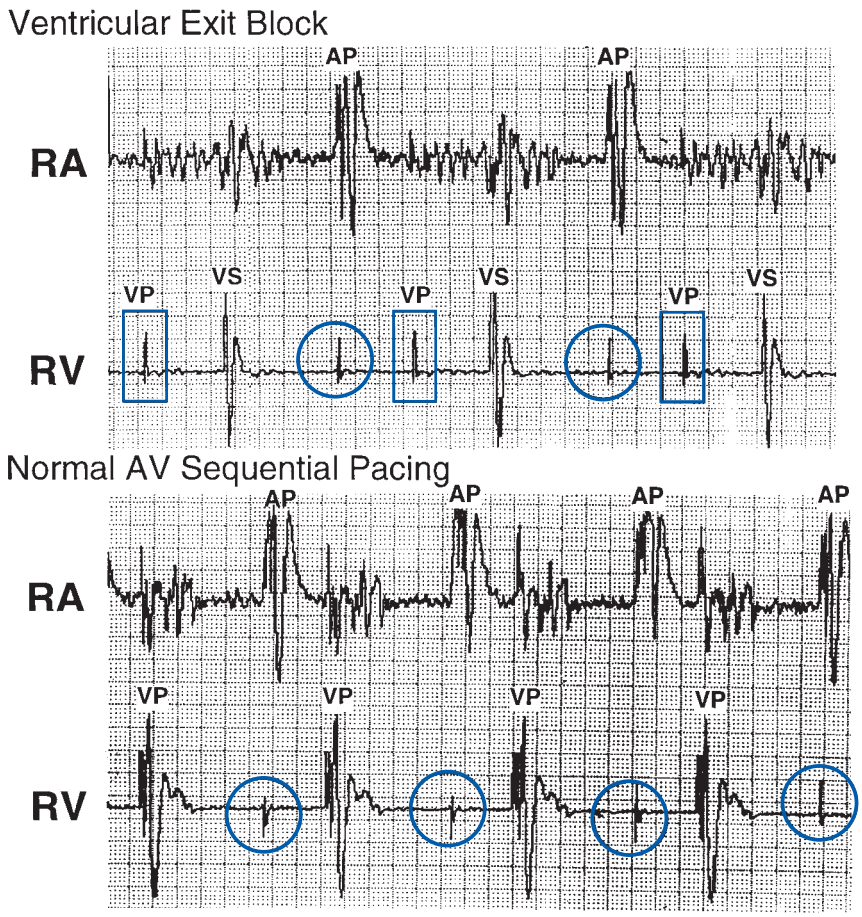


Figure 60-17. Right atrial (RA) and right ventricular (RV) unipolar electrograms in right ventricular exit block (above). Atrial (AP) and ventricular (VP) pacing are required for sinus arrest and marked first-degree atrioventricular block. Right ventricular capture is restored after RV pacing amplitude is programmed from 3.5 (above) to 5.4 V (below). Ventricular capture increases the effective heart rate, because the late, conducted ventricular electrograms (VS) in the upper tracing are sensed by the pacemaker and used to begin a new cardiac timing cycle. The circles indicate far-field sensing of the RA pacing artifact in the RV lead.

patients over 65, comparable figures were 6.1% and 4.4%, respectively.[58] Lead displacement, pneumothorax, and cardiac perforation were the most common complications. The reported incidence of late complications was 7.2%.[57] Reoperation in the authors' series was required in 4.0% of 480 patients with long-term follow-up (see Table 60-3).

Lead displacemkent

The incidence of endocardial lead displacement with early lead designs was more than 10%.[58] With tined and positive fixation leads this has fallen to the range of 2%.[8,45,46,57,58,66–68] The overall incidence of this complication was 1.5% for both atrial and ventricular leads in all locations in a recent review (see Table 60-3). Secure placement of pacemaker leads is a learned skill, and relevant technical issues have been described above. We have found that positive fixation leads can be applied in a variety of unusual locations with essentially no penalty in terms of lead displacement (Table 60-4).

Myocardial infarction

Pacemaker insertion may be indicated as an adjunct to medical therapy of angina in patients with inoperable coronary artery disease. However, increased heart rate can be detrimental if control of ischemia is marginal. Angina, myocardial infarction, or death can result from pacemaker-induced increases in heart rate of as few as 10 bpm.

Hemopneumothorax

Hemopneumothorax and pericardial tamponade can result from injury to the heart or arterial or venous system. Errors with the Seldinger technique can lead to such injuries. In patients over 65, pneumothorax has been related to subclavian puncture.[58] In our experience with pacemaker insertion in more than 1000 patients by cephalic cutdown, hemopneumothorax did not occur. In contrast, a recent review of 1088 consecutive implants by subclavian puncture revealed a 1.8% incidence of pneumothorax.[58]

Pacemaker syndrome

Loss of atrioventricular synchrony produces symptoms related to contraction of the atria against closed AV valves and reflex effects. The resulting constellation of symptoms is known as pacemaker syndrome.[69] These symptoms are quite variable, but severely affected patients may refuse pacemaker magnet testing. Symptoms are relieved immediately by conversion from VVI to dual-chamber pacing.

Lead entrapment

Entanglement of a pacemaker lead in the chordae tendineae can lead to firm entrapment. Options under these circumstances include further escalation of force, application of lead extraction techniques,[70,71] or an open procedure. Our experience with this involved three firmly entangled leads in 1000

Table 60–3.

Results of Pacemaker Implantation, Columbia-Presbyterian Medical Center 1984 to 1993*

Surgical mortality	1/616 (general anesthesia–related)
Mean follow-up	884 ± 675 (SD) days (n = 480 patients, 679 leads)
Morbidity	19 reoperations (4.0% of 480) 4 Infections (0.8%) 7 Lead displacements (1.5%) 4 Exit block (0.8%) 4 Undersensing (0.8%) 5 Suspected right ventricular perforations 2 Leads abandnoed (chordal entrapment) 41 Reprogrammed for dysfunction 0 Hemothorax 0 Pneumothorax 1 Procedure abandoned for thoracotomy (newborn)
Characteristics at generator replacement (n = 40, 75 ± 31 months after implant)	
Pacing threshold	1.3 ± 0.5 V 3.0 ± 1.3 mA
R-wave amplitude	8.9 ± 4.3 mV
Long-term DDD pacing	89% (1109 ± 34 days follow-up)
Causes of DDD failure	8.4% Atrial fibrillation 2.4% Lead dysfunction

**Models 479-01 and 435-02 unipolar, positive fixation leads, Intermedics, Inc., Bellaire, Tex.*
Source: Spotnitz HM, Mason DP, Carter YM: Unpublished observations.

Table 60–4.

Lead Stability in Unusual Locations, Columbia-Presbyterian Medical Center 1984 to 1993*

Location	n	Displaced
Coronary sinus (to left ventricle)	2	0
Atrial conduit	1	0
Right atrium of transplant	20	0
Lateral right atrium	27	1
Right ventricular outflow—single	22	0
Right ventricular outflow—paired (ICD recipients)	11(×2)	0
Infants—looped leads (<1 year old)	7	0
Children—looped leads	42	2
Total	132	3(2.3%)

**Models 479-01 and 435-02 unipolar, positive fixation leads, Intermedics, Inc., Bellaire, Tex. ICD = implantable cardioverter defibrillator.*
Source: Spotnitz HM, Mason DP, Carter YM: Unpublished observations.

lead implants. These leads were capped and abandoned rather than escalate the risk of the procedure. There were no untoward consequences of abandoning these leads. This experience taught us to avoid the anatomic center of the right ventricle when implanting positive fixation leads. This problem has not recurred in more than 750 subsequent pacemaker implants.

Infection and erosion

Pacemaker infection appears as frank sepsis, intermittent fever with vegetations or inflammation, and purulence or drainage at the pacemaker pocket. Established infection in implanted prosthetic devices can be suppressed but rarely eliminated by antibiotics. Antibiotic suppression may result in temporary resolution of signs of infection in a pacemaker or ICD pocket, but the problem usually recurs several months later.[69,70] Negative cultures from a pacemaker erosion may encourage the clinician to move the generator to a fresh, adjacent site, but the erosion usually recurs. Clinical resolution of recurrent device erosion in such individuals almost always requires removal of all hardware and insertion of a new device in a fresh site.[72,73] The incidence of erosions, infections, hematoma, and lead displacement early after pacemaker implantation is increased by operator inexperience.[68]

Pacemaker dysfunction

Mechanical defects in leads, lead displacement, or errors in connecting the lead and generator can cause pacemaker dysfunction. Most commonly, lead dysfunction represents scarring at the lead-myocardial interface, changes in myocardial properties due to tissue necrosis or drug effects, or a poor initial choice of lead position.

Generator dysfunction

Electrical component failures are rare. Three pacemaker or ICD generator failures have required urgent device replacement over the past 10 years at our center. New pacemaker and lead designs may contain flaws that do not become apparent for many years.[8,74]

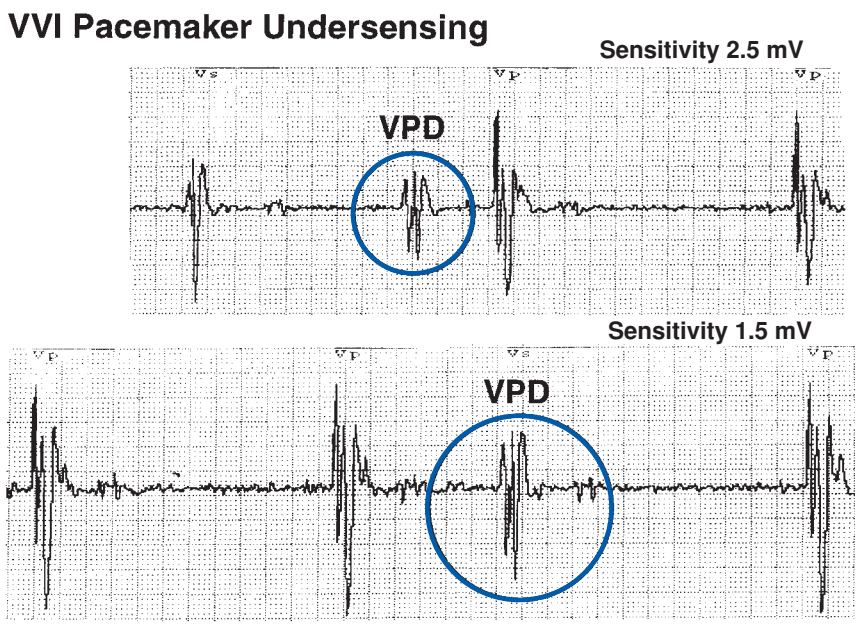


Figure 60-18. Undersensing of ventricular premature depolarizations (VPD) illustrated in the upper panel of electrograms obtained by telemetry from a VVI pacemaker. The amplitude of the electrograms increases, and sensing is corrected after reprogramming to increase sensitivity to P waves from 2.5 mV (above) to 1.5 mV (below).

Undersensing

This is failure to sense atrial or ventricular electrograms. The result is an atrial or ventricular pacing artifact that should have been inhibited by the preceding (unsensed) beat. In a dual-chamber pacemaker, undersensing may also cause failure to pace the ventricle after an atrial P wave. Undersensing can often be corrected by programming increased generator sensitivity, but this can also lead to oversensing. The latitude for reprogramming can be estimated by examining telemetered electrograms[61–64] (Figs. 60-18 and 60-19).

Oversensing

Inappropriate pacemaker inhibition or triggering in unipolar systems may result from detection of myopotentials (muscular activity). This is more common in unipolar systems and may be correctable by programming reduced pacemaker sensitivity. Oversensing in bipolar systems may indicate breakdown of lead insulation (see Fig. 60-4).

Crosstalk and far-field sensing

A deflection on the ventricular lead immediately after the atrial pacing artifact could be either premature ventricular contraction or far-field sensing of an atrial depolarization (see Fig. 60-14). Many pacemakers deal with this ambiguity by pacing the ventricle at a short (100-ms) atrioventricular delay. This short AV delay, known as "safety pacing," indicates that the pacemaker is detecting an ambiguous signal during the AV delay.[28]

Complexities of dual-chamber pacemaker programming involve blanking and refractory periods used to compensate for crosstalk or to prevent retrograde AV conduction from producing pacemaker-mediated tachycardia (see below). Crosstalk is ameliorated by bipolar lead systems.

Exit block

This is rising pacing threshold due to edema or scarring at the lead tip–myocardial interface. Pacing threshold com-

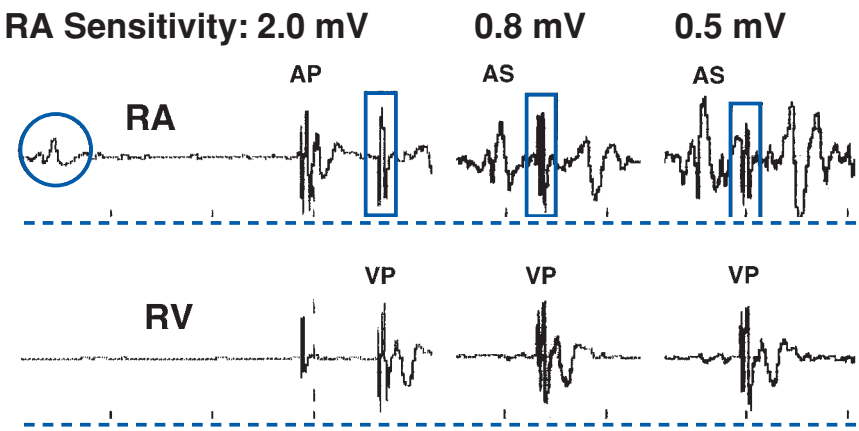


Figure 60-19. Right atrial (RA) and right ventricular (RV) electrograms telemetered from a DDD pacemaker during correction of atrial undersensing. The amplitude of the RA electrogram increases after atrial sensitivity is increased from 2.0 mV (left) to 0.8 (center) to 0.5 mV (right). The P-wave electrogram (circled) is not sensed at 2.0 mV, resulting in unnecessary atrial pacing (AP). Proper sensing is restored and the size of the electrogram increases (AS) as sensitivity is increased. VP indicates ventricular pacing. The rectangles in the RA tracing identify far-field sensing of the ventricular pacing artifact.

monly increases over 7 to 14 days after lead insertion and stabilizes at about 6 weeks. This phenomenon, which is related to inflammatory changes at the lead tip, is ameliorated by steroid-eluting leads.[8,75] Exit block may be corrected by programming increased amplitude or pulse width, but this shortens battery life. In unipolar systems, pacing of the chest wall and/or diaphragm may result from high generator output.

Lead fracture

Lead fracture, whether due to insulation or conductor breaks, is often demonstrable by chest x-ray (see Fig. 60-16). Lead impedance less than 300 ohms suggests an insulation break, while high lead impedance, more than 1000 ohms, suggests conductor problems, a loose set screw, or improperly connected lead. High impedance also can indicate incomplete extension of a loose set screw, or a bad generator connection. Office examination may detect impending lead fracture as electrical noise on telemetered electrograms when the patient hyperventilates, coughs, bends, or swings the arms. Oversensing related to body movement usually mandates lead replacement or repair.

At reoperation, dysfunctional leads can be capped or removed. Removal of chronically implanted leads is potentially hazardous and results in endothelial venous damage even when successful. Lead removal probably should be deferred unless mandated by infection or mechanical problems. The probability of lead fracture has been promoted historically by design errors, bipolar construction, certain forms of polyurethane insulation, and epicardial insertion.[64] Technical factors in fracture include tight ligatures applied to the lead without an anchoring sleeve, kinking, lead angulation, vigorous exercise programs, and subclavian crush.[8,44,51]

Subclavian crush

This refers to entrapment of a pacemaker lead between the clavicle and first rib in the costoclavicular ligament. The lead is believed to be subjected to unusual stress during body movement, resulting in early lead failure. This problem pertains to leads implanted by percutaneous puncture of the subclavian vein and may be avoided with cephalic cutdown. Techniques to minimize this problem have been described (see Fig. 60-7).[8,44,51]

Pacemaker-mediated tachycardia

DDD pacemakers can inadvertently cause a reentrant arrhythmia, pacemaker-mediated tachycardia.[64] This includes retrograde conduction through the atrioventricular node, possibly triggered by a premature ventricular depolarization. If the pacemaker senses the resulting atrial depolarization and paces the ventricle, a repetitive cycle is set up that could continue indefinitely at the upper rate limit of the pacemaker. This problem can be minimized by avoiding high upper rate limits in patients with retrograde conduction and by adjusting the postventricular atrial refractory period so that the pacemaker will ignore atrial depolarizations for 300 to 350 ms after the QRS complex. Current pacemaker circuits also have built-in safeguards that attempt to break reentrant arrhythmias by periodic interruption of continuous high-rate pacing. In addition, pacemaker interrogation provides notification of high-rate pacing suspicious of pacemaker-mediated tachycardia.

Innovations and Special Problems

Pacemaker lead extraction

Indications for lead extraction include chronic infection or life-threatening mechanical defects.[76–78] Some recommend that any dysfunctional pacemaker lead should be removed. Until recently, the techniques for extraction of a transvenous lead were external traction or thoracotomy/cardiotomy employing inflow occlusion or cardiopulmonary bypass. Chronically implanted leads can be densely fibrosed to the right ventricular myocardium, vena cava, or innominate and subclavian veins.

Lead extraction has been advanced by techniques described by Byrd.[70,71] A locking stylet is passed inside the central channel to the tip of the lead where it uncoils, allowing traction to be applied to the lead tip. Telescopic Teflon, plastic, or metal sheaths slightly larger than the pacing lead are passed over the lead to mobilize it. When the long sheath reaches the lead tip, countertraction is applied to the myocardium with the sheath while traction is applied to the lead tip with the locking stylet (Fig. 60-20). Success with this technique has been >90%, with a 3% chance of serious morbidity or death. Laser-based systems have also been used.[79] Technical details have been described.[70,71] Extraction of leads implanted for more than 10 years is difficult and tedious.

Accufix lead

An unusual form of lead fracture affected the Telectronics Accufix lead, a bipolar, Bisping type atrial screw-in lead.[76–78] A J-shape was integrated into this lead to direct the tip to the atrial appendage. A curved retention wire was welded to the indifferent ring electrode near the tip and then was bonded to the lead body with polyurethane. This retention wire proved susceptible to fracture and extrusion (Fig. 60-21). Deaths were reported from cardiac tamponade, possibly related to puncture of the atrium or aorta by protruding wire. More than 45,000 of these leads were implanted, and many were surgically extracted. Because some morbidity and mortality occurred during extraction of this lead, the manufacturer recommended conservative management.

Atrial fibrillation and mode switching

Many DDD pacemaker recipients suffer from both sinus bradycardia and intermittent, paroxysmal atrial fibrillation (sick sinus syndrome). A standard DDD pacemaker responds to atrial fibrillation by pacing at the upper rate limit. While DDD pacing was initially felt to be contraindicated in atrial fibrillation, the current view is that atrial

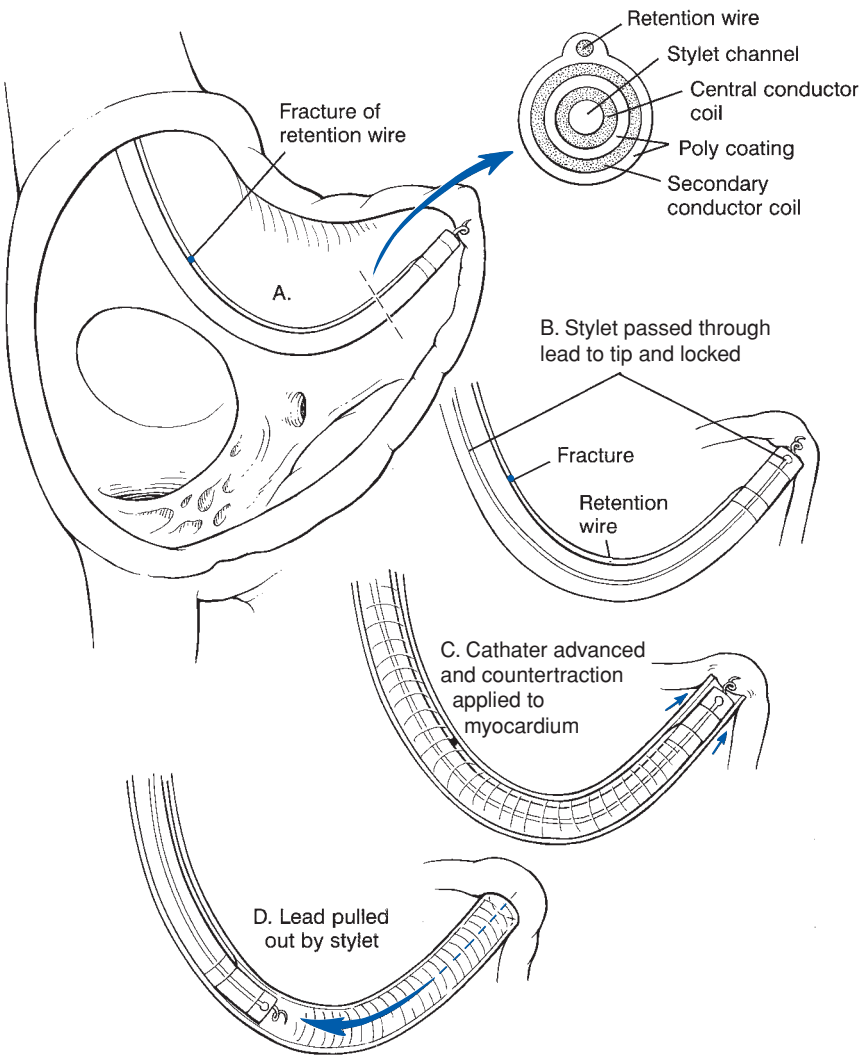


Figure 60-20. Byrd method of lead extraction using Cook catheters. Drawings illustrate successful removal of a Telectronics Accufix J-lead with a fractured retention wire.

pacing may decrease the frequency of paroxysmal atrial fibrillation. Mode switching[80] achieves a useful compromise. Mode switching can be triggered by a programmed upper rate limit or by comparing the observed atrial rate to predictions based on the patient's activity level. If an atrial tachyarrhythmia is detected, the pacemaker switches to VVIR pacing until the atrial rate again appears appropriate. Successful mode switching requires bipolar leads and high sensitivity in patients with low-amplitude atrial fibrillation. Management of atrial fibrillation in the elderly may involve fewer medications and interventions than in younger patients.[65]

Database support

Pacemaker- and ICD-related data include information for billing, for generating operative notes, serial numbers of leads and generators, records of programming, and management of follow-up visits and monitoring and patient education. A large amount of data should be available at a moment's notice in the event of a query related to device malfunction. For this purpose, a multi-user relational data-

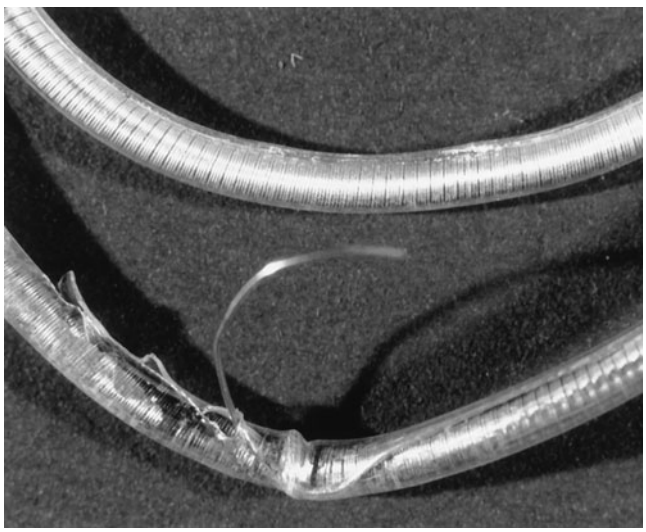


Figure 60-21. Telectronics Accufix atrial J-leads removed for retention wire fracture. The region of the fracture appears relatively benign in the upper lead.The lower lead illustrates retention wire extrusion after percutaneous extraction. Mechanical characteristics of the extruded wire resemble those of a safety pin.

base, allowing simultaneous access by multiple users, is particularly valuable. A variety of commercial and home-grown software packages are helpful for this purpose.

General surgery and pacemakers

General surgery in a pacemaker-dependent patient presents a serious problem,[81] especially for major surgery that requires unipolar cautery. Preparations should include (1) identify the manufacturer and model of the pacemaker, using the pacemaker ID card, monitoring service, medical record, or x-ray appearance;[81–84] (2) determine magnet mode (see below) and any peculiarities related to impedance sensing monitors; (3) obtain a programmer for the pacemaker; (4) interrogate the pacemaker to determine operating mode, programmed parameters, polarity, battery life, and lead characteristics; (5) determine pacemaker dependence[81] (if the electrocardiogram reveals 100% pacing, programmed reduction of the pacing rate or output with ECG monitoring should be used preoperatively to determine whether the patient has an escape rhythm; pacemaker dependence can increase during anesthesia, because of withdrawal of sympathetic stimulation); (6) implement a back-up plan (transthoracic pacing or chronotropic agents) if the patient is pacemaker-dependent; (7) program the pacemaker to VOO, DOO, or VVT mode intraoperatively and program rate response off to prevent inhibition[81] or pacemaker acceleration[82] by electromagnetic interference (EMI); (8) identify a physician responsible for dealing with any intraoperative pacemaker problem; (9) interrogate the pacemaker postoperatively to confirm thresholds and function and restore programming to appropriate values.

Electrocautery

Manufacturers recommend that electrocautery should not be employed in pacemaker patients because of the danger of EMI or pacemaker damage. If electrocautery must be used, unipolar cautery is far more likely to cause EMI than bipolar cautery. Unipolar pacemakers are also more susceptible to EMI than bipolar pacemakers. At a minimum, EMI from the electrocautery may be misinterpreted by pacemaker sensing circuits as a rapid heart rate, resulting in pacemaker inhibition. This inhibition reverses when the EMI stops. Cautery can also cause pacemaker reprogramming, acceleration of impedance-sensing pacemakers to the upper rate limit,[82] or reversion of the pacemaker to a "back-up mode" or "magnet mode" (see below). Finally, electrocautery can cause complete and permanent loss of pacing, although this is rare.[81]

One approach to avoiding pacemaker inhibition by EMI is to program sensing off and to increase the rate to minimize competition with the intrinsic heart rate. However, competition with spontaneous beats can occur, creating a risk of induction of atrial fibrillation or ventricular tachycardia in susceptible patients. In view of this, the pacemaker should be returned to an appropriate sensing mode as soon as possible after the completion of surgery.

Magnet mode

A permanent magnet placed over a pacemaker closes a magnetic reed switch and converts the pacemaker to "magnet mode." Magnet mode is not the same for all pacemakers. In some, a magnet initiates VOO mode, making the pacemaker insensitive to EMI. Other pacemakers will convert to VOO for a few beats and then revert to the underlying program. Most current generators perform a threshold margin test under the influence of a magnet; this investigates the adequacy of the pacing margin by decreasing the pulse width in a predictable pattern.

Steroid-eluting leads

A promising approach to the problem of fibrosis at the lead-myocardial interface involves incorporation of a pellet of dexamethasone at the lead tip. This improves early pacing thresholds compared to conventional leads.[75] The long-term (>1 year) advantage of steroid-eluting leads remains to be defined.

Adults with congenital heart disease

Congenital heart disease presents special challenges. A persistent left superior vena cava draining to the coronary sinus favors a right-sided approach, although the left side can be used with special techniques.[54,55] Preoperative echo Doppler or angiographic studies can define caval and coronary sinus anatomy. Persistent left superior vena cava may displace the subclavian vein, increasing the hazards of percutaneous subclavian vein puncture. High priority should be placed on the cephalic cutdown approach in patients with congenital heart disease.[54] Situs inversus and corrected transposition can be particularly confusing in the operating room if undetected prior to pacemaker insertion.

Positive fixation leads are particularly useful for atrial pacing after a Mustard operation or a caval-pulmonary anastomosis and for pacing the smooth-walled "right" ventricle in corrected transposition of the great arteries.[54] A coronary sinus lead can provide ventricular pacing in some patients after Fontan surgery (Fig. 60-22). We have also found ventricular pacing via the coronary sinus to be advantageous in patients with a mechanical tricuspid valve.

Pacing in infants and children

Transvenous pacing can be facilitated in this population by leaving an intracardiac loop to allow for growth (see Fig. 60-5). Unipolar, positive fixation leads are ideal for this purpose[54,55] but other approaches have been described.[85] We prefer a cephalic vein cutdown, with optical magnification if needed. A flexible guidewire is passed centrally and a 7F introducer is used to introduce the lead. A longitudinal split of the cephalic vein facilitates advancing the introducer (see Fig. 60-9). In very small infants, the external jugular vein at the thoracic inlet may be useful. Others prefer a subclavian vein puncture guided by a catheter introduced via the femoral vein.[85] Thoracotomy provides a third option.[42] Infants under

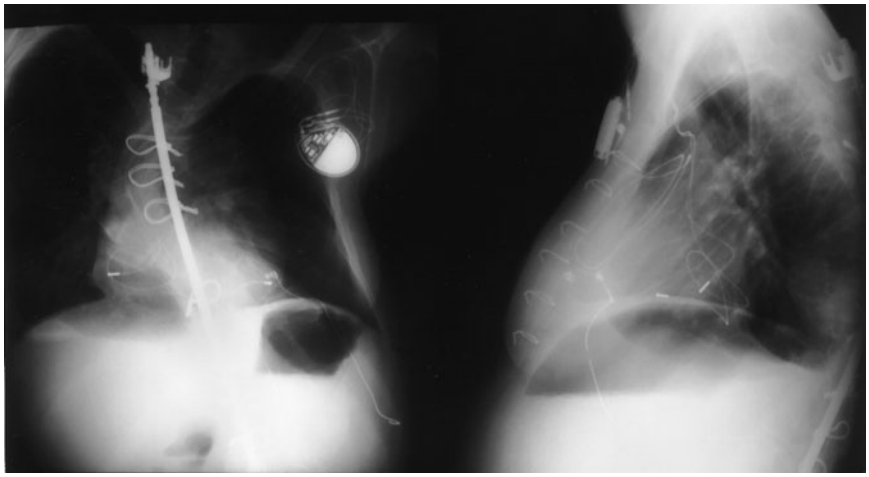


Figure 60-22. X-ray of a dual-chamber pacing system illustrates ventricular pacing via the coronary sinus after Fontan surgery. This system functioned successfully for nearly 5 years and was replaced at the time of Fontan revision. An epicardial pacing wire, which failed due to exit block, is also illustrated.

6 months of age are suboptimal candidates for transvenous pacing because of limited long-term lead utility. Generators should be placed beneath the pectoralis in children under 6 years old if possible, to reduce infection risk.

Dementia

Dementia is problematic for surgery under local anesthesia. Sedation can make dementia worse and exaggerates bradycardia. The patient's arms should be secured to prevent groping for the surgical wound. Postoperative confusion with thrashing can cause pacemaker lead displacement. A family member at the bedside may palliate this problem. Every effort should be made to anticipate and avoid such problems.

Atrioventricular node ablation

AV node ablation controls ventricular rate in refractory atrial fibrillation but leads to permanent heart block. Historically, the AV node was ablated first. Temporary pacing supported heart rate until a permanent pacemaker was inserted. Ventricular escape rhythm was often poor in these patients, favoring positive fixation leads, overnight observation on telemetry, and high pacemaker output. Alternatively, the pacemaker can be inserted and allowed to heal prior to ablation, reducing the risk of lead displacement and avoiding the need for overnight hospitalization.

Transplant recipients

The most common indication for pacemaker insertion in cardiac transplant recipients is sinus bradycardia or sinus arrest, which can be managed successfully by AAIR pacing.[38,86] In our experience, most outgrow the need for pacing within 2 years.[38,86] The surface ECG can be quite misleading, with the two sources of P waves—the atria of the donor and the recipient—suggesting heart block. Need for ventricular pacing can be evaluated by pacing the atrium at a rate of 150 bpm. If a 1:1 response of the ventricle is observed, the AV node is essentially normal. The location of the atrial appendage is more medial than usual in these patients, and positive fixation leads are preferable (Fig. 60-23).

Implantable cardioverter defibrillator recipients

Before integrated devices were available, transvenous pacing in ICD recipients had stringent requirements for lead performance. Crosstalk between devices could result in inappropriate ICD shocks or failure of the ICD to detect and correct lethal ventricular arrhythmias. While independent implantation of pacemakers and ICDs has been described,[87] ICDs with integrated DDD pacemakers render this technique superfluous.

Long QT syndrome

This is a genetically determined repolarization abnormality that is associated with a high incidence of sudden death.

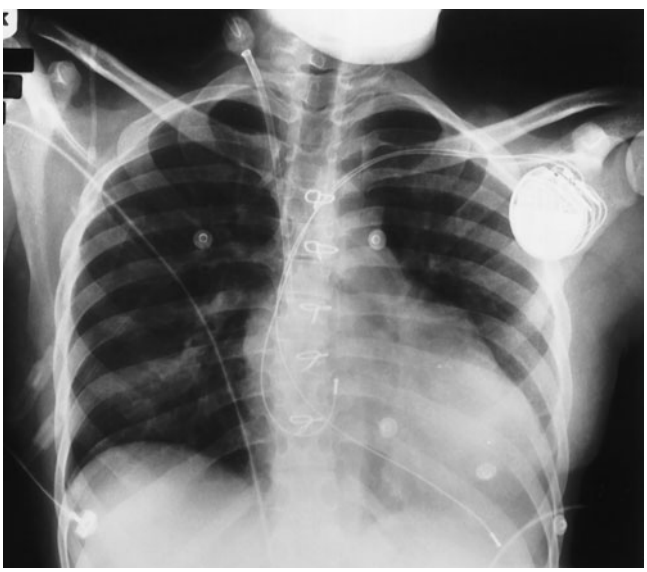
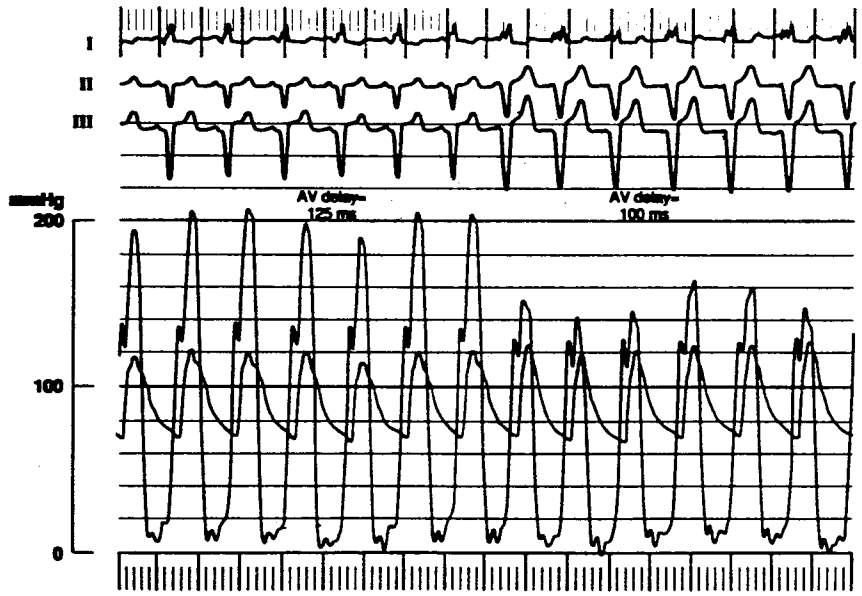


Figure 60-23. DDDR pacing system in a cardiac allograft recipient illustrates the shift of the atrial appendage toward the midline that is characteristic of these patients.



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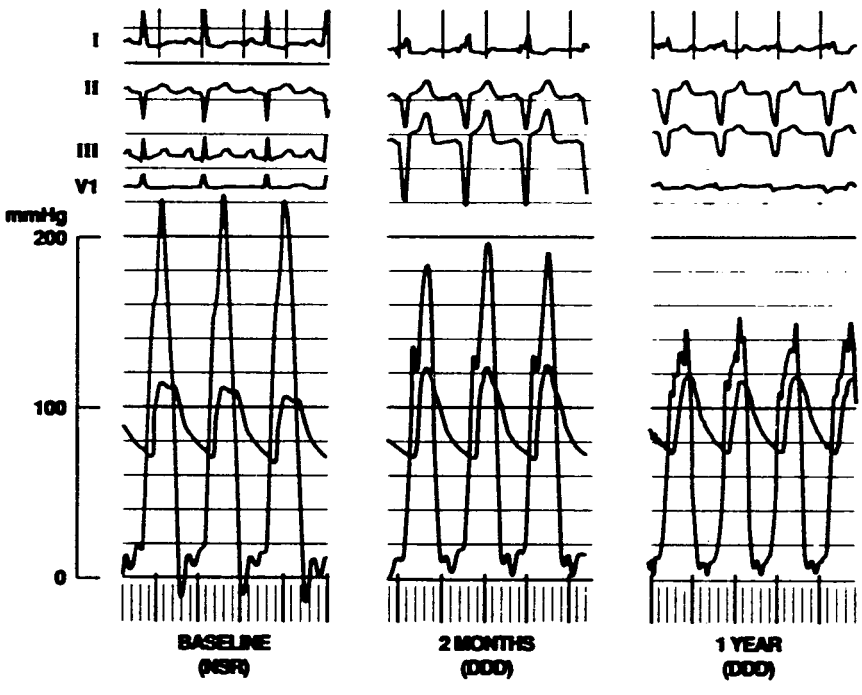

B

Figure 60-24. (A) Effect of reducing AV delay in DDD pacing from 125 ms (left tracings) to 100 ms (right tracings) on left ventricular outflow tract gradient in idiopathic hypertrophic subaortic stenosis. (B) Effect of time and DDD pacing on left ventricular outflow tract gradient in idiopathic hypertrophic subaortic stenosis. (*Reproduced with permission from Fananapazir et al.*[22])

Recommended therapy includes stellate ganglionectomy and/or adrenergic blockade.[88,89] In severe cases, the pacing threshold may be too high for ventricular pacing, and atrial pacing may be preferable.[88] ICD therapy is increasingly common for this condition.[85]

Idiopathic hypertrophic subaortic stenosis

Idiopathic hypertrophic subaortic stenosis or obstructive cardiomyopathy can cause left ventricular outflow obstruction with angina and/or syncope. Permanent right ventricular pacing at short atrioventricular intervals pre-excites the right ventricle and decreases outflow gradients in some patients[22–24] (Fig. 60-24). A reduction in the incidence of sudden death has also been claimed with this approach in patients with a history of syncope, but ICD therapy has been increasing.[88]

Biventricular pacing

End-stage cardiomyopathy and heart failure tend to progress with advancing age. Advanced therapies like cardiac transplantation or left ventricular assist devices are appropriate for some patients, but biventricular pacing is widely

applicable at a lower cost. Clinical trials demonstrate modest subjective and objective improvement in dilated cardiomyopathy with left ventricular ejection fraction <36% and QRS intervals >120 ms.[26,27,90] Marked clinical improvement is seen in some patients (see Fig. 60-13).

Atrial and ventricular tachyarrhythmias

Overdrive pacing techniques can be effective for ventricular tachyarrhythmia, Wolff-Parkinson-White syndrome, or atrial flutter.[88] Implantable defibrillators are under development for atrial fibrillation. Anti-tachycardia ventricular pacing for ventricular tachyarrhythmia has been integrated into ICD therapy.

Environmental Issues

Electromagnetic interference

EMI can be caused by electrocautery, cellular telephones, magnetic resonance imagers,[91] microwaves, diathermy, arc welders, powerful radar or radio transmitters, and theft detectors in retail stores. Any defective, sparking electrical appliance or motor, electric razor, lawn mower, or electric light can be problematic. The importance of EMI is related to pacemaker dependence. Most pacemaker recipients are not pacemaker-dependent, so a brief period of pacemaker dysfunction will not result in loss of consciousness. Patients who are pacemaker-dependent and work in electrically noisy environments may benefit from the added protection of bipolar pacing systems. Cellular telephones should be separated by several inches from pacemaker generators, preferably on the contralateral side.[92]

Mechanical interference

Lithotripsy, trauma, dental equipment, and even bumpy roads can affect pacemakers. Automobile accidents have caused pacemaker damage and disruption of pacemaker wounds.[93] Vibration in subways or automobiles causes inappropriately high heart rates in rate-responsive units. Patients with poor escape rhythms should be discouraged from exposure to deceleration injury, as in traditional contact sports as well as basketball, handball, downhill skiing, surfing, diving, mountain climbing, and gymnastics. Participants in these activities should realize that abrupt pacemaker failure could occur in the event of lead displacement related to trauma.

Radioactivity

The integrated circuits of current pacemakers can be damaged by radiotherapy. If the pacemaker cannot be adequately shielded from the radiation field, it may be necessary to remove and replace it or move the pacing system to a remote site.

Quality of life

In contrast to ICD recipients, quality of life is not a major concern for most pacemaker recipients. While many clinics require periodic visits, the model of transtelephonic monitoring with office visits only for problems is highly acceptable to most patients. This latter system involves a preoperative visit, a 10-day postoperative visit, a 1-year visit to adjust output, and no additional visits unless functional problems or impending battery depletion are detected. Some recipients are never happy with their pacemakers because of body image problems, vague symptoms, or concern that life will be artificially prolonged. The value of generator replacement in patients with advanced debilitation has been a subject of ethical concerns.[94]

IMPLANTABLE CARDIAC DEFIBRILLATORS

Background

More than 400,000 deaths in the United States each year are classified as sudden and likely to be caused by arrhythmias.[95] Michel Mirowski conceptualized the implantable defibrillator in the late 1960s. Overcoming numerous theoretical, engineering, and financial obstacles, he participated in a successful clinical trial of his device in the early 1980s.[96] Today's implantable cardioverter defibrillator (ICD) reflects dramatic and expensive growth in technology. The efficacy of the ICD in prevention of sudden death is well established. Sophisticated clinical trials, experience, and the passage of time have emphasized the survival advantages of the ICD over other modalities, including antiarrhythmic drugs and subendocardial resection. The ICD is associated with the lowest sudden death mortality (1 to 2% per year) of any known form of therapy.[97–100] The ICD is expensive ($12,000 to $20,000 for the generator and $2000 to $8000 for the lead system), with discomfort and lifestyle issues. Prophylactic ICD insertion is increasing.

Clinical trials including AVID, MUSST, MADIT, SCDHFT, and COMPANION demonstrated benefits of ICD therapy.[101–112] Only the CABG Patch Trial,[113] which compared coronary artery bypass graft (CABG) to CABG+ICD, and DINAMIT,[114] which studied ICD implantation early after myocardial infarction, failed to demonstrate advantages of ICD insertion. Trials now focus on prophylactic ICD therapy, combining ICDs with biventricular pacing, cost effectiveness, and projected costs. Accumulating evidence supports prophylactic use of ICDs and biventricular pacing in patients with ejection fractions <35%, either in association with coronary disease or in association with dilated cardiomyopathy. The appropriate role for prophylactic ICD-biventricular pacing is still evolving. The Heart Rhythm Society will not certify surgeons to implant these devices unless they have passed its certification exam. Patients with prophylactic device insertion are being followed in a national registry. Information about this can be found at http://www.accncdr.com/webncdr/ICD.

ICD battery life has increased beyond 5 years. Today's devices are highly programmable, and their size and weight are similar to those of pacemakers of the 1970s. Lead systems

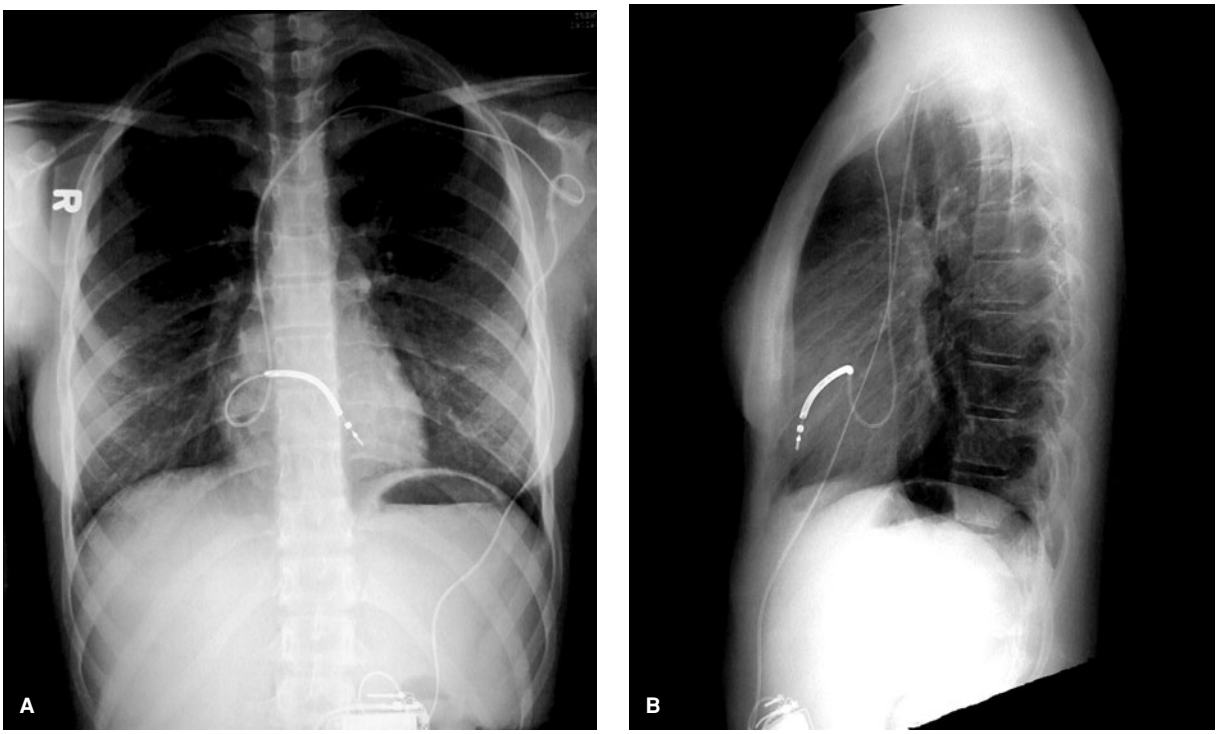

Figure 60-25. (A) ICD implant in 13-year-old female with long QT syndrome. X-rays reveal an intracardiac loop to allow for growth and a strain relief loop in the left shoulder. A single-coil, screw-in lead was used to permit an intracardiac loop, but improved leads now allow twin-coil leads to be used. This implant utilized cosmetic positioning of the generator in the posterior rectus sheath. (B) Lateral x-ray of same patient.

have evolved from epicardial patches requiring thoracotomy to endocardial systems[97–100] with defibrillation thresholds (DFTs) reduced by biphasic shocks[115] and "hot can" technology.[116] Pectoral implantation is the current standard, and many devices are placed beneath the pectoralis major. Abdominal implantation is now reserved for special cases (Figs. 60-25 and 60-26). Electrograms stored by current devices can be downloaded to expedite decisions about antiarrhythmics, to prevent inappropriate shocks, and to detect oversensing.[117] VVI, DDD, and antitachycardia pacing have been integrated into ICDs.[118] Accelerated development has pressured the Food and Drug Administration to rapidly approve new technology. When the U.S. Health Care Finance Administration refused in 1995 to allow Medicare reimbursement to support device development, ICD development shifted overseas.

Physiology

Ventricular tachycardia (VT) associated with ischemic cardiomyopathy is commonly a reentrant arrhythmia[119] that may be prevented by drugs, catheter ablation, or surgical maneuvers that alter the timing and electrical attributes of the reentrant circuit. Myocardial infarction creates areas of scarring and slow conduction needed for reentry. Other forms of VT and ventricular fibrillation (VF) involve aberrancies of automaticity related to acute myocardial ischemia, increased ventricular wall stress, and myopathic cellular injury. Some class I antiarrhythmics have been shown to increase postinfarction mortality,[120] possibly due to proarrhythmic effects.

Indications

A straightforward ICD candidate has suffered a documented VT or VF in the absence of acute myocardial infarction and has been proven unsuitable for antiarrhythmic drug or surgical therapy, based on programmed electrical stimulation studies in the EP laboratory. However, many patients who suffer cardiac arrest do not have inducible VT at EP study, and many patients with a history of syncope and presyncope have inducible VT but no history of a clinical arrhythmia. Many antiarrhythmics have negative inotropic and proarrhythmic effects. Serial EP studies of drug efficacy have been discredited in clinical trials.[115] In mid-1996 the Food and Drug Administration approved an indication for prophylactic ICD insertion based on early termination of the MADIT Trial.[106] If EP studies demonstrate inducible VT in patients with nonsustained VT and a history of myocardial infarction, an ICD is indicated. MADIT II results support ICD insertion in all patients with a history of myocardial infarction and left ventricular ejection fraction $<30\%$.

Device Description

ICDs employ two lead systems (Fig. 60-27)—one for ventricular pacing/rate sensing and the other to deliver the defibrillation current. These systems are usually bipolar, but a unipolar

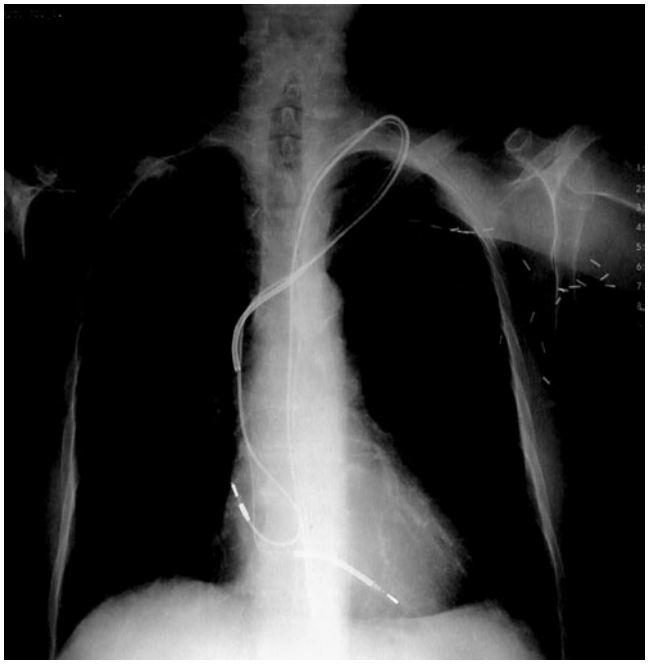

Figure 60-26. ICD/DDD pacemaker implant in a female with ventricular tachycardia and previous bilateral radical mastectomies. Venous access was obtained via the external jugular vein. Positive fixation leads were tunneled vertically in the midline, which was the only location on the chest wall with adequate subcutaneous tissue. The generator was placed subcutaneously in the abdomen. The cosmetic result was quite acceptable to the patient.

ventricular lead paired with an "active can" delivers the defibrillation current in some designs. Algorithms intended to distinguish supraventricular arrhythmias from VT have fallen into disfavor, and rate alone is currently used to determine when a patient requires treatment. As many as 30% of ICD shocks are for sinus tachycardia or other supraventricular tachyarrhythmias.[97,121] A bipolar atrial lead can be added for atrial pacing or differentiation of supraventricular arrhythmias from VT. Subcutaneous patch leads and arrays are available for patients with high defibrillation thresholds (DFTs). Leads come in standard lengths for pectoral implants and long lengths for abdominal implants. Positive fixation leads are available and preferred.

The ICD contains a high-energy battery and a capacitor to step up the output voltage to 600 to 800 V at 35 to 40 J. Biphasic (positive and negative phases) shocks reduce DFTs. The device includes integrated circuits and a telemetry antenna. A broad range of programmable diagnostic and therapeutic functions are supported.

Surgical Procedure

Patient preparation

Most potential ICD recipients would be at high mortality/morbidity risk for any surgery. Therapy of ischemia, heart failure, and systemic illnesses should be optimized before ICD implantation. The overall mortality of ICD implantation in our program has been very low since we began in 1983. We find inadequate control of ischemia in coronary artery disease to be more lethal than advanced cardiomyopathy. When ischemia is severe, a CABG, percutaneous transluminal coronary angioplasty, intra-aortic balloon pump, or deferral of DFT measurement should be considered in place of standard ICD insertion and testing.

Surgical approach

The epicardial approach[122,123] is now rarely used (i.e., for ICD implantation during cardiac surgery). This has been discouraged since the CABG Patch Trial demonstrated that infectious complications were more common in ICD recipients than in control patients.[116] Extrapericardial ICD patches cause less fibrotic reaction, less impairment of diastolic properties,[124,125] and less potential for graft impingement than intrapericardial leads. Biphasic waveforms, improved leads, high-output "hot can" generators, and ancillary subcutaneous patches and arrays contribute to a high rate of success for the endocardial approach.

Manufacturer's representatives

The complexity of current devices has legitimized the presence of manufacturer's representatives with electrophysiologists during ICD implants. This increases influence of the manufacturer on the selection of devices and techniques and warrants oversight.

Technique

We prefer local anesthesia and unipolar cautery for ICD insertion. Positioning and draping is similar to that for pacemaker insertion, with the addition of R2 electrodes over the right breast and beneath the left scapula. R2 electrodes should not be placed directly over the site of a possible subcutaneous ICD patch or array in the lateral axilla; this can result in serious equipment damage from arcing if external defibrillation is necessary.

The most distressing part of ICD insertion for the patient is the induction and reversal of VF for DFT measurement. This can be managed with deep sedation for a small number of DFTs. When multiple shocks are required, endotracheal intubation gives better control. Intravenous vancomycin and gentamicin are used for perioperative antibiotic prophylaxis in our center.

We prefer a cephalic vein cutdown via a 6-cm incision over the deltopectoral groove. If the vein is small, a guidewire is used to position a 7 or 9F introducer. Enlargement of the cephalic venotomy may be helpful if the vein is too small for the introducer (see Fig. 60-9). The guidewire can be left in place if a multiple-lead system is to be employed. Introducer kinking can lead to difficulty passing rough-surfaced ICD leads centrally. This is awkward, and high central pressures can lead to bleeding until the introducer is removed. Introducer kinking is avoided by aligning the introducer with the course of the cephalic vein before removing the obturator.

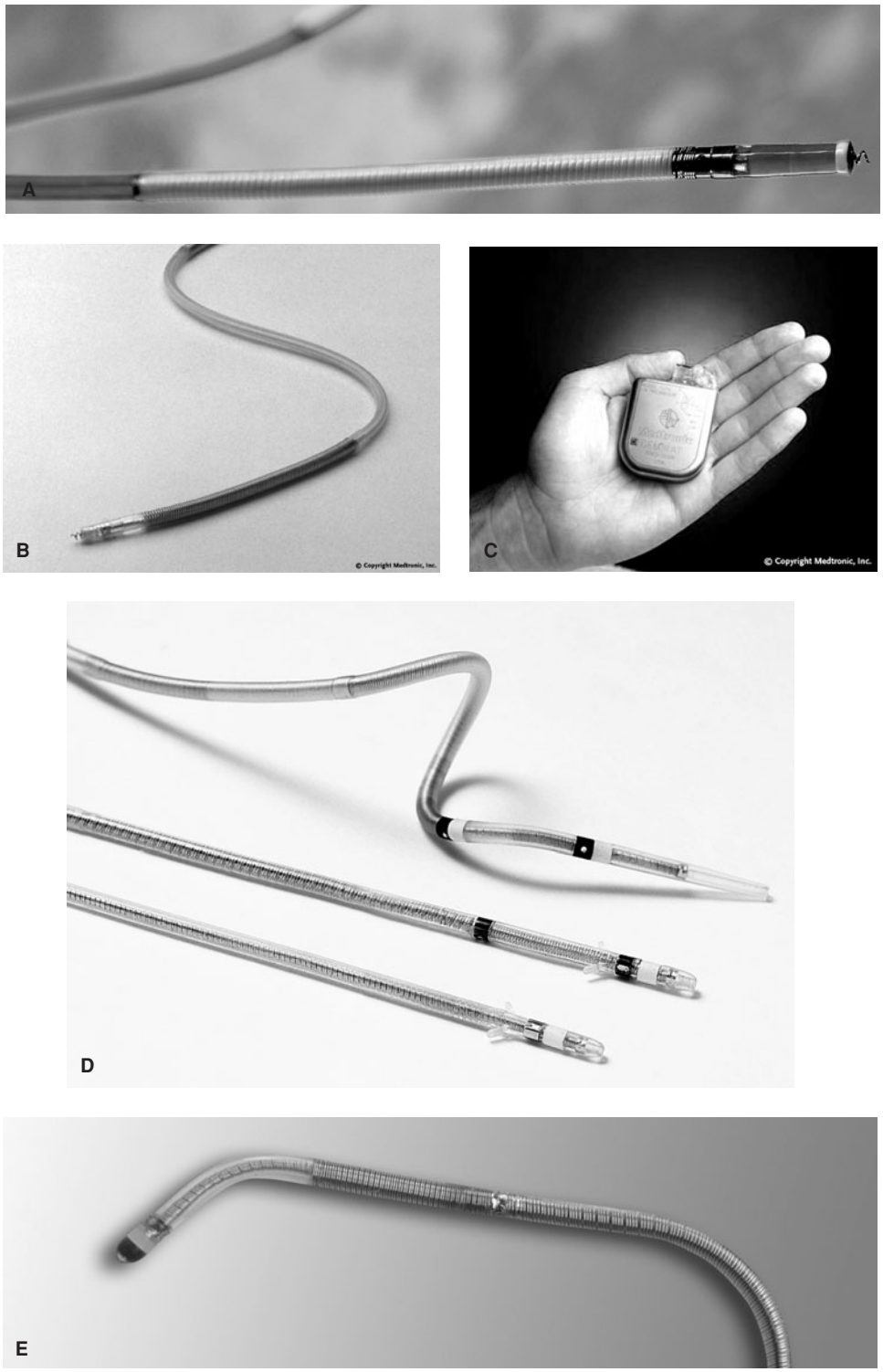

Figure 60-27. (A) Recent 9F ICD lead with Gore-Tex–coated shocking coils. (B) Recent 7F ICD lead with retractable screw. (C) Recent ICD/pacemaker . (D) Recent over-the-wire leads for coronary sinus pacing. (E) Recent over-the-wire lead for coronary sinus pacing. (*A and D: Courtesy Guidant Corp., Indianapolis, Ind; B, C, and E: Courtesy of Medtronic, Inc., Minneapolis, Minn.*)

As the lead is advanced to the ventricle, VT or VF may be triggered. This is not disruptive if an external defibrillator is available, connected to disposable R2 electrodes and precharged by a capable OR nurse. It is important to advance the ventricular lead as far as possible to the apex and to find a secure location. We prefer positive fixation ICD leads for both the right atrium and right ventricle. During measurement of DFTs, fluoroscopy should be used to check for lead displacement, particularly if external defibrillation is necessary. An intravenous infusion of norepinephrine is used when necessary to maintain systolic blood pressure. Transesophageal echocardiography is useful for monitoring patients at high risk of electromechanical dissociation during DFTs. We do not use Swan-Ganz catheters for monitoring, because their removal can lead to ICD lead dislodgment.

Locating ICDs in the left upper quadrant of the abdomen is now uncommon and is reserved primarily for cosmetic insertions, which can also include placing the generator in the posterior rectus sheath (see Fig. 60-25). With general anesthesia or sedation and local anesthesia, a tunneler is passed from the abdomen to the subclavian incision. Caution should be exercised with the tunneler; it must pass anterior to the costal margin. The lead is looped in the shoulder and firmly secured to minimize the possibility that a tug on the abdominal portion of the lead would displace the lead (see Fig. 60-25).

Defibrillation threshold

The DFT is critical to ICD insertion and the point of maximum risk. VF is generally induced twice and reversed by the ICD. The DFT should be at least 10 J less than the maximum output of the ICD. If DFTs are too high with optimized endocardial leads, an axillary subcutaneous patch or array helps distribute the defibrillation current over the lateral left ventricle. High-output generators and reversal of shock polarity may also be helpful. DFT measurement can, rarely, depress left ventricular function[106–108,126,127] and result in a low-output state. The mortality of ICD insertion with present techniques is on the order of 1%.[128] Complications include myocardial infarction, heart failure, lead displacement, infection, and venous occlusion.

Refractory ventricular fibrillation

A left-sided pneumothorax from a ruptured bleb, or technical error during subclavian puncture or subcutaneous array insertion raises the DFT, resulting in refractory VF. The differential diagnosis of refractory VF also includes myocardial ischemia, electromechanical dissociation, and poor anatomic localization of ICD shocks. Refractory VF rarely may require open cardiac massage or cardiopulmonary bypass until a solution can be found.

Postoperative care

Telemetry is indicated during an overnight stay after ICD insertion. Pacing and sensing properties of the lead should be checked to confirm lead stability before discharge. In some cases, DFTs may also be checked before discharge. Wherever patients with a fresh ICD are located, ready availability of an ICD magnet is essential. Personnel should be trained to use a magnet to inhibit inappropriate ICD shocks caused by right ventricular lead displacement or supraventricular arrhythmias. We administer ciprofloxacin for 5 days after discharge to complete prophylaxis. A postoperative office visit is scheduled 7 to 14 days after implant.

Surgical follow-up

At the postoperative office visit, lead position, patient symptoms, and the surgical wound are assessed. If drainage is present, the wound is cultured and treated appropriately. For persistent sterile drainage, ciprofloxacin or trimethoprim-sulfamethoxazole is administered for 10 days, and the patient is asked to keep the wound dry until healing is complete. Patients are referred for EP follow-up. Established infection requires hospitalization and usually ICD explantation.

Device follow-up

ICDs require outpatient EP evaluation at 1- to 3-month intervals to cycle the capacitors, confirm battery life, test pacing thresholds, and download electrograms. The electrograms define aborted charging cycles and arrhythmias. Programming is adjusted accordingly. For patients reporting ICD shocks, telemetry can confirm proper function, detect inappropriate shocks, and demonstrate electrical noise and oversensing that require lead revision.

Late Follow-Up and Generator Replacement

Battery depletion

ICD battery life is now typically more than 60 months. Complications of generator replacement include infection, myocardial infarction, and death. Progression of heart failure and/or coronary artery disease increases the risk of replacement. Replacement is now commonly done under local anesthesia, with sedation during DFT measurement. DFT measurement may be deferred if the risk of the test appears greater than the risk of sudden death. Patients are usually discharged on the same day, unless the high-voltage lead is replaced.

Lead dysfunction

The incidence of failure of any given lead progresses with implant duration. Approximately 50% of ICD recipients require lead revision at 10 years of follow-up.[129–132] Problems include lead fracture, high DFTs, oversensing, undersensing, and exit block. The incidence of transvenous lead displacement is 7% and of fracture is 6% at 2-year follow-up.[132] Oversensing can be caused by insulation damage in the ICD pocket. Oversensing can be corrected with a new transvenous rate-sensing lead, preferably of the positive-fixation type. Visible

insulation damage inside the defibrillator pocket may be repairable with silicone sleeves, silicone glue, and ligatures.[133]

Patch leads can fail due to conductor fracture or distortion by fibrosis. With endocardial leads, DFTs may increase as a result of cardiac enlargement, which shifts the left ventricle laterally, away from the original right ventricular lead system. Insertion of a subcutaneous patch and/or a high-output generator can correct high DFTs.

Additional Issues

Bridge to transplant

The benefits and liabilities of ICD therapy for VT/VF in patients who are awaiting cardiac allografting are under investigation,[134,135] with cost an important concern.

Quality of life

Issues include the discomfort and distress of repeated shocks and inconvenience of mandatory outpatient visits. These are particularly trying for elderly patients. ICD generators, though steadily shrinking in size and weight, remain bulky compared to pacemakers. While many patients are elated to be rescued by their ICD from a malignant arrhythmia, others find their plight distressing.[136–138] Many ICD patients do not comply with recommended limitations on driving automobiles. Fortunately, the rate of accidents in ICD recipients is reportedly low.[139]

Cost effectiveness

ICD therapy is expensive, but the cost of VT/VF management in the absence of an ICD is also substantial. The incremental cost per year of life added has been estimated at $10,000 to $200,000.[140–142] Reduction in the cost of ICD generators and leads would increase the economic appeal of ICD prophylaxis.

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PART

VII

Other Cardiac Operations

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CHAPTER 61

Adult Congenital Heart Disease

Hillel Laks • Daniel Marelli • Mark Plunkett • Jeff Myers

The steady rise in individuals who have survived congenital heart disease (with or without treatment) into adulthood is expected to create specialized requirements that mandate strategic collaborative care protocols for this swelling subpopulation. If one excludes all patients born before 1990 and those not diagnosed in the first year, assuming stable mortality in early adulthood, nearly 760,000 adults will have congenital heart disease by 2020.[1–6]

Adults with congenital heart disease who are referred for surgery fall into three general categories: those without previous surgery, those with previous palliation, and those with complete physiologic or anatomic repair returning for revision of their repair because of residual defects or sequelae from their repairs.[1,2,4–6]

In the current era, there is a trend toward surgical correction of congenital heart defects in the neonatal period or during infancy. This approach aims at minimizing the long-term consequences of congenital heart defects, such as myocardial dysfunction, endocarditis, and the hematologic and cerebral complications of cyanosis.[7–20]

There are, however, some patients who present as adults (particularly from underdeveloped countries) without previous surgery. More common lesions in this category include aortic valve disease, coarctation, pulmonary stenosis, atrial septal defect, and patent ductus arteriosus. Less commonly seen are tetralogy of Fallot, ventricular septal defect, Ebstein anomaly, and coronary arteriovenous fistulas. Palliated adults are also unusual and include patients with systemic-to-pulmonary artery shunts, Glenn cavopulmonary shunts, and pulmonary artery bands. The largest group includes adults who present with residual lesions or sequelae from previous surgeries. These conditions may include patch leaks, recurrent valvular or outflow tract stenoses, recurrent coarctation, pulmonary valve regurgitation, valve stenosis after tissue valve replacement or homograft insertion, or aneurysm formation in the pulmonary artery or aorta. Both primary repair and redo procedures are frequently complex and at increased risk from long-standing abnormal physiology and hemodynamics. Surgical care of the adult with congenital heart disease requires a multidisciplinary team experienced in pediatric and adult cardiology and cardiac surgery.

GENERAL MANAGEMENT

Preoperative Evaluation

The natural history of the congenital defect, the sequelae of previous surgical interventions, and the development of newly acquired cardiovascular disease mandate thorough evaluation during preoperative surgical planning. Long-standing cyanosis and pressure or volume overload may all result in right or left ventricular dysfunction and secondary valvular regurgitation that may require repair. Additionally, cyanosis and underperfusion of the lungs may cause the development of aortopulmonary collaterals that may require coil embolization prior to reoperation. Pulmonary vascular resistance is usually affected by long-standing excessive flow or by severe underperfusion and, in older patients, by ongoing pulmonary thromboembolism. Older patients may also develop coronary artery disease that requires concomitant revascularization.

Transthoracic or transesophageal echocardiography provides excellent information regarding the segmental and morphologic cardiac anatomy. Additionally, hemodynamic data can assist in evaluating valvular function, stenosis, and direction of shunting. In most complex cases, cardiac catheterization is required and pulmonary vascular resistance is calculated directly. Quantitative perfusion lung scans are useful to assess right- and left-sided blood flow. Magnetic resonance angiograms with three-dimensional reconstruction can provide excellent views of anatomy and are particularly

helpful in preparation for redo coarctation procedures to delineate the aortic arch and descending aorta.

Procedures Requiring Reoperation

Redo median sternotomy can be hazardous and result in massive hemorrhage if thin-walled vascular structures are adherent to the posterior sternum. We obtain computed tomography scans in select patients to view the retrosternal structures. In some patients, the femoral artery and vein are exposed prior to sternotomy. If the aorta, right atrium, or a conduit is adherent to the back of the sternum, cardiopulmonary bypass may be initiated with femoral artery and vein cannulation using thin-walled cannulas. If the right atrium or right ventricle is entered inadvertently, an intracardiac defect such as an atrial or ventricular septal defect could result in catastrophic systemic air embolism. This complication can be avoided by instituting deep hypothermia with cardiopulmonary bypass, keeping the heart full, and discontinuing the cardiac dissection until the heart fibrillates. In the presence of aortic regurgitation, decompression of the left ventricle is accomplished by cannulating the left ventricular apex via a small submammary incision. Bleeding may be a problem during chest opening due to the presence of numerous large thin-walled vessels throughout the mediastinum that are commonly found in chronically cyanotic patients. Chronic cyanosis and polycythemia are associated with a coagulopathy due to platelet dysfunction. Chronic hepatic congestion affects the coagulation factors and exacerbates coagulopathy. The use of antifibrinolytic agents such as aprotinin, aminocaproic acid, or tranexamic acid is considered in high-risk patients except when circulatory arrest is used. Topical hemostatic agents have proven very useful for oozing surfaces. Autologous blood donation (when not contraindicated) and the use of cell-saving devices are routine.

A polytetrafluoroethylene (GORE-TEX or PTFE) pericardial substitute is used at closure for patients requiring later surgery, such as palliative procedures or after use of homografts or tissue valves. This membrane facilitates the dissection of reentry and the risk of injuring a retrosternal structure is markedly reduced.

Myocardial Protection

Right and left ventricular hypertrophy, dilatation, or dysfunction may be present. Noncoronary collateral flow is usually increased and bronchial flow can be torrential. Myocardial protection is therefore critical to the outcome of complex procedures. A left ventricular vent and deeper hypothermia to 24°C are required, and both antegrade and/or retrograde cardioplegia are given every 10 minutes. A purse-string suture is placed around the coronary sinus to improve retrograde distribution.

Postoperative Care

The adult with congenital heart disease may present a far more complex postoperative course than the usual adult with acquired heart disease. Both right and left ventricular function may be compromised and require support. Both pulmonary and systemic vascular resistance may require manipulation. For this reason, right atrial (RA), pulmonary artery (PA), and left atrial (LA) pressure-monitoring lines are used when indicated. LA lines are used rather than attempting to obtain PA wedge pressures because of the danger of PA rupture and possible discrepancy between PA diastolic pressures and LA pressure. Transesophageal echocardiography is required postoperatively to assess left and right ventricular function, to evaluate left- and right-sided valve function, and to look for shunts. Ventilator control to reduce partial carbon dioxide pressure, as well as inhaled nitric oxide and milrinone, all are useful ways to reduce pulmonary vascular resistance.

Associated Procedures

Many adults with congenital heart disease require corrective surgery after associated procedures. In particular, all patients above the age of 40 years require preoperative coronary angiography. Due to a history of shunts or increased chest wall collaterals from cyanosis, many patients have aortic insufficiency secondary to increased venous return to the systemic ventricle. Such patients should be considered for aortic valve repair.[21]

Other associated procedures often performed in adults with congenital heart disease include bicuspid aortic valve repair or replacement, mitral or tricuspid valve repair or replacement, and implantation of epicardial pacemaker leads and generator.[22–33]

Our preferred approach for epicardial pacemaker implantation is a subxiphoid approach. Atrial tissue is easily identified near the inferior vena cava in most patients. A ventricular site is usually identified on the diaphragmatic surface of the heart. We prefer nonpenetrating steroid-eluding leads that are sutured onto the epicardium. The pacemaker battery is placed in the preperitoneal position beneath the fascia or in the subcutaneous tissues of the left upper quadrant. Transvenous leads are generally contraindicated in the systemic circulation because of the risk of thromboembolism. This is of particular importance in patients with single-ventricle physiology.

SPECIFIC CONGENITAL MALFORMATIONS

Atrial Septal Defects

Anatomy

Atrial septal defects (ASDs) of the secundum type are the most common lesions, but sinus venosus defects of both the superior and inferior vena caval types, as well as ostium primum ASDs, are seen in adults (Fig. 61-1).

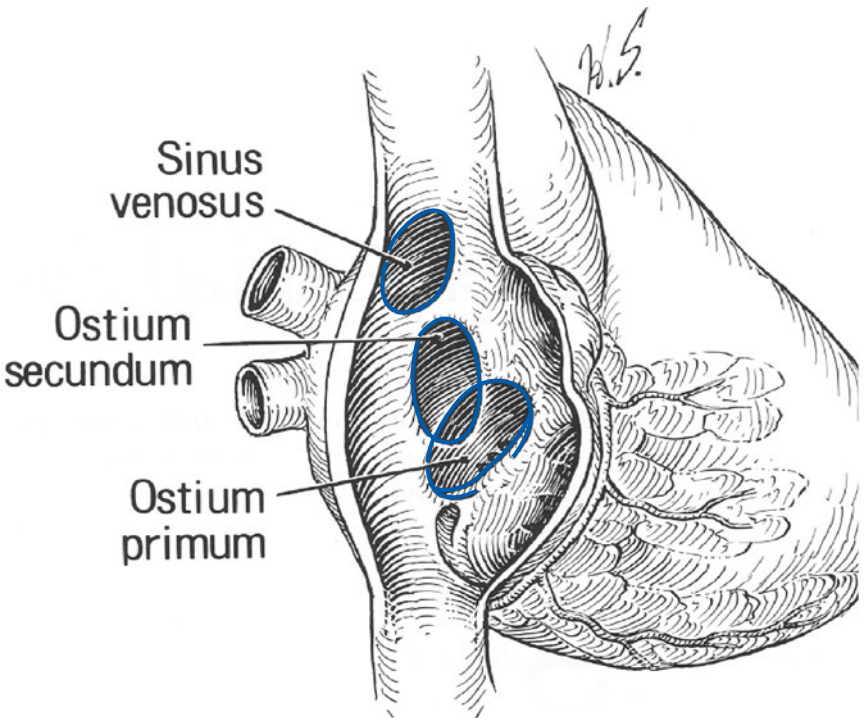

Figure 61-1. Diagram showing the locations of the most common types of atrial septal defects. Sinus venosus defects are close to the superior vena cava-to-right atrial junction and are frequently associated with partial anomalous pulmonary venous drainage (not shown). The right superior pulmonary vein may drain directly into the superior vena cava or at the junction of the superior vena cava and right atrium.

Physiology and indications for surgery

The amount of left-to-right atrial shunting is variable. In older patients, as right ventricular dysfunction and tricuspid regurgitation develop, the degree of left-to-right shunting may decrease. The left-to-right shunt may increase in other patients due to hypertension and reduced left ventricular compliance. Although most patients with an ASD are asymptomatic through the second decade, by the third or fourth decade adults commonly develop atrial fibrillation or a reduction in exercise tolerance, and eventually heart failure.[34–40] It is preferable to close the defect when the diagnosis is made, before the development of these sequelae. As long as the Qp:Qs (pulmonary flow:systemic flow ratio) is greater than 1.5:1 and the calculated pulmonary vascular resistance is less than 6 to 8 U/m^2 (or Wood units/m^2), depending on systemic vascular resistance at the time of measurement, closure is usually indicated. There is often associated tricuspid valve regurgitation, which is the result of annular dilatation due to volume overload of the right ventricle. Indeed, such regurgitation may account for shortness of breath on exertion. This can be particularly true for patients who have patch leaks after repair and who are referred for reoperation to address symptoms out of proportion to shunt size. Patients with a patent foramen ovale and systemic embolization are also candidates for closure of the defect.

About 15 to 20% of children with an ASD eventually develop pulmonary vascular disease.[41–43] If it does not occur by the end of the second decade, it is very unlikely to occur. Pulmonary vascular disease eventually causes reversal of the shunt and development of hypoxia that may be intermittent and severe, depending on right ventricular function and tricuspid regurgitation. Patients with a patent foramen ovale and systemic embolization are candidates for closure of the defect. In the past, patients with pulmonary vascular disease were considered inoperable and were candidates for eventual lung transplants and ASD closure. The use of long-term prostacyclin has allowed some patients to lower their pulmonary vascular resistance and develop a left-to-right shunt. We have successfully proceeded to ASD closure and continued prostacyclin therapy in some of these patients. Another option is an adjustable (see below) or flapped patch closure, to allow a small amount of residual right-to-left shunting postoperatively.[44]

Operative procedure

The operation is performed using cardiopulmonary bypass and moderate hypothermia. For cosmetic purposes in young women, a submammary skin incision with median sternotomy is used. For the last 10 years we have used a small right anterolateral thoracotomy (Fig. 61-2). Another option is a midline incision in the lower half of the sternum. Superior and inferior vena cava cannulation is achieved directly through the thoracotomy incision using right-angled metal-tipped cannulas. If aortic cannulation is difficult, femoral artery cannulation is used. The aorta is clamped and cold blood cardioplegia alternating with cold blood is run continuously to keep the left atrium and ventricle full to prevent air entry. The chest cavity is filled with carbon dioxide throughout the procedure. The ASD is closed either primarily or with a pericardial patch. The right-sided pulmonary veins must all be identified, and if they are draining anomalously, they are baffled to the left

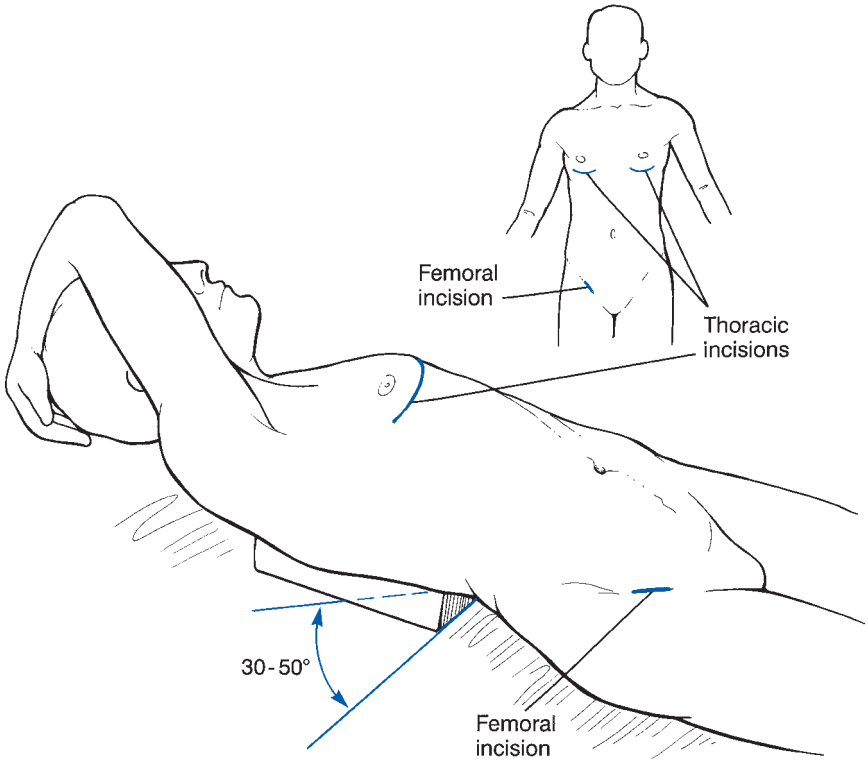

Figure 61-2. Patient position for minimally invasive right thoracotomy approach for repair of an atrial septal defect. A 5- to 7-cm incision is made in the submammary crease. An additional incision may be made in the groin crease for femoral artery cannulation.

side with a pericardial patch. It is also important to identify the inferior vena caval orifice so that it is not inadvertently baffled into the left atrium by sewing the patch to a well-developed eustachian valve.

Redundant right atrial wall may be excised and a regurgitant tricuspid valve (if present) is repaired with an annuloplasty, particularly if the tricuspid annulus is dilated to >34 to 38 mm. In patients with chronic atrial fibrillation, a Maze procedure is performed.[45,46] After closure of the defect and right atrium, extensive de-airing is performed prior to releasing the cross-clamp. This includes syringe and large-bore needles, de-airing of the left atrium, and venting of the aorta. Rarely, if air has entered the left ventricle during the procedure, a small submammary left-sided thoracotomy is made, and a small left ventricular apical vent is also inserted to assist in de-airing. The left ventricle is inspected with transesophageal echocardiography for residual air prior to release of the cross-clamp.

Outcomes

Long-term follow-up after repair of isolated ASDs is well documented.[47–51] When patients are operated on at or before 25 years of age, normal life expectancy is anticipated, but this may not be the outcome when patients are corrected after 25 years, when both right and left ventricular reserve are diminished following a long-standing ASD. However, patients with ASD closure after 40 years of age may still realize improvement of symptoms. At the University of Alabama, it was found that age and New York Heart Association (NYHA) class were fairly well correlated, thus suggesting that ASD closure is indicated when the defect is hemodynamically significant (Qp:Qs >1.5:1). Older age per se is not a risk factor for operative mortality.

Recently, keen interest in the use of intravascular devices to close ASDs has developed.[52–56] The Amplatzer device was recently approved by the Food and Drug Administration for clinical use. Follow-up of 5 to 7 years is now available showing good long-term results. This trend will grow, as the Amplatzer and CardioSEAL devices are currently approved by the Food and Drug Administration for atrial septal defect closure. Long-term follow-up is pending. There is growing interest in the use of endoscopically assisted placement of these devices, with or without robotic aid, to close these defects.[57]

Ostium Primum Defects and Late Reoperations After Repair of an Atrioventricular Canal

Ostium primum (partial canal) defects

Ostium primum defects are unusual in adults; however, survival similar to that for a large ASD is expected for partial atrioventricular canal defects with minimal valvular incompetence. The suture line is placed on the tricuspid aspect of the defect and outside the conduction tissue, which is left beneath the patch. Atrioventricular valve (right or left) regurgitation is often present and should be

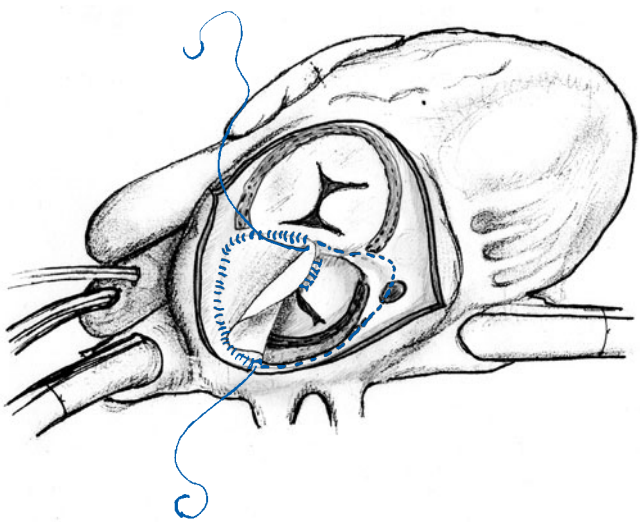

Figure 61-3. Diagram showing closure of ostium primum atrial septal defect combined with mitral valve repair and tricuspid annuloplasty. The cleft in the anterior leaflet is closed with interrupted sutures. A mitral annuloplasty is used when indicated or the commissures are plicated. Autologous pericardium is used to close the atrial septal defect. The suture line is placed on the tricuspid valve side, and then continued inferiorly on the atrial wall, outside the conduction tissue (shown by the dotted line in the diagram), then under the lip of the coronary sinus and back to the edge of the ASD. The conduction tissue is thus left under the patch, and the coronary sinus drains into the right atrium. When indicated a tricuspid annuloplasty is performed using glutaraldehyde-fixed autologous pericardium and 2-0 polytetrafluoroethylene sutures for the annuloplasty.

repaired at surgery[58–62] (Fig. 61-3). Long-term results are excellent.

Late left atrioventricular valve regurgitation after repair of atrioventricular canal

About 10 to 30% of operated atrioventricular canal patients may present because of left atrioventricular valve malfunction.[63,64] They are often successfully treated with a re-repair of the mitral valve; the most common cause is a residual or recurrent cleft in the anterior leaflet. Annuloplasty or commissuroplasty may also be needed.[65–67] This can be in the form of several isolated stitches along the annulus or a band along the posterior aspect of the annulus. There is limited experience with creating a double-orifice valve.[68,69] A unique approach has been reported by the group from Toronto. The dysplastic superior and inferior bridging leaflets are detached radially along the anterior annulus. They are then augmented using glutaraldehyde-fixed autologous pericardium, allowing for better leaflet coaptation. An annuloplasty is also performed.[70]

Some will require valve replacement which can be difficult due to the annulus projecting towards the left ventricle outflow tract. This is because the inlet septum is shortened and the outlet septum is lengthened. A crescent-shaped patch may be used to lengthen the mitral-to-aortic continuity along the circumference of the annulus in the section of A1 and P1. In this way, a low-profile mechanical valve can be positioned away from the left ventricle outflow, with a projection into the left atrium.[71] Leaflet remnants are used to anchor the valve along the other segments of the annulus.

Left ventricular outflow tract obstruction after atrioventricular canal repair

While left ventricular outflow tract obstruction (LVOTO) due to tunnel-like narrowing is unusual in the setting of either partial or complete canal, there have been reports of other types of obstruction occurring late after repair. del Nido and associates have summarized this possibility well. They observed that it is more common in partial canal, and that it may be acquired rather than congenital. This underlines the need for lifelong surveillance.[72,73] Repairs must be individualized and can be complex. Later reoperations are not uncommon.

The anatomy that results in left ventricular outflow tract obstruction may be related to left superior leaflet chordae that are attached to the outlet septum, or to outgrowths of accessory valve tissue in the left ventricular outflow tract. If they are primary chordae, the former requires division and re-attachment, repair, or valve replacement, while the latter may simply be excised. Other causes of left ventricular outflow tract obstruction include a subaortic membrane or abnormal papillary muscle position.[72] Many of these can be approached through the aortic valve.[73]

The group from Toronto has suggested that the outflow tract can be effectively shortened and widened, by augmenting or lifting the left side of the superior bridging leaflet. This is likened to conversion of a Rastelli A anatomy to a Rastelli C. This restores (increases) the angle between the plane of the outlet septum and that of the septal crest toward normal.[74] A patch of glutaraldehyde-fixed pericardium may then be used to close the resulting defect and lifts the leaflet away from the left ventricle outflow. A modified or full Konno procedure may be needed for cases in which there is tunnel-like narrowing with ventricular hypertrophy.

Ventricular Septal Defects

Unrestrictive ventricular septal defects (VSDs) are mostly associated with congestive heart failure in infancy and are usually repaired in early childhood. Adult survival with an unrestrictive VSD can occur if there is concurrent pulmonary outflow obstruction that restricts pulmonary blood flow, or if the development of severe pulmonary vascular disease reduces or reverses the left-to-right shunt (Eisenmenger syndrome). Restrictive VSDs are more commonly found in the adult and may be the result of a persistent small defect, partial spontaneous closure of a larger defect, or a residual patch leak following surgical repair.

Controversy continues as to whether restrictive VSDs should be closed. A large study by Kidd and associates showed a 25-year survival of 87%, but noted a significant increase in the risk of serious arrhythmias and sudden death.[75] The evolving concept of monitoring unoperated

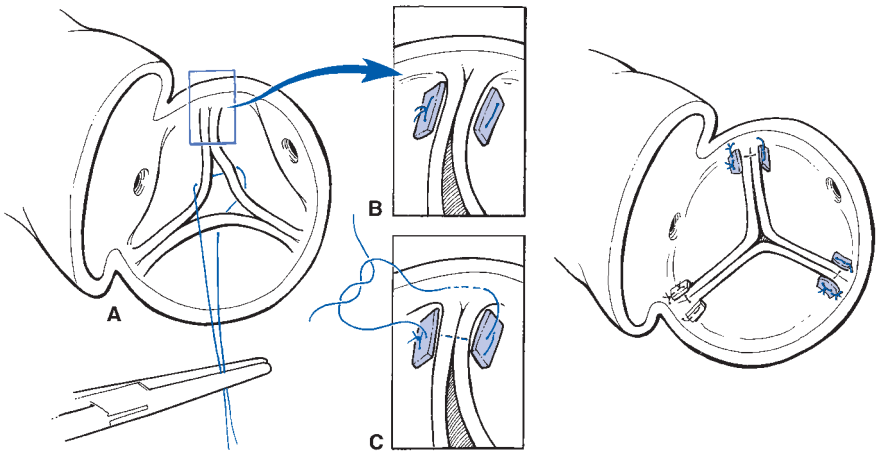

Figure 61-4. Technique of aortic valve repair using pericardial pledgeted sutures to resuspend redundant leaflets. Additional apposition can be achieved by adding sutures below the commissures or at the level of the annulus.

patients in adults with congenital heart disease was reinforced by Glen and coworkers in a study of 1448 patients with VSDs.[76] He noted that 22% of these patients had associated defects. Most were detected initially but aortic insufficiency and infundibular stenosis often developed subsequently. If follow-up of these patients was continued until age 30, 89% of patients with secondary aortic regurgitation would be detected. Nonoperative intervention is most appropriate in patients with small defects, a Qp:Qs ratio of <1.5:1.0, no left ventricular overload, and normal pulmonary artery pressures.

Anatomy

Most VSDs are categorized into four anatomic types. The *perimembranous* type is the most common. It is located under the septal leaflet of the tricuspid valve. The *subarterial* VSD is located in the supracristal area and may lie directly beneath the annulus of the pulmonary valve. Because of the proximity of the aortic annulus to such defects, the right cusp of the aortic valve may prolapse into the defect, reducing the effective orifice and limiting the shunt. Aortic regurgitation is frequently associated with this defect.[77] With surgical closure of a subarterial VSD, the aortic valve may require repair with suspension of the prolapsing valve leaflet (Fig. 61-4).

The *endocardial cushion* type of VSD is located in the inlet of the right ventricle and beneath the septal leaflet and posterior leaflet of the tricuspid valve. This VSD may have associated mitral valve defects such as cleft anterior leaflet and therefore require mitral valve repair at the time of surgery. The repair usually involves suture closure of the anterior leaflet cleft and may require reduction of the dilated annulus with annuloplasty. The *muscular* type of VSD may occur anywhere within the muscular ventricular septum. This type is unusual in adults, as it has a tendency to close spontaneously in the first years of life.[78]

Physiology

Use of the term *restrictive* implies a pressure gradient between the ventricles and a restriction to flow across the defect. The amount of left-to-right shunting across the defect can be quantified by calculation of the Qp:Qs ratio. VSDs with left-to-right shunting that results in a Qp:Qs ratio of <1.5:1 are usually not considered for repair, if there is no other associated pathology (e.g., aortic leaflet prolapse and insufficiency).

Double-chambered right ventricle is an obstruction in the mid-portion of the right ventricle that divides the chamber into two segments: a high-pressure lower chamber and a low-pressure upper chamber. The development of obstructive tissue in the right ventricle is a direct result of a restrictive VSD producing a "jet effect" that strikes adjacent myocardium and produces an area of fibromuscular proliferation. Right ventricular hypertrophy develops secondary to the obstruction and contributes to the progression of right ventricular hypertension. In many patients the VSD will eventually close, as the fibromuscular rim of tissue proliferates around and over the defect. In these patients, the VSD is often identified at the time of surgery with resection of the obstructing tissue in the right ventricle.

In patients with large unrestrictive VSDs, the probability of developing severe pulmonary vascular disease is about 50% by the third decade of life.[79,80] Consequently, patients eventually die of complications of Eisenmenger syndrome if their VSDs remain unrepaired. These patients ultimately will become cyanotic as a result of right-to-left shunting, and the only surgical options available at that point are either heart-lung transplantation or lung transplantation with repair of the VSD. A pulmonary vascular resistance greater than 6 U/m^2 is considered a high risk for isolated VSD closure. A number of promising new medical therapies are being applied to patients with pulmonary hypertension. Use of nitric oxide donors such as sildenafil, endothelin antagonists, and prostaglandin analogs may alter the outcome in these patients and potentially reverse the pulmonary hypertension to levels that will allow for surgical correction.

Preoperative evaluation

An adult patient with a VSD should be evaluated by chest radiograph and echocardiography. A chest radiograph may

show an enlarged right heart shadow and right ventricular hypertrophy. It may also reveal chronic changes in the pulmonary vasculature, prompting further evaluation by catheterization. Transthoracic and transesophageal echocardiography are both useful in defining VSDs anatomically and identifying associated lesions.[81] An estimate of the pulmonary artery pressures may also be obtained. Indications for surgery are helpful in determining the need for catheterization. Patients with embolic complications and very small defects with high gradients and no evidence of pulmonary hypertension can usually be closed without catheterization. However, patients with significant symptoms attributed to their VSD should undergo catheterization to rule out pulmonary hypertension. Right and left heart catheterization is useful to confirm the anatomic findings and to accurately measure the pulmonary vascular resistance and estimate the Qp:Qs ratio. In patients more than 40 years old or in those with increased risk factors, coronary artery disease must also be excluded by angiography.

Indications for surgery

Adults with small restrictive VSDs who are asymptomatic often require no surgical intervention and should receive endocarditis prophylaxis as necessary. In general, if the Qp:Qs ratio is >1.5:1 and the calculated pulmonary vascular resistance is under 6 U/m^2, surgical closure of a VSD can be performed safely and is recommended. The development of a double-chambered right ventricle with outflow obstruction is also an indication for operative intervention. The occurrence of infective endocarditis in an adult with a restrictive VSD is a rare but compelling indication for repair of the defect. In adults with VSD and Eisenmenger syndrome, heart-lung transplantation or lung transplantation with closure of the defect may be considered.

Operative procedure

Operative repair of VSDs is performed on cardiopulmonary bypass with moderate systemic hypothermia and blood cardioplegia for myocardial protection. Generally, greater operative exposure is required than for the repair of ASDs. However, many of the cosmetic modifications discussed in the section on atrial septal defects are appropriate here. Bicaval cannulation with caval snares helps to produce a bloodless field. A left-sided vent is also helpful in evacuating blood from the left heart. This can either be placed through the left superior pulmonary vein or through an incision in the atrial septum. An appropriately sized patch is then created and sewn in place using either interrupted, pledgeted horizontal mattress sutures or a continuous running suture. The patch is cut slightly larger than the defect so that the sutures can be placed away from the edge and the conduction system. Most adults with a perimembranous, inlet, and/or muscular VSD can have the defect repaired through the tricuspid valve annulus. If the edges of the defect are difficult to visualize due to multiple attachments of the septal leaflet to the edges of the defect, the septal leaflet may be incised at its base adjacent to the annulus or radially through the septal leaflet, exposing the VSD under the leaflet. Subarterial VSDs may be approached through the pulmonary valve or the right ventricular outflow tract. Exposure through the pulmonary valve is particularly helpful in placing sutures through the pulmonary valve annulus without damaging the valve. The patch material for closure of VSDs may be synthetic (e.g., PTFE or Dacron), or glutaraldehyde-fixed autologous pericardium, which we have preferred for over 15 years. PTFE may produce less hemolysis than pericardial patches. However, it may also be less well-incorporated and therefore small residual VSDs may not close as readily. Postoperatively, elevated pulmonary artery pressures may be treated with inhaled nitric oxide. A fenestrated VSD patch can be created to transiently allow right-to-left shunting and maintain cardiac output in the immediate postoperative period. It can subsequently be closed in the cardiac catheterization lab. Currently, transcatheter closure of VSDs remains experimental.[82,83]

Outcomes

Long-term follow-up is recommended to monitor pulmonary artery pressures in those adult patients with large VSDs that are repaired late in life.[84] This is achieved echocardiographically if there is a mild tricuspid regurgitation from which to calculate the right ventricular pressure, or by measuring the pulmonary valve opening time. The pulmonary vascular resistance may continue to rise after VSD closure, resulting in systemic or suprasystemic right ventricular pressures. This may eventually cause the onset of angina, right heart failure, or even sudden death.

In an analysis of 52 patients between the ages of 16 and 67 years repaired at the University of California, Los Angeles, there was no mortality. In most patients, the VSD repair was combined with additional procedures such as aortic valve repair, pulmonary valve replacement, and tricuspid valve repair. Except in patients with congenitally corrected transposition, the incidence of complete heart block following VSD closure is approximately 1%. Overall, the long-term outcome for these patients has been excellent.

Patent Ductus Arteriosus

Natural history and indications for surgery

Isolated patent ductus arteriosus (PDA) may present with congestive heart failure by the third or fourth decade of life.[85] Occasionally, the ductus may become aneurysmal secondary to flow characteristics. The aortic end of the PDA is usually calcified in the older adult patient. A long-standing left-to-right shunt may lead to pulmonary vascular disease. The cumulative death rate in childhood is about 0.5% per year. This doubles to 1% by adulthood and increases to 2 to 4% by midlife. There is always a risk of endocarditis (regardless of the PDA size) that is dependent on the presence of abnormal flow. Adults with

large PDAs may develop Eisenmenger syndrome and the classic finding of differential cyanosis in the lower body. It is imperative to determine pulmonary vascular resistance and reactivity preoperatively. If the resistance is >6 to 8 U/m^2, the ductus should not be closed, and the patient may be considered for lung or heart-lung transplantation.

Operative procedure

Surgical closure of a PDA is usually carried out via a small posterior thoracotomy. Thoracoscopic procedures are probably not appropriate for the adult because of the frequency of calcification and the greater risk of rupture while ligating the ductus.[86,87] In patients over 40 years of age, or in the presence of severe ductal calcification or aneurysm, consideration should be given to performing PDA ligation via a median sternotomy using cardiopulmonary bypass.[88,89] During cooling, the branch pulmonary arteries are snared. This prevents steal from the descending aorta. The ductus is exposed via an incision in the PA. Using low flow, the ductus is closed on the PA side with horizontal pledgeted mattress sutures, or the PA defect is patched with glutaraldehyde-fixed pericardium or a PTFE patch.

Patients with Eisenmenger syndrome may be candidates for either single- or double-lung transplantation combined with PDA closure, or heart-lung transplantation if there is significant ventricular dysfunction and tricuspid valve regurgitation.

Catheter closure by interventional cardiology specialists using coils or other devices may be possible depending on the size and length of the ductus.[90–93] In the last 5 years, catheter-based closure of this lesion in the adult has been reported as the most common after ASD, VSD, and coarctation.[94] Similarly, surgeons have also reported a catheter-based approach in which the patent ductus is excluded with a stent graft placed in the proximal descending aorta.[95–97]

Coarctation of the Aorta

Anatomy

Coarctation in adults may occur in previously unrepaired patients or patients who have had prior surgical correction. In unrepaired patients an abnormality of the media creates a posterior shelf, opposite the ligamentum arteriosum. This shelf may extend circumferentially. The abnormality, similar to cystic medial necrosis histologically, predisposes patients to late complications such as dissection and aneurysm formation. There is often extensive collateral circulation in adults with coarctation. The source is mainly from branches of the subclavian artery and internal mammary arteries, and intercostal chest wall circulation. Collateral flow into the descending aorta is dependent on enlarged intercostals at the level of the third and fourth ribs beyond the coarctation. Additional cardiovascular anomalies occur in 59 to 92% of patients and include a bicuspid aortic valve in 40 to 80% and aortic arch hypoplasia in 33%.[98]

Natural history and indications for surgery

Aortic coarctation in adults usually presents with upper-body hypertension, typically in the second or third decade of life.[99] Lower extremity pulses are usually weak and delayed. Although these patients comprise a selected group who have survived free of complications beyond childhood, long-term complications include aneurysm formation of the aorta and aneurysmal dilatation of intercostal arteries, which may eventually rupture. This latter anomaly is important because the initial portion of these arteries should be occluded at the time of surgery if they appear disproportionately enlarged. Other complications include premature coronary artery disease, left ventricular hypertrophy, aortic dissection and rupture, endocarditis, and intracranial hemorrhage. In adults with coarctation, congestive heart failure may develop from long-standing hypertension. Patients with an associated bicuspid aortic valve may develop stenosis and/or incompetence. [23] If aortic coarctation is left untreated, 90% of patients eventually die by the age of 50 due to cardiac causes or stoke. The oldest patient in our series was 81 years old.

Repair also may be required for patients who have had previous coarctation repairs with recurrence or for patients who have developed recurrence after previous balloon aortoplasty. As many as 70% of infants who have unrepaired arch hypoplasia at their initial operation may require reoperation as adults. Residual coarctation following repair in childhood is also due to failure of growth of the anastomosis or technical factors such as a short subclavian flap aortoplasty. In patients who were initially treated with a patch, aneurysm formation may occur and require reoperation. Surgical repair is indicated when the gradient across the coarctation is ≥30 mm Hg at rest.[100] If the gradient is less and the anatomic obstruction severe, an exercise test will reveal a more severe gradient, and repair is indicated.

Preoperative evaluation

The anatomy of the entire left ventricular outflow tract and thoracic aorta must be defined prior to surgical intervention. Previously repaired patients may have additional levels of obstruction from a hypoplastic aortic arch that has failed to grow or a stenotic/regurgitant aortic valve. Surgical intervention should be tailored to address all levels of obstruction. Echocardiography is performed to evaluate the aortic valve, ventricular function and hypertrophy, and the aorta. In adults, magnetic resonance angiography with three-dimensional computerized reconstruction to assess the transverse arch, isthmus, and descending aorta is often useful (Fig. 61-5).

Operative procedure

The preferred method is resection with extended end-to-end anastomosis (Fig. 61-6), although patch repair is used for

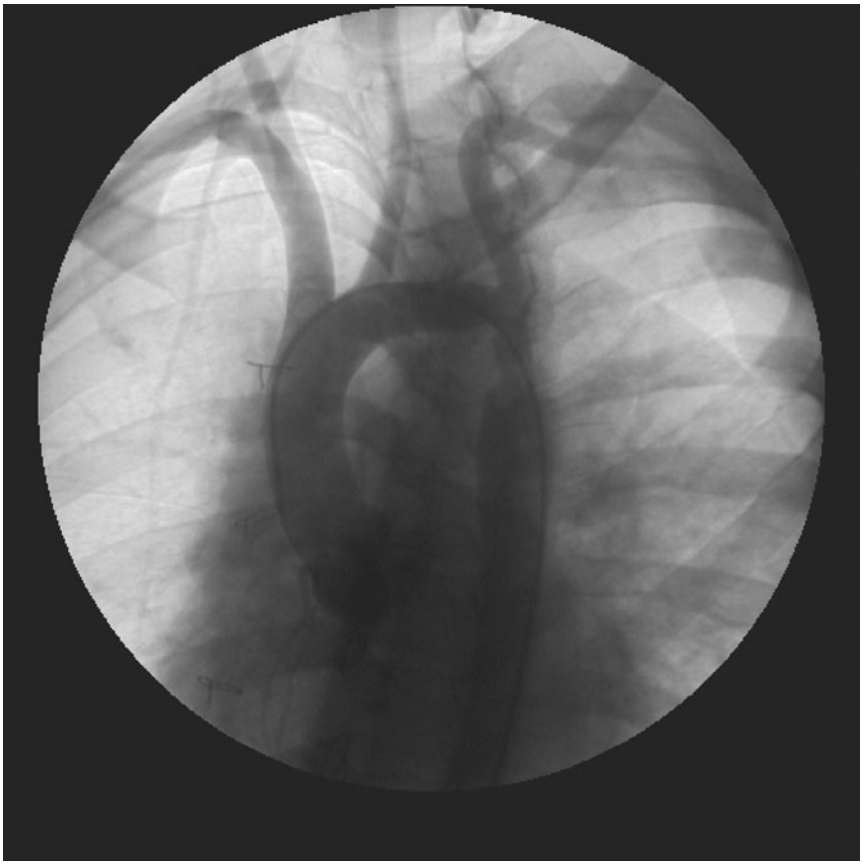

Figure 61-5. Angiogram of a 27-year-old patient who presented with residual coarctation after initial repair in which a 16-mm interposition graft was inserted. She presented with stenosis at the distal transverse arch and at the interposition graft with proximal hypertension. Repair using a left atrial-to-aortic bypass circuit involved repairing the distal arch and replacing the graft with a 20-mm PTFE conduit and extended anastomosis.

reoperations or where the collaterals are particularly enlarged and difficult to mobilize.[99,101–103] Tube-graft interposition is used when indicated to relieve long segments of obstruction. Special precautions are taken to reduce the major risk of spinal cord ischemia. Arterial lines are placed in the upper and lower extremities for monitoring blood pressure during aortic clamping. The distal pressure should be maintained above 50 mm Hg throughout the procedure. Somatosensory evoked potentials are monitored intraoperatively to aid in the decision to use extracorporeal circulation to help prevent spinal cord ischemia during aortic cross-clamping. In extensive reoperations or operations for aneurysms, the cerebrospinal fluid pressure is monitored by catheter, and the fluid is allowed to drain if pressure exceeds 10 cm H_2O (essentially central venous pressure). The cerebrospinal fluid pressure is monitored for 24 hours postoperatively. The goal is to optimize perioperative perfusion of the spinal cord by increasing the pressure gradient during and after aortic clamping.

The patient is placed on a temperature-regulated blanket and cooled to 33 to 34°C. Cold saline is used to bathe the left chest cavity to aid in cooling, and the room is cooled. Positioning for the left thoracotomy is important in that one must prep and drape the groins to have access to the femoral arteries if left atrial-to-femoral artery (or descending aorta) bypass becomes necessary during the operation. One must carefully identify chest wall collaterals, which can bleed massively and which must be ligated individually during the thoracotomy.

The aorta is mobilized extensively, and the ligamentum arteriosum is divided and oversewn. Large intercostal branches are identified and encircled in preparation for snaring. On induction of anesthesia, the patient is given 30 mg/kg of methylprednisolone sodium succinate and lidocaine 2 mg/1 kg intravenously, as well as 8 g of mannitol. The patient is anticoagulated with 1 mg/kg of heparin. The aorta is clamped when the rectal temperature is 34°C or below. Once the aorta is clamped proximally and distally, if the distal pressure is below 50 mm Hg, distal aortic bypass is instituted. The distal pressure is maintained above 60 mm Hg. This consists of left atrial-to-descending aortic bypass using a centrifugal pump. In more complex redo or aneurysm procedures, pulmonary artery-to-descending aortic bypass can be used with an oxygenator. Upper extremity pressure is maintained at about 120 mm Hg systolic. Once the aortic coarctation is resected, reconstruction with a tube graft or end-to-end anastomosis is carried out with 4-0 polypropylene suture mounted on a small needle.

For patients undergoing reoperation for recurrent coarctation, mobilization of the aorta for end-to-end anastomosis may be difficult and cause excessive blood loss. In these patients, the aorta is clamped proximal to the left subclavian artery, and a glutaraldehyde-fixed autologous pericardial patch may be used to enlarge the aorta from the base of the subclavian artery to the distal aorta. An excessively large patch should be avoided to prevent late aneurysm development.

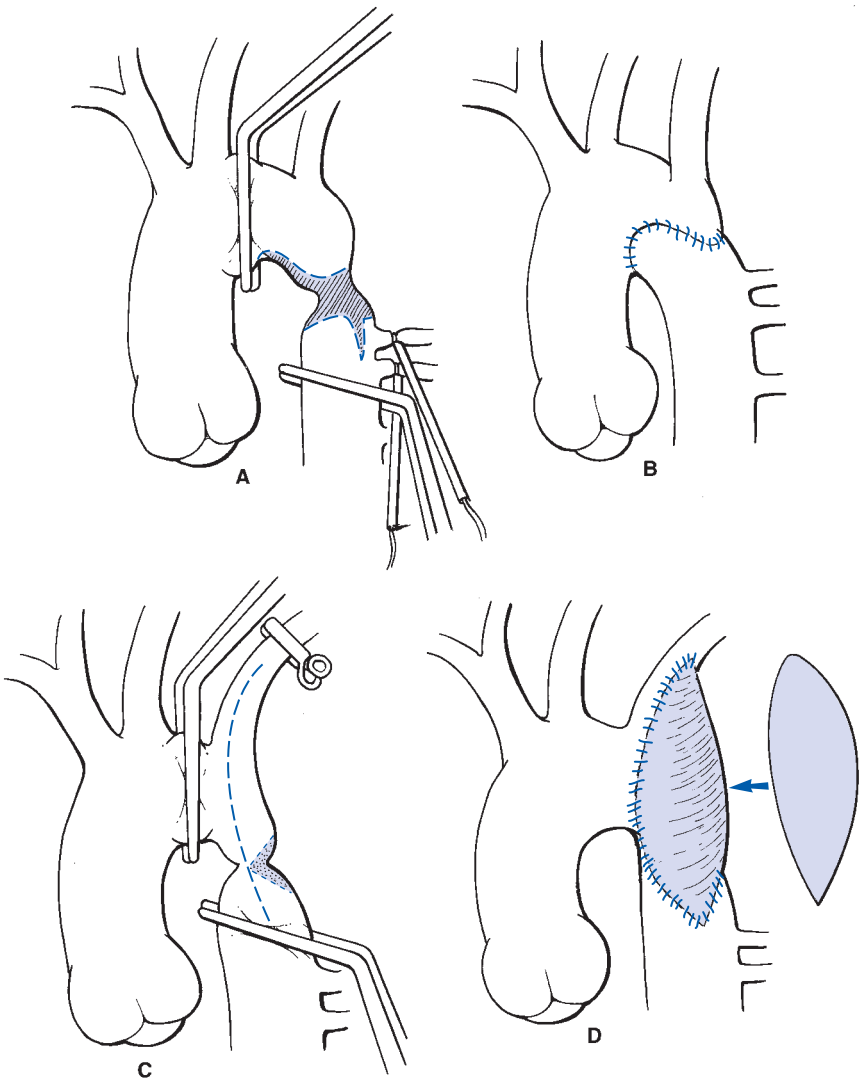

Figure 61-6. Resection of coarctation of the aorta. (A, B) With extended end-to-end anastomosis. (C, D) After excision of the coarctation site and reconstruction of the posterior wall by end-to-end anastomosis, a glutaraldehyde-fixed autologous pericardial patch is used to enlarge the isthmus and the site of coarctation repair. The patch is measured to avoid excessive dilatation, which can result in late aneurysm formation.

Some institutions prefer construction of an ascending-to-descending aortic bypass graft in patients with recurrent coarctation. The operation has been performed through either a right thoracotomy or via a posterior pericardial approach through a median sternotomy.[104,105] Both have reported a low mortality and morbidity with excellent relief of hypertension and resolution of the blood pressure gradient between the upper and lower extremities. A 16- to 20-mm graft is used and the repair through the right chest can be performed off bypass. Both approaches avoid the complications associated with a redo left thoracotomy, including injury to the recurrent laryngeal nerve, intercostal arteries, and lung. Aortic bypass graft also addresses significant arch hypoplasia and avoids the need for clamping of the "hostile aorta" that may be thin or calcified.

There should be no gradient between the upper and lower extremities upon release of the clamps. During closure, special care is taken to control intrathoracic bleeding and to check chest tube and pericostal suture sites.

Hypertension is controlled and is treated aggressively in the intensive care unit. Abdominal pain and distension may be present in 5% of patients postoperatively. Management is usually conservative. The patient is given nothing by mouth for at least 24 hours postoperatively until bowel sounds return.

In older patients who have a coarctation and also require coronary revascularization or aortic valve repair or replacement, we prefer a median sternotomy approach with cannulation of both the ascending aorta and the femoral artery. After completing the coronary revascularization, an adequately sized Dacron graft can be placed between the ascending aorta and the proximal abdominal aorta through the diaphragm. Another option to consider is a clamshell-type incision to access the descending thoracic aorta and the mediastinum simultaneously.

Outcomes

Outcome following repair is generally good, and follow-up may be assisted with transesophageal echocardiogram, computed tomographic scan, or magnetic resonance imaging. The latter is useful to detect aneurysm formation or recoarctation.[106,107] *Recoarctation* is defined as a gradient >20 to 30

mm Hg at rest. The possibility of coronary disease and systemic hypertension requires lifelong monitoring.

Catheter-based techniques are being used for both primary coarctations and recurrences.[108–110] Residual mild gradients are common after angioplasty and/or stenting of primary coarctations and we therefore prefer surgical therapy.[99] Since the presence of a residual gradient of >10 mm Hg is associated with an increased risk of adverse cardiovascular events, intervention must result in long-term, near-total resolution of the gradient.[111] Remembering that the primary goal is resolution of hypertension, surgery has consistently resulted in long-term relief in over 60% of patients. Recent analyses have shown that angioplasty alone results in a high rate of reintervention and is markedly worse at curing hypertension than surgery.[112] Angioplasty was found to be comparable to surgery with regard to morbidity, but appears to be much less effective in the cure of hypertension. For selected recurrent coarctations, stenting may be the preferred method, provided that an excellent anatomic relief of the obstruction can be achieved.[113] However, in younger patients in whom a long-term result is required, surgery may still be preferable, even in complex lesions.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common cyanotic heart defect in children, constituting approximately 10% of all congenital heart disease. It is therefore one of the most common cyanotic congenital heart defects found in adults. Successful repair of TOF in childhood has spanned almost four decades, with many of those patients now returning as adults for reoperation.[114–123] These patients constitute the majority of adults presenting for surgical intervention for TOF. There are also adults with TOF who underwent palliative procedures in childhood but never underwent complete repair of the defect.[124] Occasionally, a patient with a well-balanced TOF defect and adequate pulmonary stenosis to protect their pulmonary vasculature will reach adulthood without any operative intervention.

Anatomy

TOF is classically defined by Fallot's four original pathologic findings: obstruction of right ventricular outflow, ventricular septal defect, overriding aorta, and right ventricular hypertrophy. The defect is the result of an anterior displacement of the infundibular septum during development, resulting in obstruction to right ventricular outflow and a malalignment ventricular septal defect. The aorta is displaced toward the ventricular septum, resulting in an overriding position, and hypertrophy of the right ventricle is a direct consequence of the outflow obstruction. The obstruction to pulmonary blood flow is often at multiple levels, which may include subvalvular, valvular, and supravalvular stenosis. The pulmonary valve is frequently malformed or bicuspid and the annulus is often small. Hypoplasia of the pulmonary arteries may be present if the obstruction to pulmonary blood flow is severe, and there is often stenosis of the branch pulmonary arteries, either primarily or secondary to shunts. Aortopulmonary collaterals arising from the aorta may coexist, as is commonly found in patients having pulmonary atresia with ventricular septal defect. Occasionally, cyanotic adults will present with unrepaired TOF and severe pulmonary obstruction, but adequate collateral pulmonary blood flow to allow survival beyond childhood.

Physiology

The pathophysiology of TOF results in restriction of pulmonary blood flow secondary to obstruction of right ventricular outflow and right-to-left shunting across the ventricular septal defect. The age at presentation and the degree of cyanosis vary directly with the degree of obstruction to pulmonary blood flow. Patients undergoing palliative shunt procedures in childhood to increase pulmonary blood flow may do quite well if the resulting oxygenation remains adequate with subsequent growth. These systemic-to-pulmonary shunts are often outgrown at an early age, requiring reintervention for additional palliation or more definitive repair. While currently the modified Blalock-Taussig shunt or central shunt is used for palliation in most patients, the Potts (ascending aorta-to-right pulmonary artery) and Waterston (descending aorta-to-left pulmonary artery) shunts were used in the past and may be found in some adult patients.

Indications for surgery

Residual VSDs, residual or recurrent obstruction to pulmonary blood flow, and severe pulmonary insufficiency with progressive right ventricular dilatation and dysfunction are all indications to consider reoperation in adults who have undergone previous complete repair of TOF. Patients who have previously undergone right ventricle-to-pulmonary artery conduit placement often present later in life with conduit stenosis requiring replacement. Patients who have had TOF repair in late childhood may have other sequelae that may have an impact on late reoperative surgery. The long-term volume load from a large shunt may produce permanent left ventricular dysfunction. The pulmonary vascular resistance may be elevated. Mild or even moderate aortic valve regurgitation is not uncommon due to dilatation of the aorta and may require aortic valve repair or replacement.

Pulmonary valve regurgitation is very common after repair of TOF, since approximately 70 to 80% are repaired with a transannular patch. Even though exercise capacity may be decreased, the vast majority of patients tolerate this well unless they have an additional residual VSD or pulmonary artery stenosis. In addition, some patients, without these associated residual defects, will slowly develop right ventricular dilatation and severe tricuspid regurgitation. This may progress for over 20 years, and patients are currently presenting late as they become symptomatic from combined pulmonary and tricuspid valve regurgitation. In view of the risks of sudden death and the progressive nature of right ventricular dysfunction, surgical intervention is recommended.

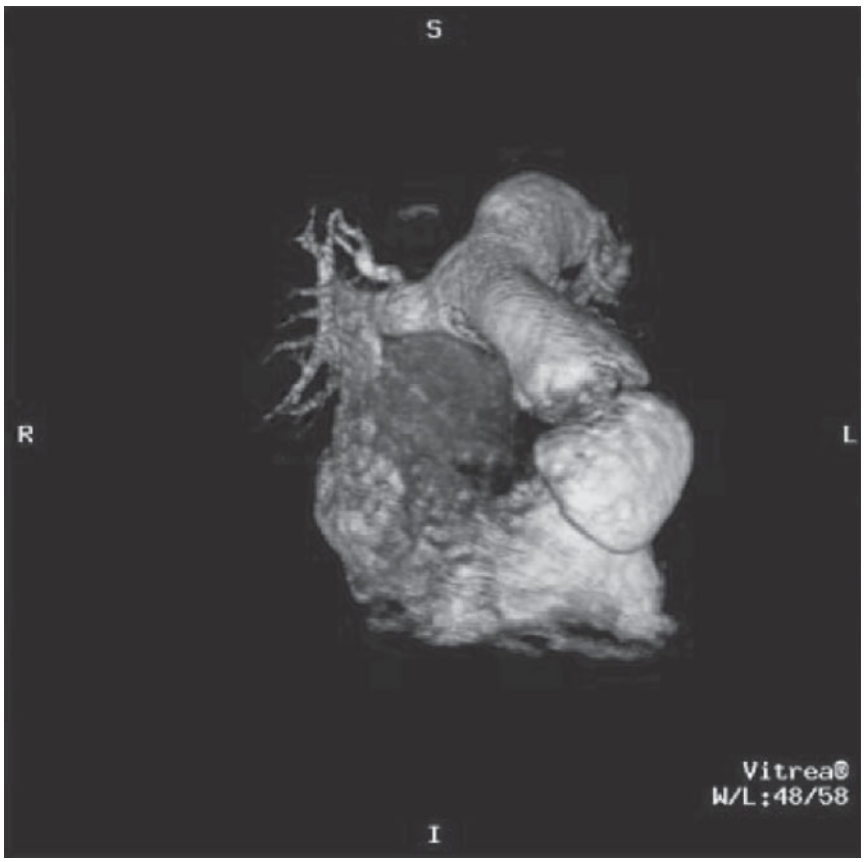

Figure 61-7. A three-dimensional magnetic resonance image documenting aneurysmal dilatation of the right ventricular outflow tract in a patient with previous repair of tetralogy of Fallot.

Aneurysms of the right ventricular outflow tract may occur following the use of an excessively large transannular pericardial patch with the initial repair (Fig. 61-7).

Such aneurysmal dilatation may progress, especially if there is associated right ventricular outflow tract obstruction.

Sudden death after TOF repair accounts for a significant number of late deaths. It usually occurs in patients who have had a right ventricular incision and have right ventricular dilatation combined with an elevated right ventricular pressure above 60 mm Hg.[125] All else being equal, a QRS duration of greater than 180 milliseconds is associated with an increased risk of sudden death, and a progressive increase in QRS duration is considered a factor in deciding on reoperation.[126] Any ventricular arrhythmias should be evaluated by electrophysiologic studies and focal pathways should be treated with catheter ablation. Pacemakers are required in fewer than 4% of patients late after TOF repair.[127] They may be indicated for sick sinus syndrome, the combination of right bundle-branch block with left anterior hemiblock, or the late onset of complete heart block.

Preoperative evaluation

The preoperative evaluation in adults with TOF must take into consideration the patient's previous operative interventions. In addition to chest radiography and electrocardiography, transthoracic or transesophageal echocardiography has become the fundamental diagnostic tool in most of these patients. Angiography is indicated to define specific hemodynamics such as the pulmonary vascular resistance and to define the pulmonary artery anatomy. Aortic and selective injections are performed to look for aorta-pulmonary collaterals. The coronary anatomy must be known, as 4 to 5% of TOF patients have an left anterior descending artery arising from the right coronary artery, which can be injured by a transannular incision. Adults over age 40 and those with risk factors for early coronary artery disease should undergo coronary angiography to evaluate the need for concomitant coronary bypass. Magnetic resonance imaging with angiography or computed tomography scans with three-dimensional reconstruction have proven valuable for defining the anatomy. In all patients with TOF, there should be an evaluation of the size and patency of the pulmonary trunk and its branches, the size of the pulmonary annulus, the stenosis and/or competency of the pulmonary valve, the proximal coronary artery location, and the presence of systemic-to-pulmonary artery collaterals. If there is a right ventricle-to-pulmonary artery conduit or an aneurysmal transannular patch present, magnetic resonance angiography or computed tomographic imaging studies should be used to evaluate the proximity of these structures to the sternum and to the midline site of the redo sternotomy. Preoperative electrophysiologic studies may be indicated if significant arrhythmias are identified.

Operative procedure

In most adults with TOF, bicaval cannulation is used, and myocardial protection involves both antegrade and retrograde cold blood cardioplegia followed by warm blood cardioplegia and warm blood reperfusion. Ventricular distension is avoided with venting of the left ventricle. Atrial septal defects should be sutured primarily or closed with a patch of native pericardium. Ventricular septal defects may be approached through the right atrium or through the right ventricular scar or outflow tract patch. A PTFE or glutaraldehyde-fixed pericardial patch may be used. The right ventricle is remodeled by resection of scar from the previous ventriculotomy and any aneurysmal tissue in the right ventricular outflow tract. The pulmonary valve is replaced, usually with an oversized porcine bioprosthetic valve seated below the native annulus in the right ventricular outflow tract (Fig. 61-8). A 27- or 29-mm porcine valve can usually be accommodated in all adults. A transannular hood of pericardium or PTFE is used to cover the porcine valve and establish continuity to the pulmonary artery. Homografts are used to replace previously inserted conduits (Fig. 61-9). The pulmonary homograft lasts longer than the aortic homograft but develops regurgitation earlier. The tricuspid valve can usually be repaired with an annuloplasty and rarely requires replacement. In some cases adherence of the septal leaflet to the VSD patch can be repaired by suturing it to the adjacent anterior and posterior leaflets.

Definitive procedures in adults may require takedown of previously placed shunts. Systemic-to-pulmonary artery type shunts should be controlled as soon as cardiopulmonary bypass is instituted. Takedown of a Waterston shunt is done from within the pericardium. The right pulmonary artery is mobilized. The aortic cannulation site for cardiopulmonary bypass is placed distally. When cardiopulmonary bypass is initiated, shunt flow is controlled with a clamp flush with the aorta, and the patient is cooled to 20°C. Cardioplegia is administered after aortic clamping. With the heart arrested and at low flow, the shunt clamp is released, and the anastomosis is excised from the aorta. This mobilizes the right pulmonary artery. The aorta is closed primarily. The incision in the right pulmonary artery is extended proximally and distally to relieve any stenoses. The right pulmonary artery is reconstructed with a pericardial or PTFE patch. Takedown of a Potts anastomosis usually requires a period of low flow or circulatory arrest.[128] The shunt is occluded by pressure on the left pulmonary artery while blood is cooled to below 20°C. With the head down, the left pulmonary artery is incised and opened under low flow so that the opening to the aorta can be occluded with a Hegar dilator. Under low flow or circulatory arrest, the aortic side is closed primarily, and the pulmonary artery is repaired with a pericardial patch (Fig. 61-10).

Takedown of a Blalock-Taussig shunt is usually achieved by dissection, ligation, and division of the shunt at the initiation of cardiopulmonary bypass.

Outcomes

Long-term results are well documented in patients who had complete repair of TOF in the late 1950s and early 1960s.[129–134] Actuarial survival ranges from 77 to 90% at between 20 and 30 years of follow-up. Late mortality from cardiac causes accounts for about two-thirds of all late deaths. Between 40 and 60% of these are sudden and presumed to be due to arrhythmias or to heart block. Other causes include right ventricular outflow abnormalities

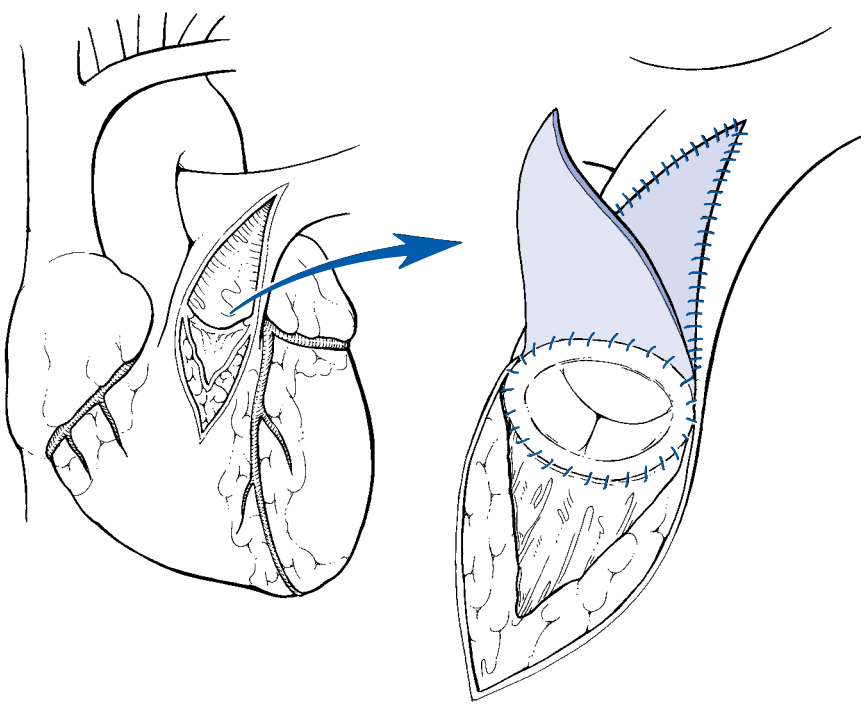

Figure 61-8. Pulmonary valve replacement with patch enlargement of the right ventricular outflow tract. The incision extends across the annulus and beyond the bifurcation to the left pulmonary artery. The outsized porcine valve (27 or 29 mm) is placed within the right ventricular outflow tract to accommodate the larger size valve.

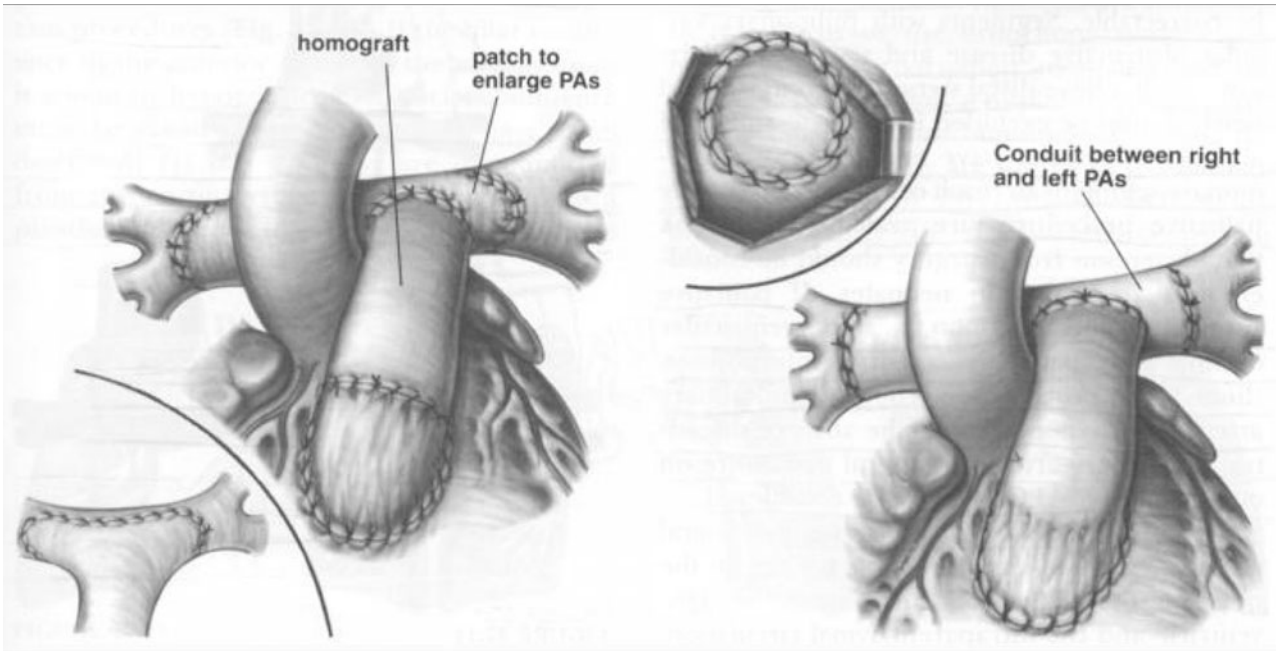

Figure 61-9. Homograft replacement of the right ventricular outflow tract with hood augmentation of the proximal anastomosis and patch enlargement of the branch pulmonary arteries. A reinforced PTFE conduit may be placed behind the aorta to re-establish continuity between the right and left pulmonary arteries.

(obstruction, pulmonary incompetence, and aneurysm) and congestive heart failure partly related to residual VSDs, which were reported in 1 to 8% of all operated patients in these early series. Currently, residual VSDs are expected in less than 5% of repairs for TOF.

The results of primary repair of TOF in adults are very good. Presbitero and colleagues reported an operative mortality of 2.8% in a series of 40 adults with TOF repairs.[129] There were two residual VSDs and two patients with residual right ventricular outflow tract obstruction. The results of

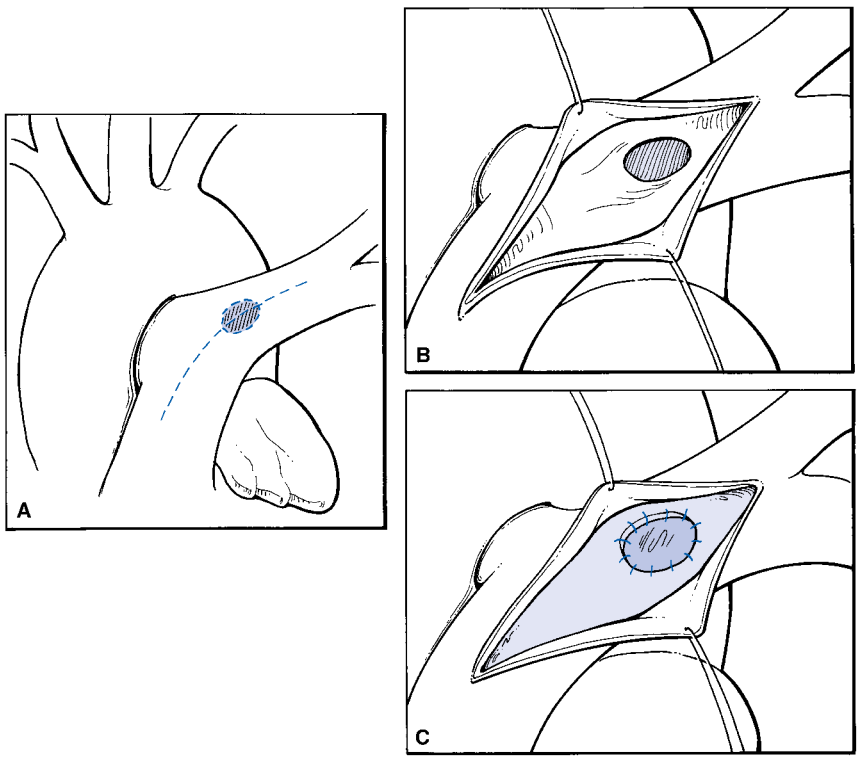

Figure 61-10. Patch repair of a Potts shunt anastomosis. The main and left pulmonary arteries are incised (A) to expose the opening (B) in the posterior proximal left pulmonary artery. The defect is closed with a pericardial or prosthetic patch (C).

reoperative surgery in adults with TOF are also generally good. Mortality ranges from 7 to 20%. Pome and associates reported an actuarial survival of 87% for 22 patients at 20-year follow-up for this particular cohort.[122] Eighty-nine percent of patients were NYHA class I, and only 1 patient (5.5%) was in class III. Two women in this series experienced uncomplicated pregnancy. In the series from the Mayo Clinic reported by Uretzky and coworkers, 5 patients (12%) had a second reoperation.[133]

At the University of California, Los Angeles, we have operated on adults with TOF ranging in age from 16 to 65 years. Most had patch repairs of the ventricular septum, insertion of a right ventricular outflow patch, and pulmonary valve replacement. The oldest TOF patient underwent primary repair and coronary artery bypass grafting. There was no mortality or significant morbidity in this series.

Pulmonary Atresia with Ventricular Septal Defect and Major Aorta-to-Pulmonary Artery Collaterals

Patients with this complex lesion sometimes survive to adulthood without surgery because of adequate pulmonary blood flow from collaterals. Others have shunts or unifocalization procedures or complete repairs.[135–140]

Anatomy

The true pulmonary arteries may be absent, hypoplastic, and continuous or discontinuous. The collaterals may be the dominant or only blood supply to the lung or supply only lesser areas of the lung. The VSD is subaortic and usually single. Depending on previous shunts, there may be stenoses in the proximal or distal pulmonary arteries. If repaired there may be a residual VSD, obstruction between the right ventricle and PA, and tricuspid valve regurgitation.

Physiology

Patients who have not had repair and who are considered "well-balanced" have a saturation of 80 to 84%. These patients with complete mixing have a left-to-right shunt of between 1.5:1 and 2:1. Therefore, they all have a volume-overloaded heart. The volume overload results in reduced exercise tolerance. Because of high flow and elevated pressure, they may have developed increased pulmonary vascular resistance in the area of some of the collaterals. The aorta and aortic valve tend to dilate, and 50% develop aortic valve regurgitation. Ventricular dilatation and dysfunction can also occur.

Preoperative evaluation

Echocardiography is used to exclude additional VSDs and to evaluate the aortic valve. Angiography is performed to delineate the collaterals and true pulmonary arteries, as well as to evaluate transpulmonary gradient, which may be high if there was uncontrolled large collateral flow hypertension. Such elevated gradients may preclude complete repair. Magnetic resonance angiograms with three-dimensional reconstruction give detailed pictures of the anatomy.

Indications for surgery

Patients with inadequate pulmonary blood flow are limited due to cyanosis and may require unifocalization if they have an adequate bed for future repair. If they do not, they may be candidates for a palliative shunt. Patients with excessive pulmonary blood flow and failure can also be treated by unifocalization with reduction of the total flow. The size of the shunt to the unifocalization is crucial to adjust flow to the pulmonary vasculature. After unifocalization on one side (Fig. 61-11), the opposite side is unifocalized 6 months to 1 year later (Fig. 61-12), followed 6 months to 1 year later by a complete repair (Fig. 61-13).

Shunted patients should be repaired if they have an adequate size pulmonary bed, unless they are inoperable because of high pulmonary vascular resistance or poor ventricular function. A residual VSD should be closed in previously repaired patients if the left-to-right shunt is 1.5:1 or above. Conduit or valve obstruction is reoperated when there are symptoms, or if the right ventricular pressure at rest is two-thirds to three-fourths of systemic pressure. If there is severe pulmonary valve regurgitation with right ventricular dilatation or tricuspid regurgitation, reoperation should be undertaken.

Staged surgical repair

The goal of surgical management of pulmonary atresia, ventricular septal defect, and multiple aorta-to-pulmonary collateral arteries is closing the ventricular septal defect and establishing continuity between the right ventricle and pulmonary artery. Ultimately, successful definitive repair requires an adequate pulmonary vascular bed, without which VSD closure and right ventricular-to-PA continuity will lead to right ventricular failure due to a prohibitively high pulmonary vascular resistance. Thus, all efforts during the operative staging are designed to maximize the size, distribution, and normal flow of the pulmonary arteries while preserving myocardial function.

Early palliative procedures in patients with excessive or inadequate pulmonary blood flow were designed to create a balanced pulmonary blood flow and encourage growth of the true pulmonary arteries.

Unifocalization procedures join the multifocal sources of pulmonary flow (true pulmonary arteries and aorta-to-pulmonary artery collaterals) into a single source that can ultimately be accessed in the anterior mediastinum via median sternotomy. The unifocalization procedure is performed through a posterolateral thoracotomy incision. A double-lumen endotracheal tube is employed, when possible, for large children and adults. Single-lung ventilation of the contralateral lung, when tolerated, greatly facilitates exposure. We prefer autologous pericardial tube unifocalization of aortopulmonary collaterals and true pulmonary arteries.

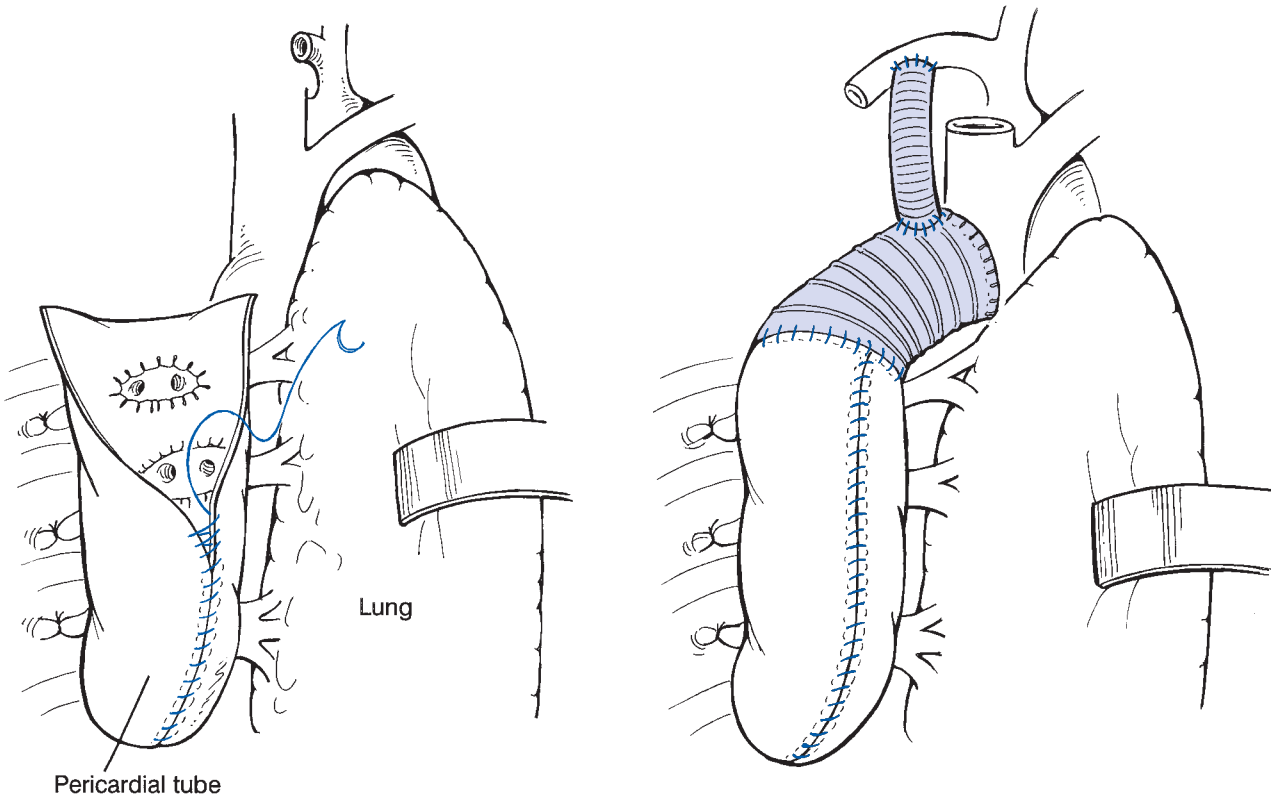

Figure 61-11. Unifocalization of the pulmonary artery blood supply to the right lung using a pericardial tube. Through a lateral thoracotomy a side-to-side anastomosis is created to each major collateral and an adjacent incision made in the autologous pericardium placed behind the lung. The pericardium is turned into a tube by suturing the edges and the collaterals are ligated proximal to the tube. The posteriorly lying tube is extended by a 16-mm PTFE graft to the anterior mediastinum. A 6-mm PTFE shunt is made between the subclavian artery and the 16-mm PTFE extension.

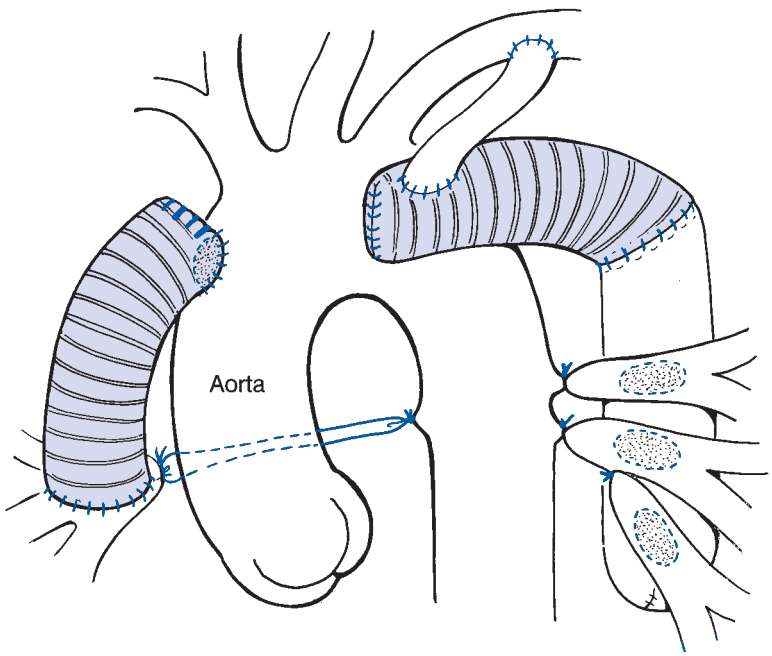

Figure 61-12. A 19-year-old patient previously underwent left pericardial tube unifocalization to three collaterals at age 18 years. On the right side there was a single collateral to a large pulmonary artery supplying the entire right lung. Right-sided unifocalization was achieved by ligating the collateral and placing a 20-mm PTFE graft from the right pulmonary artery to the ascending aorta, creating a central restrictive anastomosis.

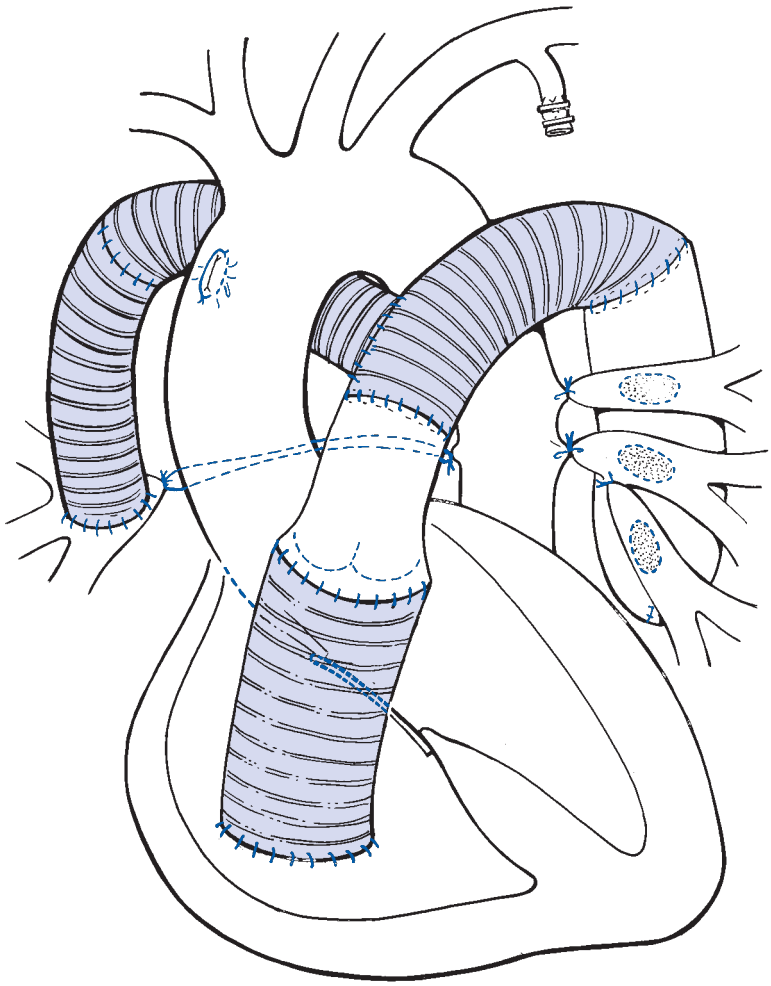

Figure 61-13. The complete repair performed 6 months after the right unifocalization shown in Fig. 61-12. The ventricular septal defect was closed. An aortic homograft conduit was placed between the right ventricle and the left unifocalization. The right unifocalization was then connected to the homograft by a 16-mm reinforced PTFE tube placed behind the aorta.

Finally, definitive repair in this disorder entails patch closure of the anterior malaligned ventricular septal defect and establishment of continuity between the right ventricle and the pulmonary arteries. All systemic-to-pulmonary artery shunts, including redundant collaterals and surgically created shunts, have been previously occluded or are readily accessible from the anterior mediastinum for occlusion at the time of definitive biventricular repair. Measurement of the ratio of right ventricle-to-left ventricle systolic pressure allows intraoperative assessment of the repair. A ratio of 0.75 or less immediately after termination of cardiopulmonary bypass is acceptable, and the ratio can be expected to decrease in the first few days after operation. Higher ratios suggest inadequate pulmonary runoff and will likely result in right ventricular failure. If the pressure on the right side is near systemic or suprasystemic, perforation of the ventricular septal defect patch may provide survival and reasonable palliation.

Outcomes

From 1983 through 2000, 105 children and adults have presented to our institution with pulmonary atresia, ventricular septal defect, and multiple aorta-to-pulmonary artery collaterals. All patients were subject to a strategy of staged repair. Sixty-four patients in this cohort underwent palliation in the newborn period at a median age of 1 week. Surgical palliation included systemic-to-pulmonary artery shunts, right ventricular outflow patches, and banding of aorta-to-pulmonary artery collaterals to reduce high pressure and flow. Interventional cardiac catheterization procedures were performed to promote growth of the pulmonary arteries as necessary.

Ninety-four patients underwent unifocalization at a median of 3.5 years (range, 6 months to 37 years). Fifty-eight (range, 1 to 34 years) of these 94 patients have proceeded to complete repair at a median of 7.2 years. Unifocalization was performed in 19 adults, and of this group, 8 patients have undergone uneventful complete repair. There was neither mortality nor significant morbidity in this group. At a median follow-up of 60 months there were a total of 18 deaths for a 17% early and late mortality rate. Survival after initial palliation was 92%, after unifocalization 91%, and after complete repair 91%. There were 36 reoperations (12%) and 16 patients required catheter-based interventions after surgery. The mean right ventricle-to-left ventricle pressure ratio was 0.46. Nearly all the survivors are asymptomatic and do not exhibit any signs of exercise intolerance.

Although there is some debate about whether a one-stage repair is preferable in neonates and children, patients

presenting as adults, with or without prior palliation, may be excellent candidates for the staged approach described above. We prefer a staged approach to one-stage correction in adults whose predominant blood supply to the lungs is from collaterals. In adults with a predominant blood supply from the true pulmonary arteries a one-stage repair may be utilized. The strategy of staged repair for patients with tetralogy of Fallot with major aorto pulmonary collaterals provides good functional results.

The mortality rate and requirements for postoperative interventional cardiac catheterization with this approach are lower than published reports of single-stage repair.

As patients age and mature they will require reoperations to replace right ventricle-to-pulmonary artery homografts and degenerative bioprostheses in the pulmonary position. Long-standing pressure and volume load on the right ventricle will lead to tricuspid regurgitation and right atrial enlargement that may predispose some patients to atrial arrhythmias.

Late Reoperations for Transposition of the Great Arteries

Anatomy and natural history

Dextraposed transposition of the great arteries is characterized by atrioventricular concordance and associated ventriculoarterial discordance. Prior to the introduction of the arterial switch procedure in 1982, the Mustard and Senning procedures were the standard operations for dextraposed transposition. In the Mustard procedure, a pericardial baffle was used to redirect the systemic and pulmonary venous return. In the Senning procedure, the atrial septum and wall were used for the baffle. This allowed deoxygenated blood to be pumped to the pulmonary circulation and the oxygenated blood to be pumped to the systemic circulation. As a consequence of these operations, such patients have the morphologic right ventricle acting as the systemic ventricle, and the natural history of such anatomy is well documented. There is about 70 to 80% survival at 20 years; 10% of patients have symptomatic right ventricular dysfunction, and about 60% have dysfunction that becomes evident at exercise testing. Additionally, atrial arrhythmias are common, and many patients are in junctional rhythm at 10 years of follow-up. With either procedure, baffle obstruction can lead to a high incidence of vena caval obstruction or pulmonary venous obstruction requiring reoperation.[141,142] Eventual morphologic right ventricular failure in these patients will require either transplantation or a staged procedure with left ventricular reconditioning and arterial switch.

Sudden death has been identified as the most common cause of mortality in patients having undergone an atrial switch procedure.[143] Most sudden death events occurred during exercise. Predictors of sudden death were found to be documented atrial fibrillation/flutter and the presence of symptomatic arrhythmias or heart failure. Electrocardiogram, chest x-ray, and Holter monitoring were not predictive.

Preoperative evaluation

Transthoracic or transesophageal echocardiography usually delineates the site of systemic or pulmonary venous obstruction, ventricular function, and valvular regurgitation. In some cases angiography is also required. Magnetic resonance imaging has become a sensitive tool for assessing ventricular function and can be used to follow patients undergoing ventricular retraining. This allows for a rapid, noninvasive assessment of ventricular function during sequential banding so that the band can be loosened in the face of left ventricular failure.[144]

Operative procedure

Reoperation for obstruction of either systemic veins or pulmonary veins can almost always be accomplished by incision of the site of obstruction and patching using a pericardial patch when it is available. Usually, with repair of the caval part of the baffle, the functional left atrium is also enlarged.

For patients who present with right ventricular dysfunction and tricuspid valve regurgitation, the choice of therapy is more complex. If the major problem is tricuspid valve regurgitation in the presence of relatively well-preserved right ventricular function, we prefer to repair or replace the tricuspid valve. The results of tricuspid valve repair or replacement in suitable patients are generally good. Care must be taken to avoid conduction tissue that is very vulnerable at the junction of the septal and anterior leaflets. If right ventricular function is significantly depressed, the left ventricular function and the left ventricular outflow tract (LVOT) and pulmonic valve are evaluated. If left ventricular function is good and there is no fixed LVOT obstruction or pulmonic stenosis, the patient may be considered for left ventricle preparation and the arterial switch procedure. Preparation of the left ventricle requires PA banding to a pressure of 60 to 70% of systemic pressures initially and then delayed rebanding to systemic pressures. It should be noted that retraining the left ventricle in the mature heart is a longer process than in the neonate, and that there is less margin for error when placing a band in a fully septated heart. Six months to a year may be required to achieve this and to obtain a normal left ventricular wall thickness.

Once this is achieved, the arterial switch operation may be performed. The atrial baffle is removed, and a new atrial septum is constructed in the anatomic position (Fig. 61-14). In adults, left ventricle preparation by successive tightening of a pulmonary artery band can be hazardous and ultimately unsuccessful with the onset of left ventricular failure. The outcomes from this approach have been quite variable and the overall experience is limited. If significant left ventricular dysfunction or fixed LVOT obstruction is identified, the patient may be considered for heart transplantation.

Results

The outcomes from reoperations to repair baffle obstructions in patients with previous Mustard and Senning procedures are quite good if the systemic right ventricular function is

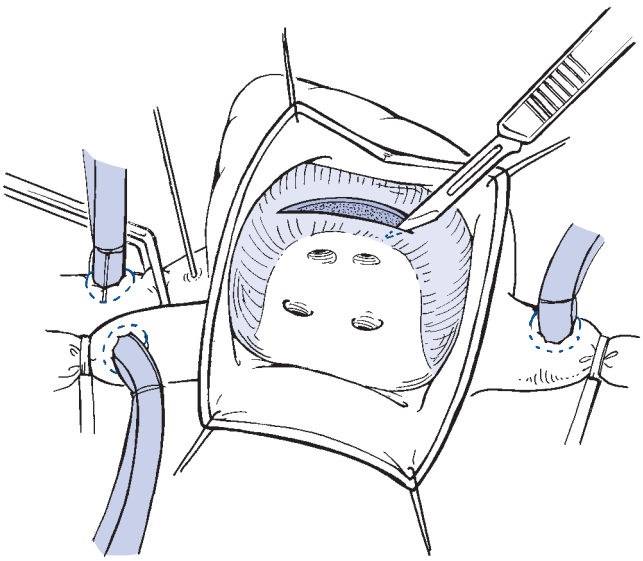

Figure 61-14. Takedown of a Mustard baffle. After opening the anatomic right (functional left) atrium, the four pulmonary veins surrounded on three sides by the Mustard baffle are visible. The illustrated incision enters the atrial chamber that receives systemic venous blood, and when completed will expose both caval-atrial junctions and the four pulmonary veins entering a common atrial chamber. For venous return to the perfusion circuit, the superior and inferior venae cavae can be cannulated directly or via peripheral venous cannulas.

preserved.[141,142,145–157] Generally adolescents and adults are highly variable in their response to a staged conversion to an arterial switch procedure.[148,153] This is a critical point since few patients have undergone atrial switch procedures for transposition in the last 20 years, and most new patients will be in the third decade of life and later. While no age cutoff has been identified, attempts to identify risk factors indicate that complex coronary anatomy, severe morphologic right ventricular failure, and supraventricular arrhythmias result in worse outcomes. In these patients cardiac transplantation as an initial therapy may be the preferred course.

Single Ventricle

Anatomy

Single ventricle is a term that describes various forms of congenital heart disease characterized by malformation and hypoplasia of one ventricular chamber, resulting in a single functioning ventricle. The specific defects include tricuspid atresia, mitral atresia, unbalanced atrioventricular canal defects, severe forms of pulmonary atresia with intact ventricular septum, hypoplastic left heart syndrome, double inlet left and right ventricles, and absent ventricular septum (Holmes heart). Malposition or transposition of the great arteries is present in many of these patients.

Physiology

All of these patients have single-ventricle physiology with initial mixing of the systemic oxygenated blood and the venous deoxygenated blood within the ventricle. Pulmonary blood flow is supplied by either a true pulmonary artery (PA), a patent ductus arteriosus, systemic-to-pulmonary collaterals, or a surgical shunt. The PA may have pulmonary or subpulmonary stenosis or may have been surgically banded. With complete intracardiac mixing, pulmonary blood flow must be approximately 1.5 times the systemic blood flow (Qp:Qs = 1.5), to achieve a systemic arterial oxygen saturation of 80 to 85%. This increased pulmonary blood flow results in a volume overload on the ventricle and the aorta. The clinical manifestations in patients with any form of single ventricle are directly related to the pulmonary blood flow and pulmonary artery pressure. These will be determined by the presence or absence of pulmonary stenosis and the pulmonary vascular resistance. Of note, over half of these patients will have some form of pulmonary stenosis or atresia.

Indications for surgery

There are a few patients reported in the literature with single ventricle who have survived to adulthood without surgical intervention.[23] Most patients will require intervention because of too much pulmonary blood flow, causing heart failure, or too little pulmonary blood flow, causing cyanosis. Patients are stratified according to their pulmonary artery pressure, pulmonary vascular resistance (PVR), ventricular function, and anatomic complexity into low-, medium-, and high-risk candidates for a Fontan procedure. In medium- and high-risk patients with elevated PA pressure, PVR, and impaired ventricular function, a bidirectional Glenn shunt is performed as a first stage to a Fontan procedure or as long-term palliation until a heart transplant may be considered.

Glenn shunt

PHYSIOLOGY: By connecting the end of the superior vena cava (SVC) to the superior aspect of the right PA, about one-third of the systemic venous return is diverted to the lungs for oxygenation. This is a more efficient shunt than a systemic-to-PA shunt and does not cause a volume overload on the ventricle. It is therefore better tolerated in the presence of impaired ventricular function. Provided the SVC pressure is 18 mm Hg or less, the elevation in SVC pressure is well tolerated.

OPERATIVE PROCEDURE: As shown in Fig. 61-15, the Glenn shunt is performed without cardiopulmonary bypass in most patients by using an SVC-to-PA shunt. If additional procedures are required, such as the relief of subaortic obstruction, atrial septectomy, or atrioventricular valve repair, an open procedure on cardiopulmonary bypass is required. An additional source of pulmonary blood flow aims for a pulmonary-to-systemic blood flow ratio of 1 to 1.3, depending on the PVR. Either a banded pulmonary artery or a small systemic-to-PA shunt is used. The additional source of blood flow improves oxygenation at rest and with exercise, and may prevent late arteriovenous fistula development in the lungs.

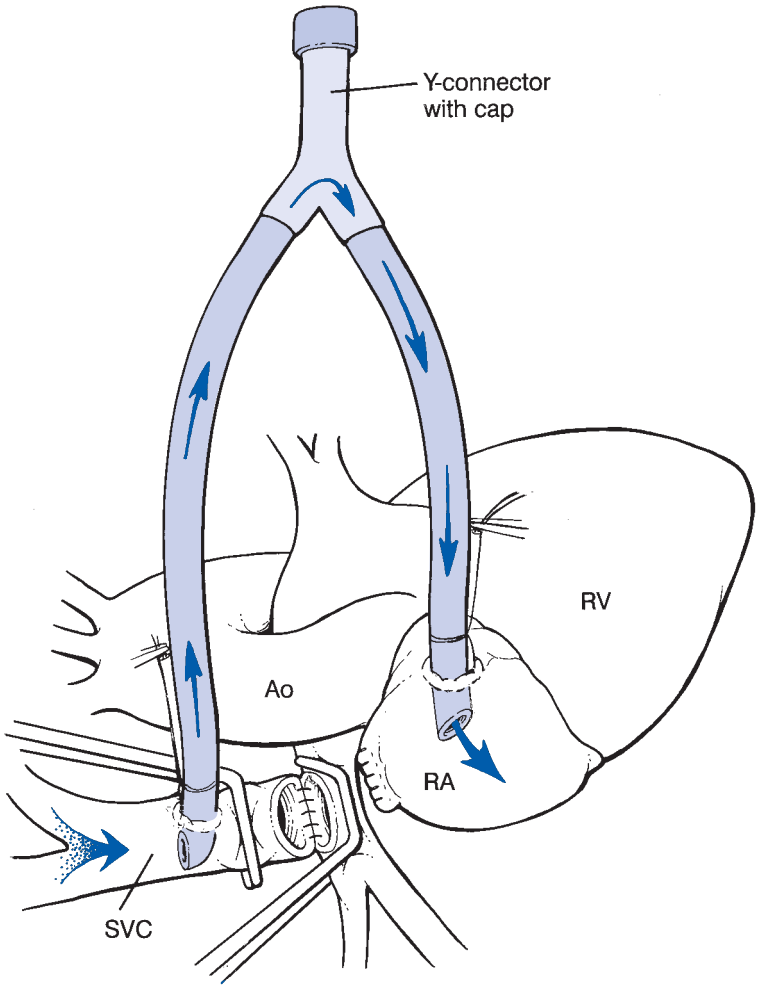

Figure 61-15. Creation of a bidirectional Glenn shunt (superior vena cava to right pulmonary artery) using an extracorporeal shunt (with systemic heparin) to maintain superior vena caval flow into the right atrium. A de-airing chamber and port are needed to prevent air entry into the heart.

OUTCOMES: The early mortality for an isolated Glenn shunt is low (1 to 4%), depending on factors such as the PVR and ventricular function.[158–161] Additional intracardiac procedures increase the risk. In the long term the Glenn shunt slowly loses its effectiveness due to the development of venous collaterals from the superior vena cava to the inferior vena cava.[158,160,161] These can be coil embolized by catheter technique. If there is no additional source of pulmonary blood flow, there is usually severe desaturation on exercise and systemic-to-PA collaterals develop over time. Intrapulmonary arteriovenous fistula can also develop in this situation, resulting in desaturation. In patients with no additional source of pulmonary blood flow and with severely impaired ventricular function, oxygenation can be improved with a controlled shunt by performing an axillary artery-to-vein fistula.[162]

Modified Fontan procedure

INDICATIONS: Because of the limited palliation provided by the Glenn shunt, patients who meet hemodynamic criteria should be considered for a Fontan procedure. The criteria include good ventricular function, ejection fraction 50% or higher, normal or close-to-normal PVR, PA pressure <20 mm Hg, and no additional severe hemodynamic lesions that require prior attention, such as residual coarctation of the aorta, severe subaortic obstruction, or severe atrioventricular valve regurgitation. Generally, correctable lesions should be addressed at the time of the Glenn shunt or before completion of the Fontan procedure.

OPERATIVE PROCEDURE: Many different modifications of the Fontan procedure have evolved to connect both the superior and inferior vena caval blood to the pulmonary arteries. Currently, the two most commonly performed operations are the lateral tunnel Fontan (Fig. 61-16) and the extracardiac Fontan (Fig. 61-17). The lateral tunnel has the advantage of not requiring warfarin anticoagulation in the majority of cases, and a fenestration can be easily included in the procedure. The extracardiac Fontan can be done without arresting the heart and is therefore associated with improved postoperative ventricular function. It can be fenestrated with a separate small shunt from the conduit to the atrium. Treatment with warfarin anticoagulation is indicated for at least 1 year and possibly for life to reduce the incidence of conduit thrombus. Because of the extensive atrial suture lines, arrhythmias and sick sinus syndrome may be more common with the lateral tunnel Fontan. A newer modification of the

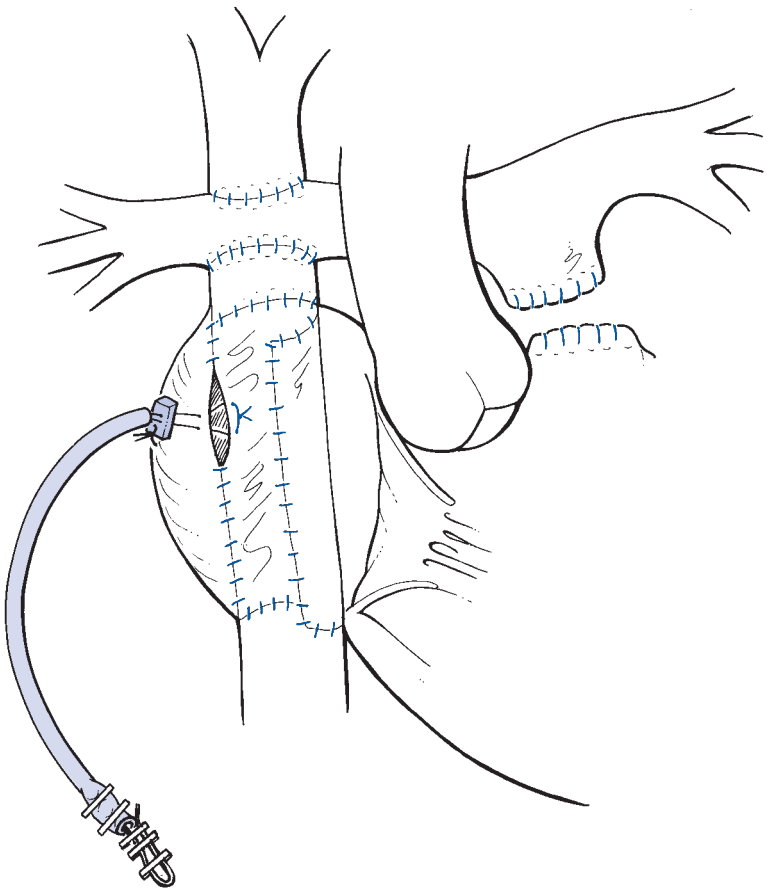

Figure 61-16. A lateral tunnel Fontan operation enlarges the right atrium and directs inferior caval flow into the right pulmonary artery using an end-to-side anastomosis to provide bidirectional flow into both pulmonary arteries. A snared purse-string suture adjusts the size of an atrial septal opening that is used to decompress caval pressures and to control the amount of right-to-left shunting.

extracardiac Fontan using bovine pericardium and the native atrial wall has recently been reported.[1]

OUTCOMES: The early mortality of the Fontan procedure in adults depends on selection of patients and the presence of risk factors. Reported series have an early mortality of 5%.[163,9,21] Fontan patients may be candidates for pacemakers (10%) and reoperations for valvular (5%) and obstructive problems, and may require transplantation for deteriorating ventricular function.[164] Protein-losing enteropathy can occur in 5 to 10% of patients.[163,165,166]

Late Reoperations after Modified and Classic Fontan Procedures

Surgical reintervention following a Fontan procedure may be indicated for arrhythmias, cyanosis, exercise intolerance, protein-losing enteropathy, atrioventricular valve regurgitation, or failing Fontan circulation. Surgical procedures include pacemaker insertion, revision of Fontan, fenestration of Fontan, Maze procedure, repair or replacement of the atrioventricular valve, and heart transplantation.[8] Patients who have had a right atrial-to-PA connection may develop massive right atrial enlargement.[164,165,166] This can eventually result in atrial arrhythmias, thrombus formation, and thromboembolism. Supraventricular arrhythmias as well as atrioventricular node dysfunction are common, and preoperative evaluation by an electrophysiologist is usually indicated. When the right atrium is enlarged, warfarin anticoagulation is indicated. Such patients should be considered for reoperation with conversion to either a lateral tunnel or to an extracardiac conduit with reduction of the enlarged right atrium, and a right-sided Maze procedure has resulted in improved NYHA functional class and reduced incidence of arrhythmias.[7,22,24,25,167] Many will require a permanent pacemaker. If they do not meet the criteria for Fontan conversion, they could be considered candidates for a heart transplant.

The long-term results after modified Fontan procedures have shown that a significant number of patients require late reoperation. The highest incidence was for patients in whom a valved conduit was used.[168,169] Older age at operation remains a risk factor for late death after the Fontan procedure. Revision of the atrioventricular valve closure in double-inlet ventricles or repair of the atrioventricular valve in tricuspid atresia is needed in more than 5% of patients. Adult patients with systemic single right ventricles have significant risk for ventricular dysfunction with congestive heart failure and increased mortality.[26] In addition to arrhythmias and reoperations, adult Fontan patients may also suffer from clinically silent pulmonary emboli and thromboembolic events that may reduce the quality of life and have severe long-term consequences.[10,27]

Protein-losing enteropathy occurs in about 10% of Fontan patients. It is characterized by a low serum albumin level, persistent ascites, and peripheral edema with or without

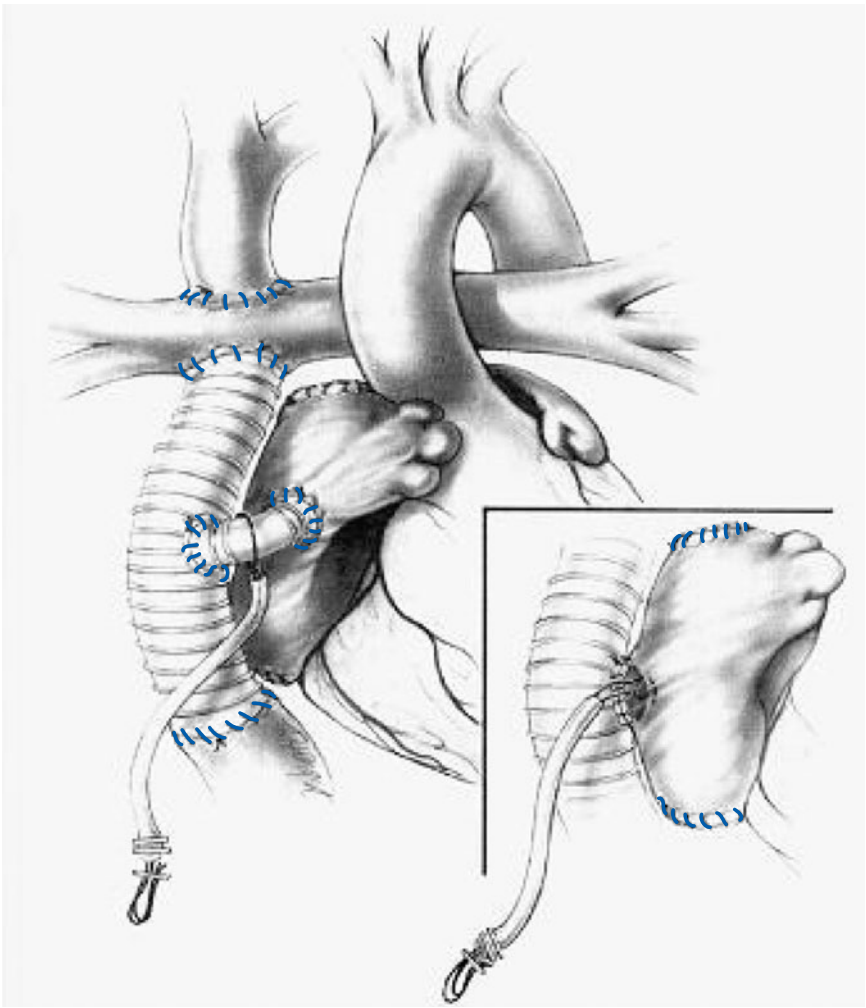

Figure 61-17. Extracardiac Fontan with adjustable conduit-to-atrial connection.

diarrhea. It may be associated with a mortality up to 20%.[163,164,166] It occurs more frequently in patients with heterotaxia or polysplenic syndromes, as well as in those with elevated pulmonary vascular resistance or abnormal systemic venous drainage. Some of these patients can be helped by transcatheter fenestration of the atrial septum or Fontan conduit with stenting.[2] If they do not meet criteria for a Fontan revision, they should be evaluated for transplantation.[170–177] In many patients, protein-losing enteropathy will resolve following successful heart transplantation.

Ebstein Anomaly

Ebstein malformation is a rare congenital cardiac defect accounting for less than 1% of all congenital heart disease. The primary pathologic finding is an abnormal development of the tricuspid valve marked by a downward displacement of the septal and posterior leaflets into the cavity of the right ventricle. This defect is characterized by a remarkable morphologic variability and a broad spectrum of clinical presentations. Consequently, the diagnosis may be made in symptomatic newborn infants, in children, or in adults.[178,179] The degree of tricuspid regurgitation varies depending on the anatomic abnormality. If there is an atrial septal defect, patients may present with cyanosis. If the atrial septum is intact, they may present with cardiomegaly, right-sided heart failure, or arrhythmias. Those patients with atrial or ventricular arrhythmias may present with episodes of syncope, near syncope, or recurrent palpitations.

Paroxysmal supraventricular arrhythmias occur in 25 to 40% of patients and are most often found in teenagers or young adults.[180] Aberrant right atrial to right ventricular tracts resulting in tachycardia (Wolff-Parkinson-White syndrome) occur in 10 to 18% of patients.[181] Sudden death due to ventricular arrhythmias may occur in as many as 5 to 7% of patients. Likewise, patients with mild manifestations of the Ebstein malformation may present as late as the third or fourth decade of life with complaints of palpitations or mild exercise intolerance.[182,183] While some patients may reach advanced age without serious clinical manifestations, most will eventually develop significant symptoms.[184] The most common causes of death are congestive heart failure, severe hypoxia, and cardiac arrhythmias.[185]

Anatomy

Ebstein malformation is defined by a downward displacement of the annular attachments of the septal and posterior

leaflets of the tricuspid valve into the inlet portion of the right ventricle.[186] This downward displacement of the leaflets reduces the distal chamber of the right ventricle, leaving part of the ventricle above the valve as an extension of the right atrium. The atrialized right ventricle is variable in size and thickness, depending on the extent of downward displacement of the leaflets. The entire wall of the right ventricle, both above and below the tricuspid valve, is often thin, dilated, and dysfunctional. In most patients, annular dilatation and malformation of the leaflets result in moderate to severe insufficiency of the tricuspid valve. It usually occurs in the pulmonary right ventricle, but can occur in the systemic right ventricle in patients with corrected transposition of the great arteries. An atrial septal defect or patent foramen ovale is present in more than 50% of patients, allowing predominantly right-to-left shunting at the atrial level.

Physiology

In patients with Ebstein malformation, the tricuspid valve is incompetent, but the degree varies depending on the anatomic features. In addition, there is some degree of functional impairment of the right ventricle. The atrialized right ventricle moves paradoxically with right atrial and right ventricular contractions. The net effect is reduced forward blood flow through the right ventricle and pulmonary arteries. The impaired filling of the functional right ventricle and the incompetence of the tricuspid valve both result in systemic venous hypertension. The right atrium and the atrialized right ventricle become dilated, often to extreme degrees. In patients with atrial septal defects, right-to-left shunting occurs, resulting in cyanosis. Both atrial and ventricular arrhythmias may contribute to impaired right ventricular function.

Although the primary pathology involves the right ventricle, patients with Ebstein malformation may also demonstrate abnormal left ventricular geometry and function. The severity of left ventricular dysfunction is associated with the degree of displacement of the tricuspid valve, the size and dysfunction of the right ventricle, and the severity of paradoxical motion of the interventricular septum.

Preoperative evaluation

On a chest radiograph, the right border of the heart in the area of the right atrium is enlarged and there may be massive cardiomegaly. Typically, the shadow of the great vessels is narrow due to a small aorta and main pulmonary artery. Right atrial and right ventricular enlargement produce a globular shape to the heart shadow. The apical region of the left ventricle may be elevated from the diaphragm, as seen in right ventricular enlargement. Pulmonary vascularity may range from normal to significantly decreased in the presence of an ASD. A cardiothoracic ratio greater than 0.65 has been shown to be a predictor of sudden death and is considered by some to be an indication for surgery.

Echocardiography has evolved as the primary diagnostic tool for patients with Ebstein malformation. The preoperative echocardiogram is helpful in predicting the ability to repair the valve. Echocardiography can define the morphology of the tricuspid valve and the specific abnormalities of the leaflets. Of the greatest importance are the length and mobility of the anterior leaflet. In addition, the function, thickness, and size of the right and left ventricles can be assessed. Coexisting cardiac lesions can also be identified. Color flow Doppler allows a better assessment of tricuspid valve incompetence and the degree of shunting at the atrial level.[187] If echocardiography is inadequate, magnetic resonance angiography imaging with three-dimensional reconstruction is useful for diagnostic purposes. Diagnostic cardiac catheterization should be avoided, as it is usually unnecessary and can result in arrhythmias. Currently, cardiac catheterization is reserved for patients with associated cardiac defects, previous shunt placements, possible pulmonary artery stenosis, or possible coronary artery disease. Therapeutic catheterization may be performed in older patients for identification and ablation of accessory conduction pathways prior to surgical intervention.

Indications for surgery

The indications for surgical intervention in patients with Ebstein malformation include the following: functional NYHA class III or IV symptoms; significant or progressive cyanosis; decline in exercise tolerance; severe cardiomegaly (cardiothoracic ratio >0.65); associated cardiac anomalies (including right ventricular outflow tract obstruction); refractory atrial or ventricular arrhythmias; and a history of paradoxical embolus. With the improved outcomes and a greater ability to repair the valve, there is a trend to perform early repair in the presence of severe tricuspid regurgitation and atrial enlargement.

Operative procedure

The goals of surgical intervention in patients with Ebstein malformation are to increase pulmonary blood flow, minimize tricuspid insufficiency, reduce or eliminate right-to-left shunting, optimize right ventricular function, and reduce or eliminate arrhythmias. Ideally, the tricuspid valve can be repaired, which may avoid valve replacement with a bioprosthetic valve and the need for future valve replacements. Patients with preoperative Wolff-Parkinson-White syndrome are treated by catheter ablation prior to the surgery.

If the anterior leaflet is adequate in size and is not extensively bound down by muscular attachments, repair is almost always possible. Two main techniques of repair have been described. Danielson and colleagues were the first to demonstrate the ability to repair these valves and avoid replacement.[188] Repair includes plication of the atrialized right ventricle back to the true annulus and an annuloplasty (Fig. 61-18).

Carpentier and associates described a technique in which the atrialized right ventricle is plicated perpendicular to the valve annulus toward the apex of the heart.[189] The displaced leaflets are detached from the right ventricle at their

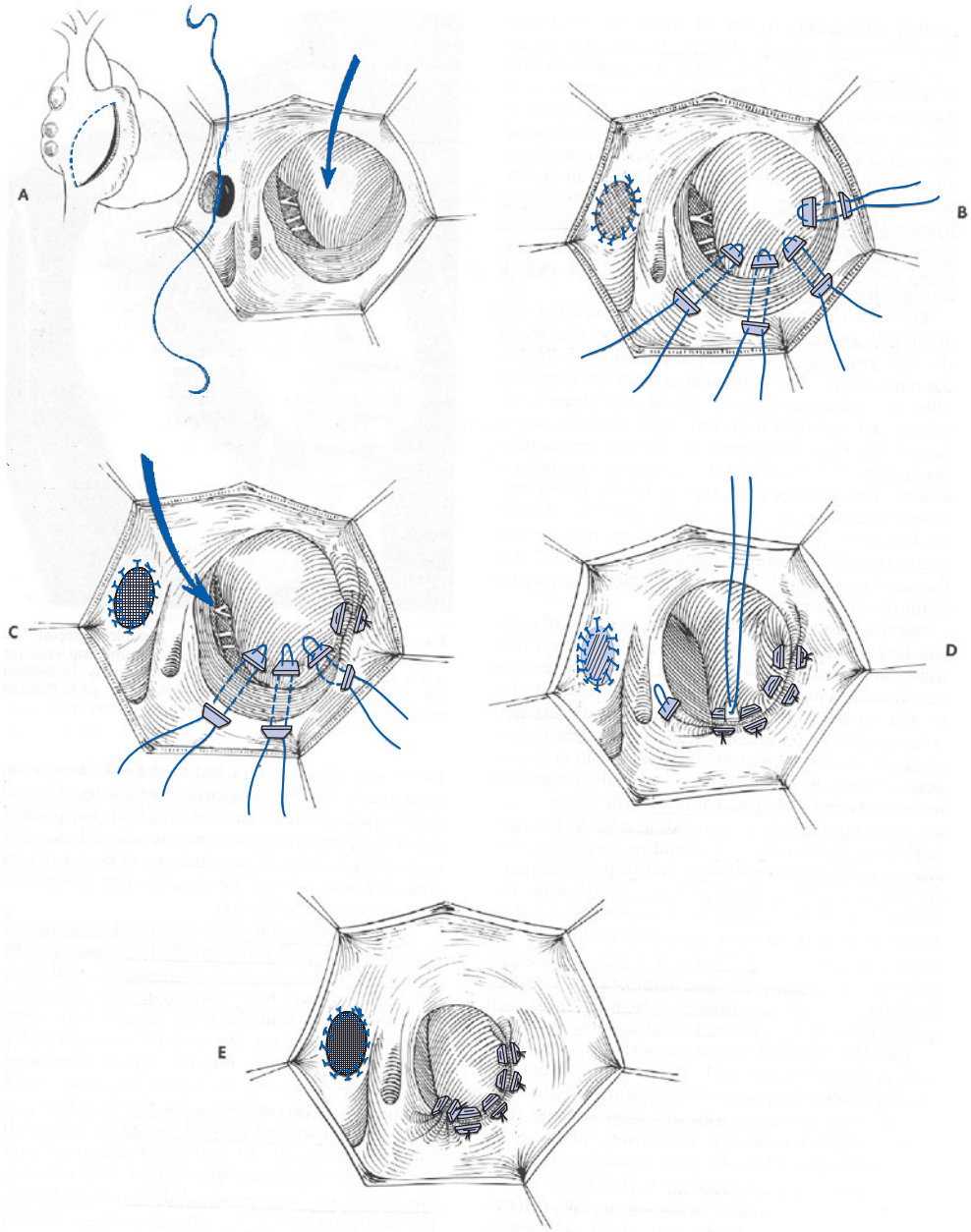

Figure 61-18. Danielson's repair of the tricuspid valve in Ebstein anomaly.

base and attached to the true annulus (Fig. 61-19). We perform an annuloplasty using a glutaraldehyde-fixed strip of pericardium. The redundant right atrium wall and appendage are excised, and the ASD is closed. In patients with a large preoperative right-to-left shunt and a thinned-out underdeveloped right ventricle, a snare-controlled adjustable atrial septal defect may be used to allow continued controlled right-to-left shunting until the right ventricle recovers. The ASD can then be closed using the snare, which is exposed under local anesthesia. In addition, electrophysiologic mapping for localization of accessory pathways may be performed in patients with arrhythmias.

A recently described technique of posterior annular plication without plication of the atrialized right ventricle or repositioning the tricuspid valve has been successful in non-neonatal patients.[2] Further experience and follow-up will be needed to determine the usefulness and efficacy of this type of tricuspid repair in adults with Ebstein anomaly.

For tricuspid valve replacement, we prefer to use a porcine bioprosthetic valve. In the absence of atrial arrhythmias or severe atrial wall thickening, this allows anticoagulation with aspirin only. Generally, tissue valves are preferred in the tricuspid position because of the risk of thrombosis of a right-sided mechanical valve in a low-pressure setting.

The right atrial Maze procedure is a modification of the Maze procedure and has been used to treat atrial arrhythmias in patients with Ebstein malformation. This procedure may reduce or eliminate atrial arrhythmias by preventing reentry conduction at the atrial level (Fig. 61-20).

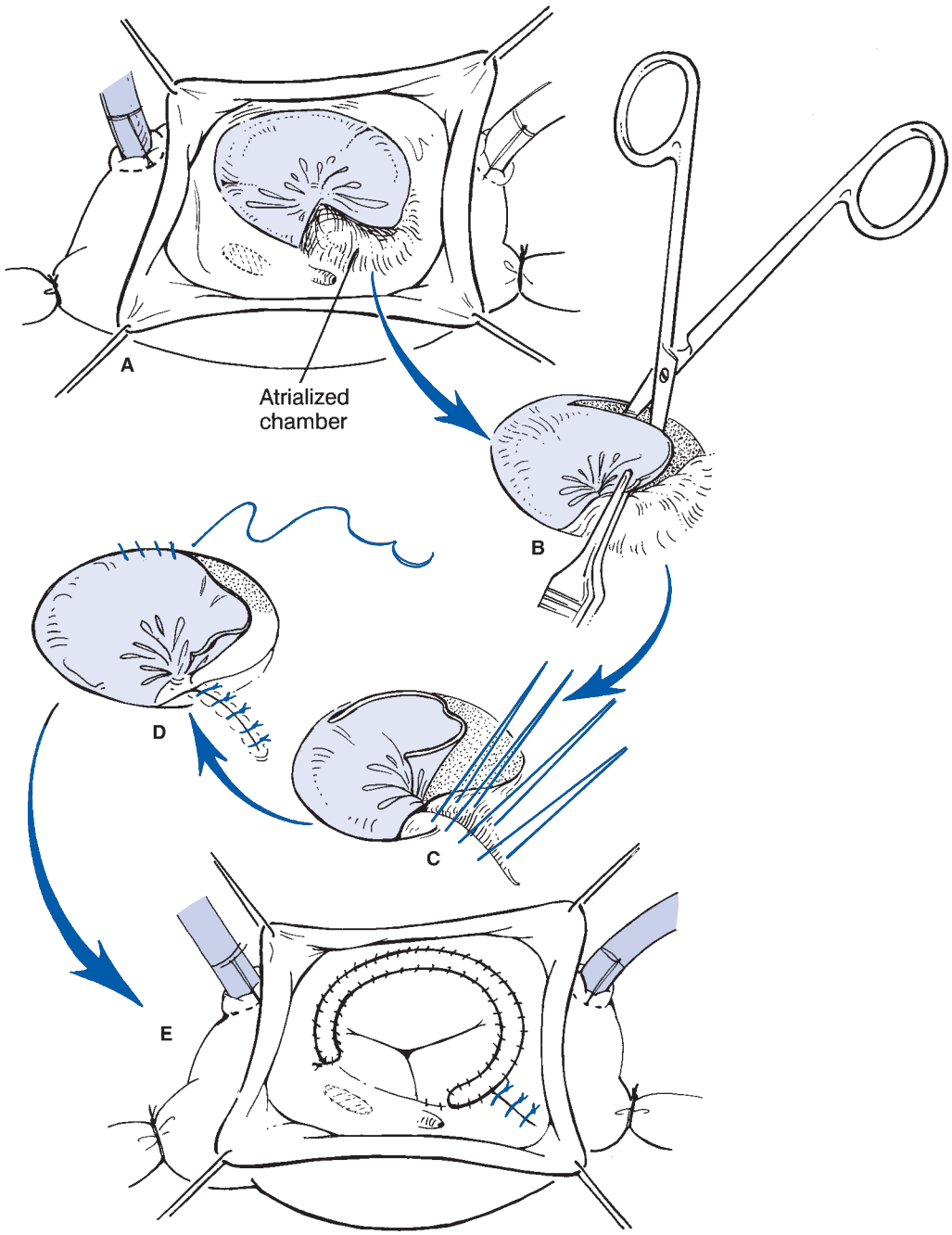

Figure 61-19. Carpentier's repair of the tricuspid valve in Ebstein anomaly.

Outcomes

Results of surgical repair for Ebstein anomaly in children and adults continue to improve. Patients who present at a younger age with associated defects or severe symptoms have a worse prognosis. Those patients presenting in early adulthood for surgical repair have a much better prognosis.

Danielson and colleagues at the Mayo Clinic currently have a surgical experience of more than 500 patients with Ebstein malformation.[190] The data have been analyzed for the first 312 patients who had surgical intervention dating back to 1972. The ages in this series range from 9 months to 71 years, with a mean age of 20.7 years. There were no neonates in this group. In 43% a tricuspid valve repair was successful, and in 53% a bioprosthesis was used to replace the tricuspid valve. Approximately 4% of patients underwent a Fontan reconstruction or other procedures. There were 20 hospital deaths (6.4% early mortality) in this series. Forty-four patients had accessory conduction pathways (Wolff-Parkinson-White syndrome) and underwent successful pathway ablation as part of their repair. Fifteen patients underwent right-sided Maze procedures for control of atrial dysrhythmias and four underwent ablation of the atrioventricular

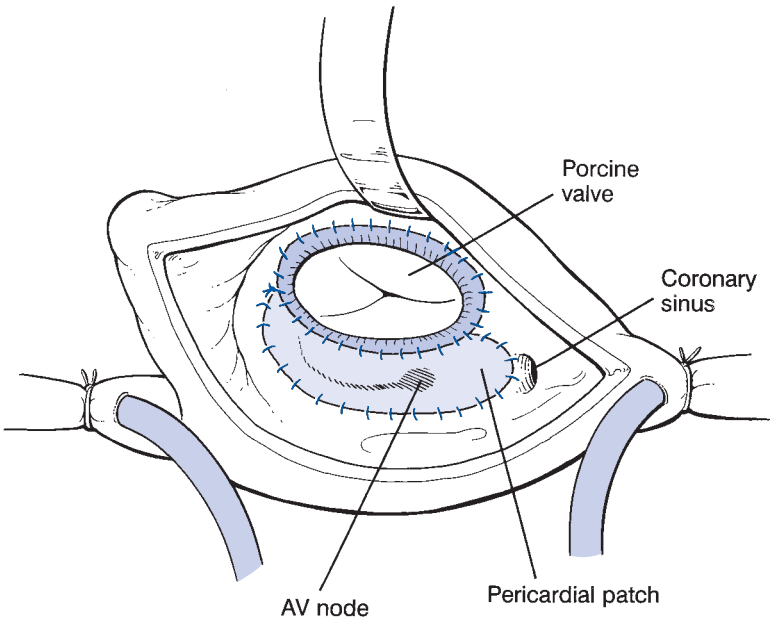

Figure 61-20. Injury to the conduction system may be avoided during tricuspid valve replacement by suturing a triangular patch of pericardium over the atrioventricular (AV) node and triangle of Koch.

node for re-entry tachycardia. There were 24 late deaths (7.3%). Seventeen of the 135 patients (12.6%) who underwent valve repair required reoperation for valve regurgitation 1.5 to 18 years later (mean, 8.7 years). Eight bioprosthetic valves required replacement 1 to 16 years after implantation. Follow-up of those patients evaluated more than a year after operation determined that 93% were in NYHA functional class I or II.

Other authors have recently reported similar results using different repair techniques in a smaller series of patients.[191,192] The addition of a right atrial Maze procedure to the repair is often successful in reducing or eliminating atrial arrhythmias. Furthermore, the addition of epicardial mapping and intraoperative ablation of accessory pathways at the time of repair has also been successful.[1,7,193,194] The durability of a porcine bioprosthesis for tricuspid valve replacement in these patients has been quite favorable, with freedom from reoperation of 97% at 5 years and 81% at 15 years.[195]

Heart Transplantation

Adults with congenital heart disease may not be amenable to palliation or repair due to severe ventricular dysfunction or pulmonary vascular disease. They may be candidates for heart, lung, or heart-lung transplantation. In addition, patients previously repaired may deteriorate and may have no other options.[196–211]

Other reparative options are always considered prior to choosing heart transplantation as a surgical treatment. In this regard, there have been several reports of "one and one-half" ventricle repairs in cases of right ventricular pathology.[212–215]

In symptomatic patients who are NYHA class III or IV and who have an acceptable pulmonary vascular resistance, heart transplantation is usually feasible. Anomalies of systemic and pulmonary venous return can be corrected. Deformities of the pulmonary artery can be repaired. This may require quite extensive repair, particularly in some patients after the Fontan procedure. Dextrocardia and transposition may be challenging, but with current reconstructive techniques, transplantation is almost always possible.[204–208,216,217]

Preoperative evaluation

General evaluation is as for all heart transplant recipients. Cardiopulmonary exercise testing, and pulmonary, dental, and psychosocial evaluations are routine. Pulmonary vascular resistance must be carefully assessed; the cutoff is at 4 to 6 Wood units or a transpulmonary gradient of 12 to 14 mm Hg. Panel-reactive antibody screening is essential, as most patients have had previous surgery and blood transfusions. If these values are higher than 10%, then prospective cross-matching is preferable. Chest wall collaterals may increase left-sided return, particularly after previous surgery or cyanosis, and therefore it is usual to oversize donors by 20%. Some larger aortopulmonary or veno-venous collaterals may be coil embolized preoperatively.[218]

Renal and liver function and reserve require careful evaluation. Renal function may be compromised due to a low-output state, as well as renal vein congestion from elevated central venous pressure. Ideally, pretransplant creatinine clearance should be at least 40 mL/min.[219] Cardiac hepatopathy is poorly understood. Our experience is that these patients are at high risk for liver dysfunction due to frequent right ventricular failure or Fontan physiology. Many of these potential recipients will have normal liver function tests but abnormal liver histology. Preoperative histology may be useful to rule out cirrhosis. Centrilobular fibrosis may be seen on occasion.[220,221] Our experience has revealed that noninvasive imaging may underestimate the possibility

of cardiac cirrhosis. Even though this is rare, it is an important contraindication to heart transplantation.

Two to three hours of cardiopulmonary bypass time will unmask poor liver reserve. This is especially true in the third decade of life. Postoperatively, one may observe increasing total bilirubin with minimal rise in other tests of liver function. Total bilirubin may rise as high 35 to 40 mg/dL before returning to normal levels over a period of as many as 3 to 4 weeks.[222] Such a clinical course may be explained by a compromised liver preoperatively, to which is added an ischemic insult. Such livers require high flows during cardiopulmonary bypass and are thought to poorly tolerate hypothermia.[223] As described below, this may not always be possible.

Operative procedure

It is important to anticipate the recipient anatomy. For example, in tricuspid atresia dextraposed transposition is common, and the aorta may be immediately behind the sternum. A computed tomography scan is obtained preoperatively to assess the retrosternal structures. It is rarely necessary to institute bypass before opening the sternum. Aprotinin is used in all cases and it is important to plan correct timing for the arrival of the donor heart, since redo sternotomy in these patients is more complex than usual. Meticulous hemostasis is essential prior to starting cardiopulmonary bypass, as postoperative coagulopathy is common. If needed, patients are cooled to 22 to 24°C in order to minimize the pulmonary venous return, which can be torrential. This can warm the donor heart, and after the aortic anastomosis is completed, may wash out the preservation solution if the aortic root is not vented. A vent in the left atrium is therefore used to collect this return. Anomalies in systemic or pulmonary venous return and the pulmonary arteries are reconstructed prior to bringing the donor heart onto the field. We apply intracardiac cooling to the left ventricle using a catheter passed through the left atrial anastomosis into the left ventricle apex. Generally, we prefer a bicaval anastomosis (Figs. 61-21 and 61-22).

Outcomes

Due to previous surgeries, anatomic complexity, borderline pulmonary vascular resistance, hepatic congestion, and other factors, these patients (particularly the Fontan patients) are at higher risk for transplantation. Between 1984 and 2002, 30 adults and adolescents with congenital heart disease have undergone transplantation at our institution. Close to 50% of the patients had single-ventricle physiology, and on average all had had at least two previous sternotomies. Age range was 13 to 49 years old. The early mortality for this high-risk group was 18%. The single-ventricle-physiology patients are probably the highest-risk recipients. Quaegebeur, Addonizio, and Hsu and colleagues have reported a cohort of 35 recipients with 28% early mortality.

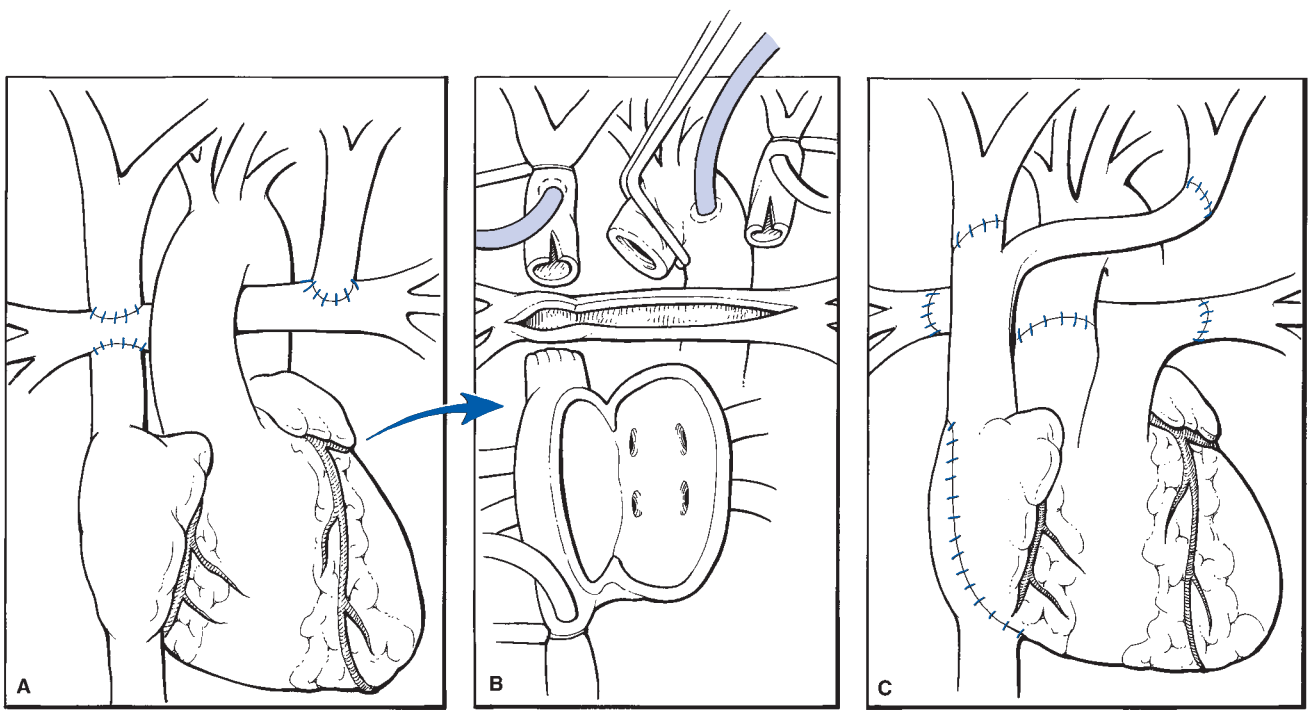

Figure 61-21. Heart transplantation after total cavopulmonary connection in a patient with bilateral superior venae cavae. The innominate vein from the donor is used to reconstruct the left superior vena cava. Alternatively (not shown), if the left superior vena cava is too short, a synthetic graft can be used to route the left superior vena caval blood along the coronary sinus of the donor heart into the recipient native inferior vena cava.

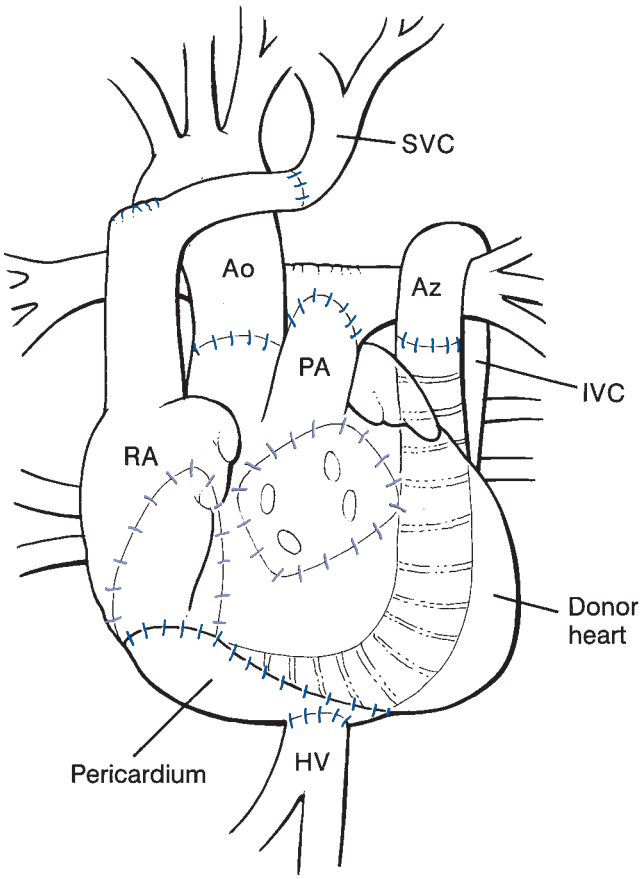

Figure 61-22. Heart transplant in a patient with dextrocardia, right-sided arch, and interrupted inferior vena cava with azygos continuity who previously had undergone a Fontan procedure. Ao = aorta; Az = azygos vein; HV = hepatic vein; IVC = inferior vena cava; PA = pulmonary artery; RA = right atrium; SVC = superior vena cava.

Similar results have been reported by Dark and associates. The group in Bergamo has reported a survival of 86% for heart transplantation in patients with previous Fontan operations.[224–226]

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CHAPTER 62

Pericardial Disease

Abeel A. Mangi • David F. Torchiana

The pericardium envelops the heart like a cocoon; when incised and suspended from a chest retractor it nicely presents the heart for surgical correction. The surgical significance of the pericardium arises from its involvement in derangements of cardiac filling. When the limited space between the noncompliant pericardium and heart is acutely filled with blood or fluid, cardiac compression and tamponade may result. When inflammation and scarring cause the pericardium to shrink and densely adhere to the surface of the heart, constrictive pericarditis is the consequence. In this chapter, we will discuss pericardial anatomy and function and describe the conditions that commonly give rise to the surgical problems of pericardial constriction and tamponade. The chapter also includes steps for the diagnosis and therapy of these entities, the management of tamponade early and late after cardiac surgery, and the rationale for and against pericardial closure at the time of cardiac surgery.

ANATOMY AND FUNCTION

The pericardium serves two major functions: (1) to maintain the position of the heart within the mediastinum, and (2) to prevent cardiac distention by sudden volume overload. The position of the pericardium is maintained by loose attachments to the undersurface of the sternum and to the vertebral bodies, and by firm attachment to the central tendon of the diaphragm. The pericardium attaches to the ascending aorta, just inferior to the innominate vein, and attaches to the superior vena cava several centimeters above the sinoatrial node. The pericardial reflection encompasses the superior and inferior pulmonary veins, and encircles the inferior vena cava, thereby making it possible for the surgeon to control the inferior vena cava from within the pericardium. The pericardial reflection attaches to the left atrium near the entrances of the pulmonary veins just below the atrioventricular groove (Fig. 62-1). The pericardium is perfused by the pericardiophrenic arteries that travel with the phrenic nerves, as well as by branches of the internal mammary arteries and feeder branches directly from the aorta. It is innervated by vagal fibers from the esophageal plexus, and the phrenic nerves course within it.

The pericardium is made up of two layers. The inner layer (visceral layer) of the pericardium is transparent, and is made up of a monolayer of mesothelial cells, making it essentially indistinguishable from the epicardium. Parietal pericardial lymphatic drainage is largely to the anterior and posterior mediastinal nodes, whereas visceral pericardial lymphatic drainage is via the tracheal and bronchial mediastinal lymph nodes.[1] The pericardial mesothelial cells contain dense microvilli that are 1 μm wide and 3 μm high,[2] ideal for facilitating fluid and ion exchange.[3]

The parietal layer is made up of elastin fibers interspersed among dense parallel bundles of collagen, which render this layer relatively noncompliant. Because the pericardium is stiffer than cardiac muscle, it tends to equalize the compliance of both ventricles. By doing so, the pericardium contributes to the resting cavitary diastolic pressure of both ventricles, maximizing diastolic ventricular interaction.[4] An example of this phenomenon is the diminution of systemic arterial pressure during inspiration. Intrapericardial pressure tends to approximate pleural pressure, and varies with respiration. The negative intrathoracic pressure generated during inspiration augments right ventricular filling. The interventricular septum shifts toward the left to accommodate the increase in right ventricular volume. Because pericardial constraint does not allow equal filling of the left ventricle, the decrease in volume ejected by the systemic chamber results in a slight diminution of systemic arterial pressure during inspiration. This phenomenon is greatly magnified with an increase in intrapericardial pressure (for example, during acute filling of the pericardial space or circulatory volume overload), resulting in production of the pulsus paradoxus.[5–7]

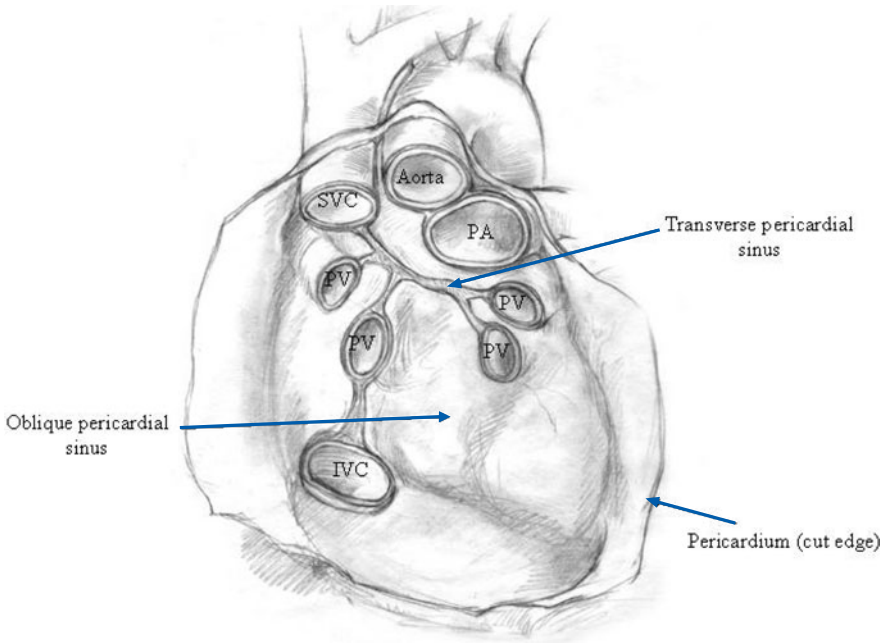


Figure 62-1. Pericardial attachments and reflections. IVC = inferior vena cava; PA = pulmonary artery; PV = pulmonary vein; SVC = superior vena cava.

Normally, the volume of the pericardium exceeds that of the heart by about 10 to 20%.[8] The pericardium contains several sinuses and recesses that are not readily evident at the time of surgery or at postmortem examination (Fig. 62-1). The largest (the transverse pericardial sinus) is the space between the ascending aorta and pulmonary artery bifurcation anteriorly, and the dome of the left atrium and superior vena cava posteriorly. Such potential spaces allow the pericardium to expand and accommodate a limited volume load. Under normal conditions, the pericardium contains approximately 20 mL of fluid, which is an ultrafiltrate of plasma. This pericardial fluid serves to lubricate the moving surfaces where the beating heart makes contact with fixed structures.[9]

CONGENITAL ABNORMALITIES

Most congenital abnormalities of the pericardium are discovered accidentally at cardiac surgery, on routine chest imaging, or while investigating unrelated problems.[10] They are rare, and less than 200 cases have been reported in the world literature.[11] The rarest of congenital pericardial abnormalities are pericardial bands that obstruct the superior vena cava. The most common are pericardial celomic cysts.

Partial absence of the pericardium is the most common form of pericardial agenesis. It occurs in approximately 1 out of 14,000 births, and has a male preponderance.[11] It is usually associated with cardiac, pulmonary, or skeletal anomalies.[11] Most defects tend to occur on the left side, and are due to premature atrophy of the left common cardinal vein, or duct of Cuvier, which normally goes on to form a portion of the left superior intercostal vein. The right duct of Cuvier goes on to form the superior vena cava and ensures closure of the right pleuropericardial membrane.[12] Accordingly, right-sided defects tend to be lethal. While complete pericardial agenesis is of little clinical significance, unilateral absence is potentially problematic, as it may accentuate cardiac mobility and allow the heart to be displaced into the pleural space with resulting incarceration[13] and tricuspid insufficiency.[12] The treatment for this lesion is pericardial resection, which may be accomplished thoracoscopically.[11] Alternatively, the pericardium can be replaced using patch material via thoracotomy. Both therapies appear to yield good outcomes.

Cysts can occur anywhere on the pericardium, but are found most often in the right costophrenic angle.[10] They do not communicate with the pericardial space, and contain a clear yellow fluid. They are typically unilocular, smooth, and less than 3 cm in diameter. Most remain clinically silent, and are discovered on routine chest imaging. Cysts have been associated with chest pain, dyspnea, cough, and arrhythmias, probably owing to compression and inflammatory involvement of adjacent structures. They can also become secondarily infected.[14,15] Cysts are relatively easy to diagnose by echocardiography or computed tomographic imaging, and can be followed in asymptomatic patients. In symptomatic patients, cysts can be aspirated under radiologic guidance, or resected either via the thoracoscope or at thoracotomy.[16]

PATHOPHYSIOLOGY OF PERICARDIAL COMPRESSION

The relative noncompliance of the pericardium results in a nonlinear relationship between intrapericardial volume and intrapericardial pressure. Although the pericardium may gradually expand to accommodate large volumes over time without appreciable increases in intrapericardial pressure, acute volume overload may result in a large increase in intrapericardial pressure (Fig. 62-2).

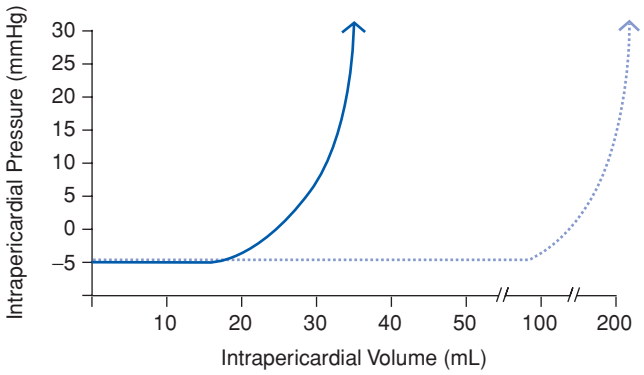


Figure 62-2. Relationship of intrapericardial volume and pressure. The pericardium of a healthy individual can accommodate 15 to 20 mL of fluid with minimal increases in intrapericardial pressure. However, when the elastic limit of the pericardial space is acutely exceeded, small increases in intrapericardial volume will result in large increases in intrapericardial pressure (solid line). Intrapericardial volume and pressure are not linearly related. With gradual development of an effusion, the pericardial space can dilate considerably (dotted line). It may therefore accommodate a relatively large effusion without an appreciable increase in intrapericardial pressure. (*Modified with permission from Harken et al.*[8])

Tamponade

Tamponade results from cardiac compression due to increased intrapericardial pressure with low cardiac output and elevated systemic venous pressure due to compromised cardiac filling. The clinical spectrum of tamponade varies widely, and is a reflection of the severity of hemodynamic impairment, as well as the physiologic resilience of the host. Although blood in the pericardial space is the most common etiology, exudative effusions, clot, pus, or gas, or any combination of these may also produce tamponade. When the pericardium is filled with fluid acutely, pericardial reserve volume (10 to 20 mL) is rapidly depleted. As fluid enters the pericardial space faster than the rate at which the parietal pericardium stretches, the noncompliant parietal pericardium prevents further expansion and intrapericardial pressure rises abruptly. At this point, pericardial volume can only increase by reducing cardiac chamber volumes. As a result, diastolic compliance is reduced equally in all chambers of the heart. This loss in compliance, coupled with the increase in intrapericardial pressures, means that higher pressures are required to fill the cardiac chambers, which may be partially achieved by parallel increases in systemic and pulmonary venous pressure by vasoconstriction.[17,18] Other compensatory mechanisms include tachycardia, time-dependent pericardial stretch, and blood volume expansion.[19] The latter two mechanisms have little impact in acute tamponade. The rapid accumulation of as little as 150 mL of fluid in the pericardial space (for example, after a penetrating cardiac wound) does not allow the parietal pericardium to develop any degree of compliance. In such a setting, the rapid accumulation of a relatively small volume of blood in the pericardial space can result in critical tamponade. On the other hand, the gradual accumulations of large pericardial effusions (over 1 L) can be compensated for in a chronic inflammatory condition such as rheumatoid arthritis. Chronic distention of the pericardial space is usually obvious on chest x-ray (Fig. 62-3) or echocardiogram (Fig. 62-4). In acute tamponade, the cardiac silhouette may appear normal.

Pericardial Constriction

A wide range of disease processes can result in formation of a pericardial scar, the pathologic process behind constrictive pericarditis (CP). As with tamponade, the physiologic basis of the disease is compromised cardiac filling leading to

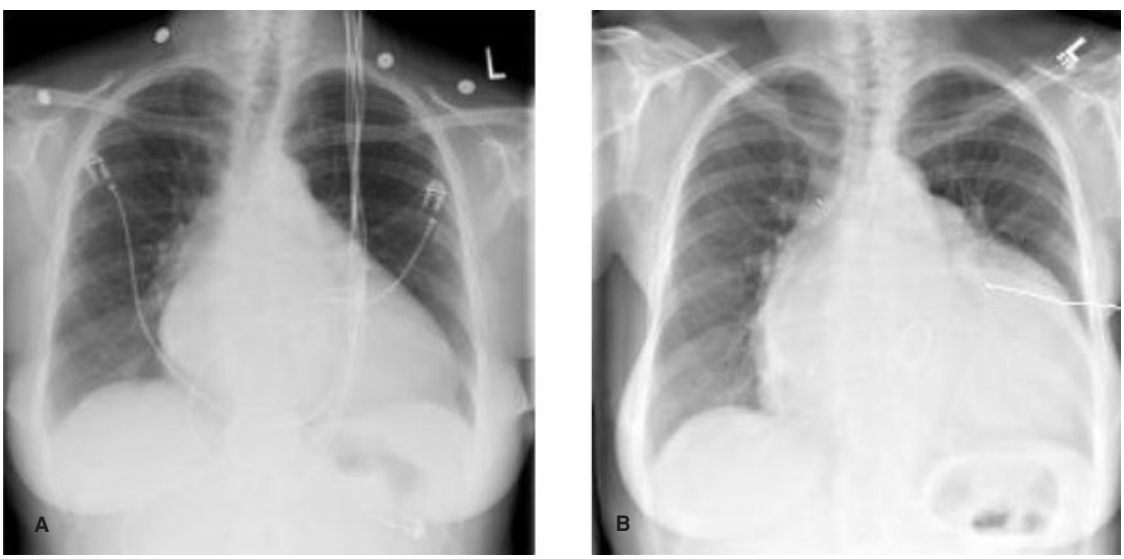


Figure 62-3. Enlarging pericardial effusion detected on chest x-ray. (A) At discharge; (B) 3 weeks after discharge.

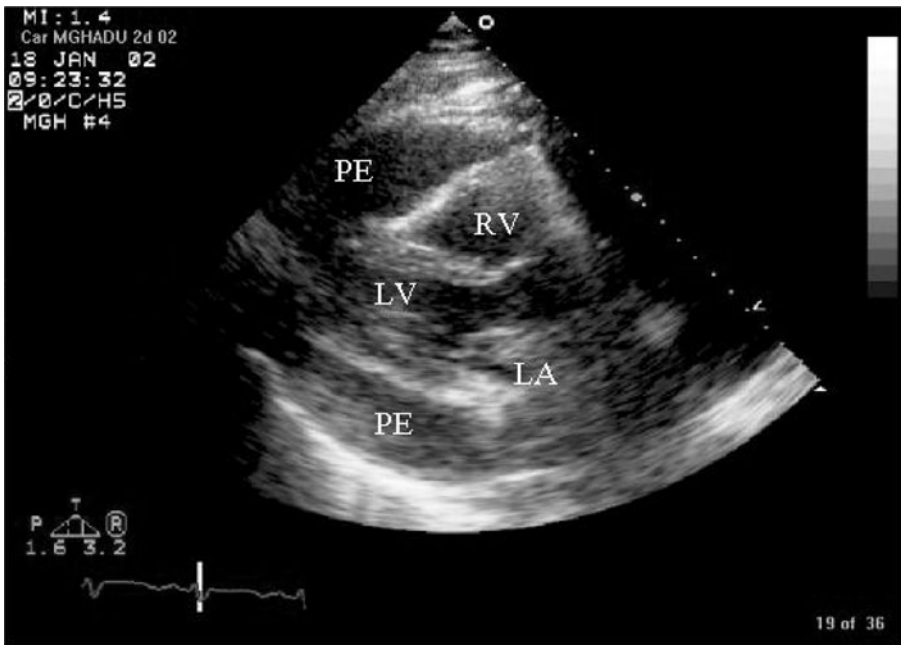


Figure 62-4. Large pericardial effusion detected on echocardiogram. LA = left atrium; LV = left ventricle; PE = pericardial effusion; RV = right ventricle.

systemic venous congestion and low cardiac output. In contrast to tamponade, patients with CP present with a subacute onset, often after a year or more of symptoms consisting of fatigue, decreased exercise tolerance with dyspnea/orthopnea, as well as peripheral edema and ascites from hepatic congestion in advanced disease. The principal etiologies behind pericardial scar formation have changed over the last 25 years. The incidence of infectious etiologies (particularly tuberculosis) has declined, whereas the incidence of cases resulting from therapeutic irradiation of the mediastinum and cardiac surgery (Fig. 62-5) has been increasing.[20]

Constrictive pericarditis is important to recognize, because it is curable with surgery. Evaluation begins with echocardiographic evaluation which typically shows small, normally contracting ventricles, and relatively dilated atria. The abrupt end to ventricular filling that occurs when the ventricles encounter the noncompliant scarred pericardium creates a phenomenon described as "septal bounce," the echocardiographic correlate to the "square root" sign described below. The hallmark of echocardiographic examination in CP is the reciprocal variation of right- and left-sided Doppler flows with inspiration, caused by interventicular

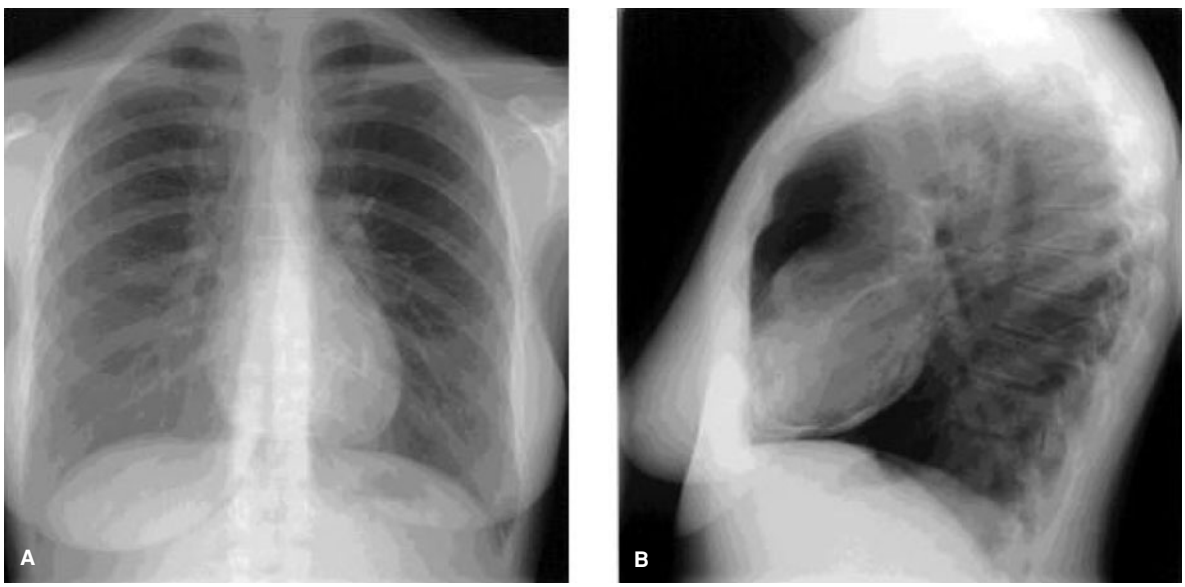


FigurE 62-5. Pericardial calcification on posteroanterior (A) and lateral (B) chest x-ray in a young patient with a history of thoracic trauma.

dependence ; again this has a hemodynamic correlate that will be discussed below. Modern axial imaging with spiral computed tomographic scanning or magnetic resonance imaging has helped greatly in being able to visualize thickened and/or calcified pericardium, with or without coexisting effusion. Importantly, while pericardial thickening is usually present in constrictive pericarditis, it remains possible to have CP with normal pericardial thickness and also to have thickening of the pericardium without CP.[21]

Pericardial constriction exerts its pathophysiologic effects by limiting cardiac filling. Unlike tamponade, in which cardiac filling is limited right from the beginning of diastole, constriction does not restrict filling in the very earliest stages of diastole. As the ventricles fill, they are prevented from their normal distention as they encounter the stiff, contracted, and noncompliant pericardium. As a result, in patients with CP, 70 to 80% of diastolic filling is forced to occur in the first 25 to 30% of diastole.[22] Although early diastolic filling pressures are normal (while the ventricle is free from the overlying stiff pericardium), later diastolic filling pressures are much higher. This sudden increase in diastolic pressure is reflected in the dip and plateau or "square-root" sign (Fig 62-6), which occurs when ventricular pressures are measured during cardiac catheterization. Similarly, right atrial pressure tracings reveal a deep *y* descent, which correlates to the nadir of the square-root sign. The clinical manifestation of this phenomenon is seen in the Kussmaul sign, which is frequently present in CP, although it is not specific for CP. Under normal circumstances, inspiration results in a 3- to 7-mm Hg drop in right atrial pressure. The high pressure of pericardial constriction prevents the right atrium from accepting inspiratory acceleration of blood from the neck veins. Instead, neck veins become prominently distended during inspiration in patients with CP, a phenomenon referred to as Kussmaul sign.[23]

Prior to the modern era of echocardiography and axial imaging, the diagnosis of CP was dependent on hemodynamic tracings obtained at cardiac catheterization. Catheterization tracing remains a valuable illustration of the underlying

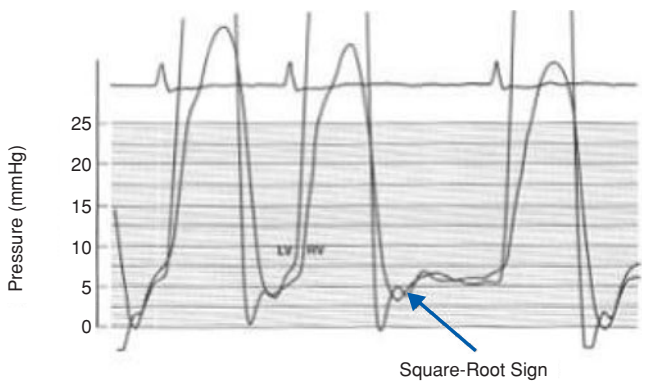


Figure 62-6. Square-root sign in right ventricular pressure tracing in constrictive pericarditis. (*Modified with permission from Spodick DH [ed]: The Pericardium: A Comprehensive Textbook. New York, Marcel Dekker, 1997; p 4.*)

physiology of CP, and in some cases may help in making the critical differentiation between CP and restrictive cardiomyopathy (RCM):[24,25]

1. *Equalization of pressures.* When pericardial compression is a dominant determinant of hemodynamic status, left and right ventricular end-diastolic pressures are within 5 mm Hg of each other. This classic criterion, however, has limited sensitivity and specificity.
2. *Elevation of mean atrial pressures.* Mean atrial pressure of over 10 mm Hg is suggestive of either cardiac tamponade or of pericardial constriction.
3. *Square-root sign.*
4. *Prominent* y *descent* in right atrial pressure tracing.
5. *Elevated right ventricular end-diastolic pressure.* This should be more than one-third of right ventricular systolic pressure. This criterion has a sensitivity of 93% and a specificity of 57% for constrictive pericarditis.

RCM is characterized by noncompliant ventricular muscle and diastolic dysfunction which hamper cardiac filling. RCM is caused by a variety of infiltrative or fibrosing conditions (e.g., amyloidosis, sarcoidosis, radiation, carcinoid, and anthracycline toxicity). While RCM may mimic some of the presenting features of CP, it is not a surgical disease and must be distinguished from CP for this reason. Systolic ventricular function may be normal or near normal function. RCM patients tend to have a poor prognosis. Criteria for the diagnosis of restrictive cardiomyopathy include:

1. Increased jugular venous pressure
2. Prominent *x* and *y* descents
3. A small or normal-sized heart
4. Pulmonary congestion
5. Hepatic congestion
6. Absence of ventricular hypertrophy or dilatation
7. Normal to mildly depressed ventricular systolic function

Additional criteria to help in distinguishing CP from RCM include evidence of thickened pericardium, which favors but does not clinch the diagnosis of CP, as there are instances, particularly in radiation-induced CP, in which the conditions coexist. Distinctive myocardial speckling may be found on echo with amyloidosis or other infiltrative conditions. Endomyocardial biopsy is useful to establish the presence of one of the conditions known to be associated with RCM; unfortunately a negative biopsy does not rule it out.[24]

In an attempt to provide additional criteria to differentiate patients with CP and RCM, Hurrell and colleagues[26] measured the respiratory variation of the gradient of left ventricular pressure to pulmonary capillary wedge pressure during the rapid filling phase of diastole. This was done to assess the dissociation of intrathoracic and intracardiac pressures that is seen in constrictive pericarditis. A difference of 5 mm Hg in the gradient between inspiratory and expiratory cycles had 93% sensitivity and 81% specificity for constrictive

pericarditis. Furthermore, increased ventricular interdependence was assessed by comparing left ventricular systolic pressure and right ventricular systolic pressure during respiration. Although concordant increases in left ventricular systolic pressure and right ventricular systolic pressure are expected during inspiration, discordant pressures are encountered during inspiration in patients with constrictive pericarditis. This finding has 100% sensitivity and 95% specificity for constrictive pericarditis.[26]

ACQUIRED ABNORMALITIES

A large number of factors can cause irritation of the pericardium, inducing the condition known as pericarditis (Table 62-1). The etiologies include myocardial infarction (Dressler syndrome); drugs such as procainamide and hydralazine; viral, bacterial, and fungal infections; metabolic (e.g., uremia) and autoimmune diseases (e.g., rheumatoid arthritis); neoplasms; trauma; and mechanical irritation at the time of surgery. The clinical syndrome is similar regardless of cause, and includes pain, constitutional symptoms (such as weakness and malaise), fever (occasionally with rigors), and other symptoms such as cough or odynophagia. The pain is variably described as sharp, dull, aching, or pressure-like. It is generally acute in onset and precordial but can follow referred patterns similar to those of angina, such as to the arm, epigastrium, jaw, shoulder, or ridge of the trapezius. The pain is generally pleuritic, and exacerbated by inspiration, cough, or recumbency. These patients therefore like to sit up and lean forward for relief.

The cardinal sign of pericarditis is the pericardial rub. Echocardiogram may reveal fibrinous thickening of the pericardium with or without a small effusion. The electrocardiogram may range from normal, to nonspecific ST-segment deviations, to diffuse concave elevation of the ST segments without reciprocal depressions. This may be associated with PR-segment depression, and T-wave inversions in V_3 to V_6. It should be noted that ventricular arrhythmias and conduction abnormalities are not commonly seen in pericarditis, and are suggestive of an underlying cardiac abnormality if present.

After excluding other entities in the differential diagnosis, such as myocardial ischemia, pneumonia, chest wall pain, and pulmonary embolism, treatment of pericarditis should aim to relieve symptoms and eliminate etiologic agents. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment,[27] and may be supplemented with colchicine.[28] Further treatment must be tailored to address the specific etiologic agent, some of which are discussed in greater depth below.

Infectious Pericarditis

Viral pericarditis

The cardiotropic viruses that cause myocarditis are the ones most likely to cause pericarditis as well. Pericardial inflammation is a result of immune complex deposition, direct viral attack, or both.[27] The clinical illness involves pain, friction rub, and typical changes on the electrocardiogram. Treatment is expectant, and symptoms generally resolve within 2 weeks. Surgical intervention is rarely required.

Bacterial pericarditis

Microorganisms may invade the pericardial space from contiguous infections in the heart, lung, subdiaphragmatic space, or from the wound in postoperative patients. Patients with septicemia can also seed the pericardial space. This problem is more common in immunosuppressed patients.[29]

Acute suppurative pericarditis is a life-threatening disease that has the potential to induce tamponade and septicemia. The most common organisms remain streptococcal, pneumococcal, and staphylococcal,[30,31] but the incidence of gram-negative organisms such as *Escherichia coli*, *Salmonella*, and opportunistic infections is increasing. In adults, pneumopyopericardium is often due to fistula formation between a hollow viscus and the pericardium. However, invasion from contiguous foci, implantation at the time of surgery or trauma, mediastinitis, endocarditis, and subdiaphragmatic abscess can all induce this condition. The clinical course is acute and fulminant. The patient appears toxic and can have a high fever. Acute surgical intervention is required in the setting of purulent pericarditis, which may result in tamponade in a third of cases,[29] or in cases in which scarring results in pericardial constriction.

Tuberculous pericarditis

After decades of decrease, the incidence of tuberculous pericarditis has been increasing recently because of the rising numbers of immunocompromised patients, particularly those with human immunodeficiency virus.[32] The pericardium is infected by hematogenous, lymphatic (from lung, bronchial, and mediastinal lymph nodes), peribronchial, or contiguous spread of tuberculosis. The classic pathologic stages of this entity include:[31]

1. Fibrinous exudation, with robust polymorphonuclear infiltration
2. Serous or serosanguineous effusions with a mainly lymphocytic exudation
3. Absorption of effusion, with organization of caseating granulomas, and pericardial thickening due to fibrin and collagen deposition and fibrosis
4. Constrictive scarring, often with extensive calcification occurring over a period of years

Most often, the clinical course of this entity is insidious. Children and immunocompromised patients may, however, present with a more fulminant course, often demonstrating both constrictive and tamponade physiology.[32] The diagnosis is established by examining pericardial fluid for the presence of the mycobacteria. These patients require urgent institution of triple drug therapy. In addition certain groups advocate addition of aggressive surgical management in order to avoid development of chronic constrictive pericarditis.[33,34]

Table 62–1.

Acquired Etiologies of Acute Pericarditis

- INFECTIOUS
  - Bacterial
    - Tuberculous (mycobacterial)
    - Suppurative (streptococcal, pneumococcal)
  - Viral
    - Coxsackie
    - Influenza
    - HIV
    - Hepatitis A, B, C
    - Other
  - Fungal
  - Parasitic
  - Other
    - Rickettsial
    - Spirochetal
    - *Spirillum*
    - *Mycoplasma*
    - Infectious mononucleosis
    - *Leptospira*
    - *Listeria*
    - Lymphograuloma venereum
    - Psittacosis
- AUTOIMMUNE/VASCULITIDES
  - Rheumatoid arthritis
  - Rheumatic fever
  - Systemic lupus erythematosus
  - Drug-induced lupus erythematosus
  - Scleroderma
  - Sjögren syndrome
  - Whipple disease
  - Mixed connective tissue disease
  - Reiter syndrome
  - Ankylosing spondylitis
  - Inflammatory bowel diseases
    - Ulcerative colitis
    - Crohn disease
  - Serum sickness
  - Wegener granulomatosis
  - Giant cell arteritis
  - Polymyositis
  - Behçet syndrome
  - Familial Mediterranean fever
  - Panmesenchymal syndrome
  - Polyarteritis nodosa
  - Churg-Strauss syndrome
  - Thrombohemolytic-thrombocytopenic purpura
  - Hypocomplementemic uremic vasculitis syndrome
  - Leukoclastic vasculitis
  - Other
- METABOLIC DISORDERS
  - Renal failure
    - Uremia in chronic or acute renal failure
    - "Dialysis" pericarditis
  - Myxedema
    - Cholesterol pericarditis
    - Gout
  - Scurvy
- DISEASE OF CONTIGUOUS STRUCTURES
  - Myocardial infarction/cardiac surgery
    - Acute myocardial infarction
    - Post-myocardial infarction syndrome
    - Postpericardiotomy syndrome
    - Ventricular aneurysm
  - Aortic dissection
  - Pleural and plumonary disease
    - Pneumonia
    - Pulmonary embolism
    - Pleuritis
  - Malignancies of lung
- NEOPLASTIC
  - Primary
    - Mesothelioma
    - Sarcoma
    - Fibroma
  - Secondary
    - Metastatic; carcinomas, sarcomas
    - Direct extension; bronchogenic, esophageal carcinomas
    - Hematogenous; lymphoma, leukemia
- TRAUMA
  - Penetrating
    - Stab wound or gunshot wound to the chest
  - latrogenic
    - During diagnostic or therapeutic cardiac catheterization
    - During pacemaker insertion
  - Radiation pericarditis
- UNCERTAIN ETIOLOGIES AND PATHOGENESIS
  - Pericardial fat necrosis
  - Loffler syndrome
  - Thalassemia
  - Drug reactions
    - Procainamide
    - Hydralazine
    - Others
  - Pancreatitis

Table 62–1.

Acquired Etiologies of Acute Pericarditis (*continued*)

UNCERTAIN ETIOLOGIES AND PATHOGENESIS	
Sarcoidosis	Takayasu syndrome
Fat embolism	Castleman disease
Bile fistula to pericardium	Fabry disease
Wissler syndrome	Kawasaki disease
PIE syndrome	Degos disease
Stevens-Johnson syndrome	Histiocytosis X
Gaucher disease	Campylodactyly-pleuritis-pericarditis syndrome
Diaphragmatic hernia	Farmer lung
Atrial septal defect	Idiopathic
Giant cell aortitis	

Fungal pericarditis

Fungal pericarditis is an unusual entity and occurs predominantly in immunocompromised or debilitated individuals, patients with severe burns, infants, and patients taking steroids. *Candida* and *Aspergillus* generate an insidious clinical picture, and may come to attention after the patient develops tamponade or constriction. Fungi such as *Histoplasma* that tend to be endemic to certain geographic areas may cause pericarditis in young, healthy, immunocompetent patients, and will often resolve within 2 weeks. There may be late sequelae such as constriction, but this is rare. Similarly, *Coccidioides* can also infect young healthy individuals, but will generally produce a more severe illness. Acute pericardial coccidioidomycosis usually will accompany pneumonia from the same organism, with systemic adenopathy, osteomyelitis, or meningitis. The potential for chronic constriction is higher in this disease. These conditions all tend to resolve either spontaneously or after treatment with appropriate antifungal medical regimens. Surgical intervention is not usually required in the acute setting.

Metabolic Causes of Pericarditis

Pericarditis has been recognized to occur in the presence of renal failure, hypothyroidism, and autoimmune diseases (such as rheumatoid arthritis), in response to certain drugs (e.g., procainamide and hydralazine), and after mediastinal radiation.

Uremic pericarditis

Uremic pericarditis was first recognized by Bright in 1836.[35] Although it is recognized that nitrogen retention (blood urea nitrogen levels are generally >60 mg/dL) is required for uremic pericarditis, the inciting agent is still unknown. The clinical profile is of a patient with chronic renal insufficiency who has symptoms of pain, fever, and a friction rub. There is usually a pericardial fluid collection, which can be exudative or transudative, and is usually hemorrhagic. Tamponade may occur; although the incidence of tamponade is decreasing due to the more widespread use of renal dialysis,[36,37] it remains the primary danger of this condition. Management of uremic pericarditis is controversial. Initial therapy includes NSAIDs and aggressive dialysis, and there is also a role for pericardiocentesis or drainage. The timing, however, remains uncertain.[38,39] Drainage has been advocated if a pericardial effusion persists despite 2 weeks of aggressive dialysis.[40] Any patient with hemodynamic compromise deserves immediate drainage.

Drug-induced pericarditis

Procainamide (with or without associated lupus syndrome), hydralazine, methysergide, and emetine have all been associated with pericardial inflammation. Minoxidil has been associated with pericardial effusion.[41] The clinical presentation and guidelines for management in these settings are similar to those for other types of pericarditis. The inciting agent should be discontinued.

Pericarditis associated with rheumatoid arthritis

Pericarditis is common in patients with rheumatoid arthritis (RA). Approximately half of patients with RA have pericardial effusions, and almost half of all patients with RA have significant pericardial adhesions at autopsy.[42] The condition is encountered more often in patients with advanced RA, and is thought to be due to the higher rheumatoid factor titers. The deposition of immune complexes in the pericardium appears to be the inciting event behind the inflammatory response.[43] The clinical syndrome varies widely. The most common mode of presentation is a friction rub that lasts days to years with an asymptomatic effusion. The diagnosis is often complicated by the many clinical variants, and by intercurrent diseases such as viral pericarditis and drug-induced pericarditis. Treatment is required only in patients with symptomatic effusions. Constriction may occur late in RA patients. These patients should then be considered for pericardiectomy.

Hypothyroidism

Severe hypothyroidism produces large, clear, high-protein, high-cholesterol, and high-specific-gravity effusions in 5 to 30% of patients. The effusion may precede other signs of

hypothyroidism.[44,45] These effusions are often asymptomatic and are recognized on chest x-ray. Clinical tamponade is rare because of the slow accumulation of fluid. However, acute exacerbations due to intercurrent acute pericarditis, hemorrhage, or cholesterol pericarditis can induce cardiac tamponade.

Radiation Pericarditis

Radiation is now the most common etiology of constrictive pericarditis in the United States.[46] This was first recognized in patients who received high-dose mantle radiation for Hodgkin lymphoma in the 1960s and 1970s and developed cardiac and pericardial pathology, on average 10 to 15 years after therapy. Radiation induces acute pericarditis, pancarditis, and accelerated coronary artery disease in a dose-dependent fashion.[47,48] Patients may present with a combination of pericardial constriction, restrictive cardiomyopathy, valvular heart disease, and coronary artery disease with a predilection for ostial lesions.[49,50]

Neoplastic Pericarditis

Secondary neoplasms of the pericardium (i.e., tumors that involve the pericardium by metastasis or by infiltration from adjoining structures) account for over 95% of pericardial neoplastic diseases. Primary pericardial tumors are rare, and paraneoplastic effusions can also occur that are in response to remote tumors.[51]

The most common secondary tumors involving the pericardium in males (including both metastasis and local extension) are carcinoma of the lung (31.7%) and esophagus (28.7%) and lymphoma (11.9%). In females, carcinoma of the lung (35.9%), lymphoma (17.0%), and carcinoma of the breast (7.5%) are most common.[52] Tumors of the lung, thymus, chest wall, or esophagus are more likely to involve the pericardium by direct spread. Lymphomas, Hodgkin disease, leukemias, melanomas, and multiple myeloma can infiltrate the pericardium as well as the myocardium. Primary pericardial tumors are uncommon. Benign tumors are generally encountered in infancy or childhood. Malignant tumors such as mesotheliomas, sarcomas, and angiosarcomas most often present in the third or fourth decade of life.[53]

In both primary and secondary tumor involvement, the clinical presentation is usually silent, and may be associated with large pericardial effusions. Tamponade can result if hemorrhage occurs into a malignant effusion. Occasional tumors can induce constriction, due to neoplastic tissue, adhesions, or both. The role of the surgeon is limited to diagnosis and palliation in most of these cases.[54] Large refractory and tamponading effusions may need to be surgically drained. Pericardiocentesis has a high failure rate. Subxiphoid drainage or percutaneous balloon pericardiotomy are transiently effective. A pericardioperitoneal shunt may be considered in children. While extensive resection and debulking may be necessary in persistent or recurrent malignant pericardial constriction, it has only transient benefit without effective adjunctive chemotherapy and/or radiation therapy. Life expectancy in cancer patients with malignant pericardial involvement averages less than 4 months.[55,56]

Traumatic Pericardial Disease

Penetrating trauma

Knives, bullets, needles, and intracardiac instrumentation are the most common causes of penetrating trauma to the pericardium.[57] Tamponade is more common in stab wounds than in gunshot wounds. The right ventricle is most often involved in anterior chest wounds. Because tamponade provides hemostasis and prevents exsanguination, patients in tamponade have a better survival rate than patients with cardiac stab wounds not in tamponade.[58] Pericardiocentesis has no role in the management of penetrating wounds to the heart. Stable patients can be explored in the operating theater, but unstable patients should undergo thoracotomy in the emergency department.

Blunt trauma

Blunt injuries to the pericardium rarely occur in isolation. Trauma due to compression, blast, and deceleration will produce a spectrum of injuries, ranging from cardiac contusion to cardiac rupture, and pericardial laceration with herniation or luxation of the heart. Patients with pericardial laceration and cardiac herniation typically have suffered deceleration injuries and are invariably hypotensive. They may initially respond to volume resuscitation. A pericardial rub may be the only physical finding, but is not specific for this entity. On chest imaging, free air may be seen in the pericardium, and the heart may be displaced. Intra-abdominal organs may have migrated into the pericardial sac. If the heart has herniated into the left pleural space, positioning the patient right side down may reduce the herniation. Thoracotomy is required for definitive treatment and repair of associated injuries.[59–61]

Pericarditis Associated with Myocardial Infarction/Dressler Syndrome

This entity is thought to occur in almost half of patients suffering a transmural myocardial infarction, although it is symptomatic in far fewer.[62] Chest pain is almost universally present, and it is important to distinguish the pain of pericarditis from ischemic pain by its positional and pleuritic nature. The pain of pericarditis tends to start 1 week after myocardial infarction. A rub is present on auscultation. The electrocardiographic signs of pericarditis may be obscured by those of infarction. Patients may develop a small pericardial effusion. Patients suffering from pericarditis appear to have a worse long-term prognosis than those without post-infarct pericarditis,[63] possibly because they tend to have larger infarctions as judged by enzyme release and degree of ST-segment elevation. The diagnosis is clinical, and is treated with aspirin and/or NSAIDs.

Cardiac Surgery and the Pericardium

Postinfarction pericarditis

Postinfarction pericarditis is an important entity for the surgeon to be mindful of in the evaluation of patients with acute coronary syndromes. To the unwary it may masquerade as postinfarction angina and lead to a needless early operation after a myocardial infarction. Extensive fibrinous adhesions and murky gelatinous fluid may be present in the pericardial space and obscure epicardial vessels. When the pericardium is opened late in such a patient, the surgeon should expect dense pericardial adhesions.

Postpericardiotomy syndrome

Pericardial friction rubs are almost universal after cardiac surgery, and some patients will develop Dressier syndrome[64] with pleural and pericardial effusions, pleuritic pain, and generalized malaise. Such patients will almost always respond to NSAIDs or a short course of corticosteroids when the symptoms remain refractory.

Cardiac tamponade

Early postoperative tamponade rarely goes undetected for long because of the high level of vigilance and close hemodynamic monitoring that attend the patient during this time. It is equally important for surgeons to be aware of the potential for late cardiac tamponade that presents after hospital discharge and often initially to a clinician other than the cardiac surgeon. This entity is a potentially lethal complication and occurs in between 0.5 and 6% of patients after heart surgery, almost exclusively in those taking warfarin. Late cardiac tamponade (i.e., tamponade occurring more than 7 days after cardiac surgery) is more common in younger patients who have undergone isolated valve (as opposed to coronary artery bypass graft) surgery. Patients present on average 3 weeks after surgery, frequently in the setting of an elevated prothrombin time. They are often severely symptomatic, with declining exercise tolerance, dyspnea, an inability to urinate, and sometimes hypotension. Classic physical signs of tamponade like distant heart sounds, pulsus paradoxus, or distended neck veins may or may not be present. A high index of suspicion is required; any patient on warfarin whose recovery begins an otherwise unexplained decline in this interval should be suspected of having late tamponade and undergo echocardiographic examination. Echocardiography will demonstrate a pericardial effusion, although the typical echocardiographic signs of tamponade are detected in less than half of all patients. The diagnosis is therefore a clinical one. Nearly all patients with late tamponade will respond favorably to pericardiocentesis, and are able to safely resume anticoagulation.[65]

Pericardial closure

Redo sternotomy may be more hazardous when the heart is adherent to the inner table of the sternum. Closing the pericardium at the time of surgery interposes a protective layer of tissue between the sternum and the heart and may reduce the risks of redo sternotomy. Surgeons vary in their approach toward closing the pericardium after routine cardiac surgery. The value of any added protection against cardiac injury on sternal reentry is limited by the relative infrequency of reoperation and the already low incidence of cardiac injury at resternotomy when the pericardium is left open. On the negative side, closing the pericardium can cause kinking of bypass grafts after coronary bypass surgery and may result in hemodynamic compromise due to cardiac compression.

Rao and associates demonstrated that pericardial closure at the time of cardiac surgery adversely affects postoperative hemodynamics.[66] In this ingenious study, the pericardial edges were marked with radiopaque markers and the pericardium was closed with a running suture, the ends of which were exteriorized. After obtaining a postoperative chest film that demonstrated pericardial approximation, a set of baseline hemodynamics were measured. The suture was then removed, another x-ray taken to demonstrate that the pericardial edges had become distracted, and then the hemodynamic measurements were repeated. Pericardial closure reproducibly resulted in transient, moderate hemodynamic compromise in the first 8 hours after operation (Table 62-2). The risks of pericardial closure must therefore be weighed against its potential benefits if it is to be used in everyday clinical practice, and the practice should be individualized to the patient. Pericardial closure is probably not advisable after coronary artery bypass graft or in a patient with marginal hemodynamics.

OPERATIONS

Mediastinal Reexploration

Standard management for the postoperative cardiac surgical patient involves leaving the pericardium open, and placing anterior and posterior mediastinal thoracostomy drains. Despite this, postoperative tamponade may occur. The typical clinical scenario is one in which chest tube output falls after a period of early postoperative bleeding, the patient develops tachycardia, narrowing of the pulse pressure, increase in right-sided filling pressures, decrease in urine output, and a drop in the cardiac index. This setting is diagnostic of tamponade, and arrangements should be made for expedient mediastinal exploration. Echocardiography is not routinely helpful because the pericardial space is difficult to visualize in the immediate postoperative patient and thrombus may be difficult to resolve. Subtle echocardiographic findings that have been reported include an inspiratory increase in right ventricular end-diastolic diameter and a reciprocal decrease in left ventricular end-diastolic diameter,[67] as well as an increase in early peak tricuspid flow velocity and reduction in flow across the mitral valve.[68]

Table 62–2.

Structural and Hemodynamic Changes After Pericardial Closure in Patients Undergoing Elective Isolated Coronary Artery Bypass Grafting

Parameters measured	Open pericardium	Closed pericardium	*p* value
Retrosternal space at 1 wk (cm)	13 ± 5	20 ± 7	.0003
Retrosternal space at 3 mo (cm)	7 ± 3	14 ± 7	.0001
CI L/min/m^2 1 h postoperation	3.1 ± 0.8	2.3 ± 0.6	.003
CI L/min/m^2 4 h postoperation	3.1 ± 0.9	2.7 ± 0.7	.156
CI L/min/m^2 8 h postoperation	3.0 ± 0.8	2.8 ± 0.5	.402
LVSWI g/m/m^2 1 h postoperation	72 ± 18	52 ± 13	.002
LVSWI g/m/m^2 4 h postoperation	68 ± 17	54 ± 8	.016
LVSWI g/m/m^2 8 h postoperation	62 ± 22	52 ± 10	.087

CI = cardiac index; LVSWI = left ventricular stroke work index.

Pericardiocentesis

Pericardiocentesis can be performed at the bedside under local anesthesia in a calm patient, but it is usually performed in the catheterization laboratory and at some institutions, by interventional radiology under computed tomographic guidance. Arterial and right heart catheterization monitoring are frequently used. After administration of 1% lidocaine to the skin and the deeper tissues of the left xiphocostal area, a 25-mL syringe is affixed to a three-way stopcock and then to an 18-gauge spinal needle. This pericardial needle is connected to an electrocardiograph "V" lead. Under electrocardiographic and imaging guidance, the needle is advanced from the left of the subxiphoid area aiming toward the left shoulder. A discrete pop may be felt as the needle enters the pericardial space. ST-segment elevation may be seen on the V lead tracing when the needle touches the epicardium. Under these circumstances, the needle is retracted slightly until ST-segment elevation disappears. Once the pericardial space is entered, a guidewire is introduced into the pericardial space through the needle. The needle is removed and a catheter is inserted into the pericardial sac over the guidewire. At our institution, a pigtail-shaped drainage catheter with an end hole and multiple side holes is used. Intrapericardial pressure is measured by attaching a pressure transducer system to the intrapericardial catheter. Pericardial fluid may then be removed. Symptom relief may be immediate and dramatic. When appropriate, samples of pericardial fluid are sent for cell count, chemistry, cytology, cultures, and special stain studies to assist with the diagnosis of the etiology of the effusion. In the presence of pericardial tamponade, aspiration of fluid is continued until there is clear clinical and hemodynamic improvement. If blood is withdrawn, 5 mL should be placed on a sponge to see if it clots. Clotting blood suggests that the needle has either inadvertently entered a cardiac chamber or caused epicardial injury. Defibrinated blood that has been present in the pericardial space for even a short time usually does not clot.[69] The catheter is frequently left in place to monitor pericardial fluid drainage. It is secured to the skin with 4-0 silk sutures and covered with a sterile dressing, and the patient is started on prophylactic antibiotics. The pericardial space is drained every 8 hours and the catheter is flushed with heparinized solution and in general is removed within the next 24 to 72 hours. Pneumothorax is a potential complication, and chest x-ray is mandatory after the procedure.

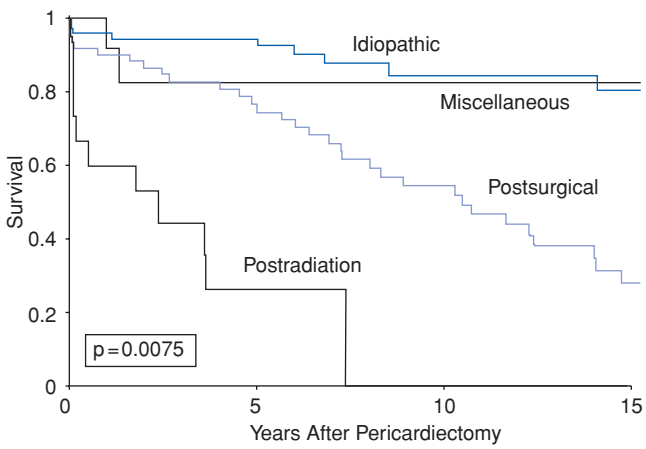
Pericardial Window

The purpose of partial pericardial resection (window) is to drain fluid into the pleural or peritoneal compartment in order to avoid the reaccumulation of pericardial fluid if the patient has had prior pericardiocentesis and reaccumulation. The procedure can be performed via thoracoscopy, anterior thoracotomy, or subxiphoid incision. General anesthesia is desirable, with the caveat that it may be poorly tolerated in patients with cardiac compression. When the pericardium is incised, fluid will invariably drain under pressure. The excised portion of pericardium should be as large as is feasible. Through an anterior thoracotomy, all accessible pericardium ventral to the phrenic nerve should be excised. The surgeon should remain mindful of the rare possibility of cardiac prolapse. Similarly, via the subxiphoid approach, as much diaphragmatic pericardium should be excised as is possible. Thoracostomy drainage catheters should be left within the pericardium.

Pericardial Stripping

Chronic pericardial constriction is treated by pericardial excision. Because of dense adhesions and calcification that can penetrate into the myocardium, pericardial resection can be a technical challenge. At most centers, the procedure is done via median sternotomy with the capability to use cardiopulmonary bypass as needed.[18,33] Practice is variable, as some use cardiopulmonary bypass routinely, while others prefer to avoid the additional burden of coagulopathy unless absolutely necessary. Left anterior thoracotomy is preferred by some surgeons, and was the approach taken by Dr. Edward Churchill, who reported the first pericardiectomy for CP done in the United States.[70] The objective of the procedure is to release the ventricles from the densely adherent pericardial shell. The lack of a surgical plane can make this a bloody operation, and attention must be paid to salvage and reinfusion of blood. Epicardial coronary vessels are at risk in this dissection and particular care must be taken when dissecting in the regions of these vessels. The goal is to excise the pericardium from phrenic nerve to phrenic nerve, and also posteriorly, around the entrance of the venae cavae and pulmonary veins to the pericardium. Complete resection should restore pressure-volume loops to their normal position.[71] Complete pericardial resection is not feasible in all cases, notably with radiation-induced disease, and leaving densely adherent scar, particularly over the venae cavae and atria, may be safer for the patient.

The results vary with the etiology and severity of the disease. Operative mortality has been reported as high as 10 to 20%,[72,73] and varies based on severity of heart failure, elevation of right atrial pressure, and comorbidities. Although surgery alleviates or improves symptoms in the vast majority of patients, long-term survival is diminished in patients who have had prior heart surgery, and particularly in patients with radiation-induced constrictive pericarditis (Fig. 62-7).[20,74,75]



Number at risk				
Idiopathic	75	48	30	21
Miscellaneous	12	10	10	5
Post-surgical	60	38	24	9
Post-radiation	15	6	0	0

Figure 62-7. Kaplan-Meier curve showing a significant difference (log-rank test, $p = 0.0075$) in overall survival of patients after pericardiectomy, based on the presumed cause of constrictive pericarditis. (*Reprinted with permission from Bertog et al.*[75])

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CHAPTER 63

Cardiac Neoplasms

Jon-Cecil M. Walkes • W. Roy Smythe • Michael J. Reardon

Neoplasms of the heart can be divided into primary cardiac tumors arising in the heart and secondary cardiac tumors that have metastasized to the heart. Primary cardiac tumors can be further stratified into benign and malignant tumors. Secondary involvement of the heart is relatively uncommon; between 10% and 20% of patients dying of disseminated cancer have metastatic involvement of the heart or pericardium.[1,2] Surgical resection is seldom possible or advisable for these tumors, and surgical intervention usually is limited to drainage of malignant pericardial effusions and/or diagnostic biopsies.

Primary tumors of the heart are uncommon but not rare. The incidence of primary cardiac neoplasm ranges between 0.17% and 0.19% in unselected autopsy series.[3–8] Approximately 75% of primary cardiac tumors are benign, and 25% are malignant.[2,9] Approximately 50% of the benign tumors are myxomas, and about 75% of the malignant tumors are sarcomas.[2,9] The clinical incidence of these tumors is approximately 1 in 500 cardiac surgical patients, and with the exception of myxomas, most surgeons will encounter primary cardiac tumors rarely. The purpose of this chapter is to summarize useful information for the evaluation and management of patients with primary and secondary cardiac tumors and to provide a reference for additional study on these subjects.

HISTORICAL BACKGROUND

A primary cardiac neoplasm was first described by Realdo Colombo in 1559.[10,11] Alden Allen Burns of Edinburgh described a cardiac neoplasm and suggested valvular obstruction by an atrial tumor in 1809.[12] A series of six atrial tumors, with characteristics we now recognize as myxoma, was published in 1845 by King.[13] In 1931, Yates reported nine cases of primary cardiac tumor and established a classification system similar to what we use today.[14] The first antemortem diagnosis of a cardiac tumor was made in 1934 when Barnes diagnosed a cardiac sarcoma using electrocardiography and biopsy of a metastatic lymph node.[15] In 1936, Beck successfully resected a teratoma external to the right ventricle,[16] and Mauer removed a left ventricular lipoma in 1951.[17] Treatment of cardiac tumors was profoundly influenced by two events: the introduction of cardiopulmonary bypass in 1953 by John Gibbon, which allowed a safe and reproducible approach to the cardiac chambers, and the introduction of cardiac echocardiography, which allowed safe and noninvasive diagnosis of an intracardiac mass. The first echocardiographic diagnosis of an intracardiac tumor was made in 1959.[18] An intracardiac myxoma was diagnosed by angiography in 1952 by Goldberg, but attempts at surgical removal were unsuccessful.[13] A large right atrial myxoma was removed by Bhanson in 1952 using caval inflow occlusion, but the patient died 24 days later.[19] Crafoord in Sweden first successfully removed a left atrial myxoma in 1954 using cardiopulmonary bypass,[20] and Kay in Los Angeles first removed a left ventricular myxoma in 1959.[21] By 1964, 60 atrial myxomas had been removed successfully, with a steady increase owing to the increasing safety of cardiopulmonary bypass and increased use of echocardiography for detection.[22] Operations are currently performed routinely on the vast majority of patients with atrial myxoma with minimal mortality.[9,23–33] Primary malignant tumors, however, continue to represent a challenge.

CLASSIFICATION

Surgeons generally classify cardiac tumors as primary or secondary, as noted previously, and divide primary tumors into benign and malignant categories. However, the tissue of origin may influence clinical behavior, and an understanding of the pathologic classification of cardiac tumors is important. Pathologic classification is listed in Table 63-1. Mural thrombus is listed as a pseudotumor. Although not really a cardiac tumor, its presentation may mimic myxoma clinically and

Table 63–1.

Types of Cardiac Tumors by Pathology

Pseudotumors
Mural thrombi
Heterotopias and tumors of ectopic tissue
Tumors of the atrioventricular nodal region
Teratoma
Ectopic thyroid
Tumors of mesenchymal tissue
Hamartoma of endocardial tissue
Papillary fibroelastoma
Hamartomas of cardiac muscle
Rhabdomyoma
Histiocytoid cardiomyopathy (Purkinje cell hamartoma)
Tumors and neoplasms of fat
Lipomatous hypertrophy, interarterial septum
Lipoma
Liposarcoma
Tumors and neoplasms of fibrous and myofibroblastic tissue
Fibroma
Inflammatory pseudotumor (inflammatory myofibroblastic tumor)
Sarcomas (malignant fibrous histiocytoma, fibrosarcoma, leiomyosarcoma)
Vascular tumors and neoplasms
Hemangioma
Epithelioid hemangioendothelioma
Angiosarcoma
Neoplasm of uncertain histogenesis
Myxoma
Neoplasms of neural tissue
Granular cell tumor
Schwannoma/neurofibroma
Paraganglioma
Malignant schwannoma/neurofibrosarcoma (rare)
Malignant lymphoma
Malignant mesothelioma
Metastatic tumors to the heart

pathologically. Most mural thrombi are associated with underlying valvular disease, myocardial infarction or dysfunction, or atrial fibrillation.[32] Mural thrombi also have been noted in hypercoagulable syndromes, particularly antiphospolipid syndrome.[33] With increasing use of long-term central catheters, we have seen several right atrial masses that were difficult to tell from myxoma; these masses turned out to be mural thrombi on removal. Simple removal must be combined with addressing the underlying cause, and long-term anticoagulation is needed frequently.

Heterotopias and tumors of ectopic tissue include cystic tumors of the atrioventricular node consisting of multiple benign cysts in the region of the atrioventricular node that can cause heart block or sudden death. Most are diagnosed at autopsy, but biopsy diagnosis of atrioventricular nodal tumor has been reported.[34] Germ cell tumors of the heart usually are teratomas, occurring within the pericardial sac, but yolk sac tumors have been described in infants and children.[35,36] Ectopic thyroid tissue may occur within the myocardium and is referred to as *struma cordis*. Right ventricular outflow track obstruction may be present, but most patients are asymptomatic.[37,38]

Most of the remaining tumors arise in the mesenchymal, fat, fibrous, neural, or vascular cells of the heart, with myxoma representing a tumor of undetermined histogenesis. Primary cardiac lymphoma and mesothelioma and metastatic tumors to the heart represent the remaining pathologic categories that comprise the greater part of this chapter.

PRIMARY BENIGN TUMORS

Myxoma

Myxoma comprises 50% of all benign cardiac tumors in adults but only 15% of such tumors in children. Occurrence during infancy is rare (Tables 63-2 and 63-3). A vast majority of myxomas occur sporadically and tend to be more common in women than men.[4,31] The peak incidence is between the third and sixth decades of life, and 94% of tumors are solitary.[39] Approximately 75% occur in the left atrium.[31] The deoxyribonucleic acid (DNA) genotype of sporadic myxomas is normal in 80% of patients.[40] Tumors are unlikely to be associated with other abnormal conditions and have a low recurrence rate.[4,39]

About 5% of myxoma patients show a familial pattern of tumor development based on autosomal dominant inheritance.[41,42] These patients and 20% of those with sporadic myxoma have an abnormal DNA genotype chromosomal pattern.[40] In contrast to the "typical" sporadic myxoma profile of a middle-aged, frequently female patient with a single left atrial myxoma, familial myxoma patients are more likely to be younger, equally likely to be male or female, and more often (22%) have multicentric tumors originating from either the atrium or ventricle.[43–48] Although familial myxomas have the same histology as sporadic tumors, familial myxoma has a higher recurrence rate after surgical resection (21 to 67%).[44,49,50] Approximately 20% of familial patients have associated conditions such as adrenocortical nodule hyperplasia, Sertoli cell tumors of the testes, pituitary tumors, multiple myxoid breast fibroadenomas, cutaneous myomas, and facial or labial pigmented spots.[39,49] These conditions often are described as *complex myxomas* within the

Table 63–2.

Benign Cardiac Neoplasms in Adults

Tumor	No.	Percentage
Myxoma	118	49
Lipoma	45	19
Papillary fibroelastoma	42	17
Hemangioma	11	5
AV node mesothelioma	9	4
Fibroma	5	2
Teratoma	3	1
Granular cell tumor	3	1
Neurofibroma	2	<1
Lymphangioma	2	<1
Rhabdomyoma	1	<1
Total	241	100

Source: Reproduced with permission from McAllister HA Jr, Fenoglio JJ Jr: Tumors of the cardiovascular system, in Atlas of Tumor Pathology. Washington DC, Armed Forces Institute of Pathology; 1978, fas. 15.

group of familial myxoma.[40] A familial syndrome with autosomal X-linked inheritance characterized by primary pigmented nodular adrenocortical disease with hypercortisolism, cutaneous pigmentous lentigines, and cardiac myxoma is referred to as *Carney's complex.*[39,49]

Pathology

Myxomas occur in any chamber of the heart but have a special predilection for the left atrium, from which approximately 75% originate.[32] The next most frequent site is the right atrium, where 10 to 20% are found. The remaining 6 to 8% are equally distributed between the left and right ventricles.[2] Both biatrial and multicentric tumors are more common in familial disease. Biatrial tumors probably arise from bidirectional growth of a tumor originating within the atrial septum.[51] Atrial myxomas generally arise from the interatrial septum at the border of the fossa ovalis but can originate anywhere within the atrium, including the appendage[4] (Figs. 63-1 and 63-2). In addition, isolated reports confirm that myxomas arise from the cardiac valves, pulmonary artery and vein, and vena cava.[52,53] Right atrial myxomas are more likely to have broad-based attachments than left atrial tumors; they also are more likely to be calcified[45,46] and thus visible on chest radiographs (Fig. 63-3). Ventricular myxomas occur more often in women and children and may be multicentric.[2,54] Right ventricular tumors typically arise from the free wall, and left ventricular tumors tend to originate in the proximity of the posterior papillary muscle.

Grossly, about two-thirds of myxomas are round or oval tumors with a smooth or slightly lobulated surface.[31] Most are polypoid, relatively compact, pedunculated, mobile, and not likely to fragment spontaneously.[2,4] Mobility depends on the

Table 63–3.

Benign Cardiac Neoplasms in Children

	0–1-year-olds		1–15-year-olds	
Tumor	Number	Percentage	Number	Percentage
Rhabdomyoma	28	62	35	45.0
Teratoma	9	21	11	14.0
Fibroma	6	13	12	15.5
Hemangioma	1	2	4	5.0
AV node mesothelioma	1	2	3	4.0
Myxoma	—	—	12	15.5
Neurofibroma	—	—	1	1.0
Total	45	100	78	100

Source: Reproduced with permission from McAllister HA Jr, Fenoglio JJ Jr: Tumors of the cardiovascular system, in Atlas of Tumor Pathology. Washington DC, Armed Forces Institute of Pathology, 1978; fas. 15.

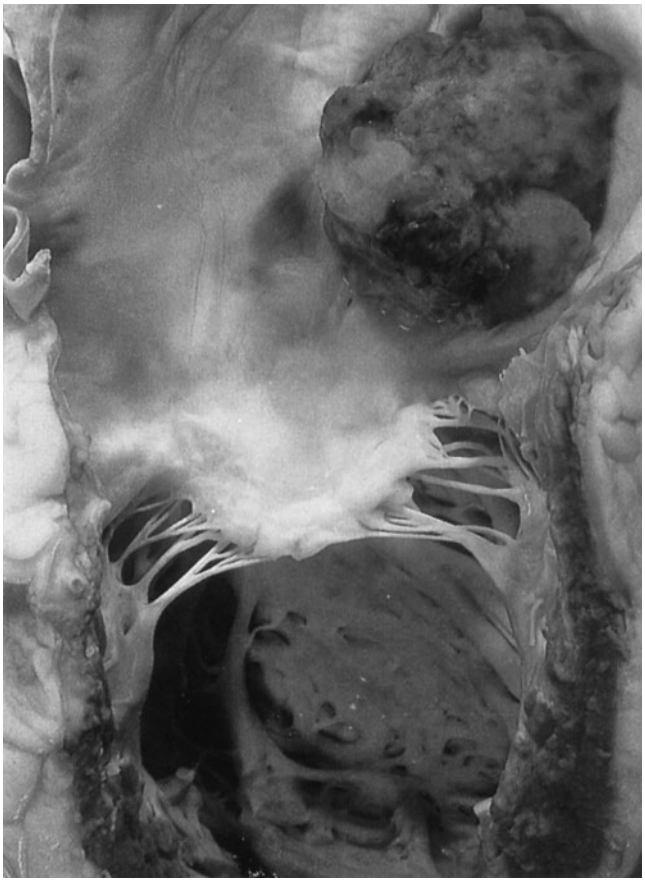

Figure 63-1. Left atrial myxoma obstructing the mitral orifice. *(Reproduced with permission from Hurst JW et al: Atlas of the Heart. New York, McGraw-Hill, 1988.)*

length of the stalk, the extent of attachment to the heart, and the amount of collagen in the tumor.[4] Most tumors are pedunculated with a short, broad base, and although sessile forms occur, they are unusual.[2,55] Less common villous or papillary myxomas are gelatinous and fragile and prone to fragmentation and embolization, occurring about one-third of the time.[31,56] Myxomas are white, yellowish, or brownish in color, frequently covered with thrombus.[2] Focal areas of hemorrhage, cyst formation, or necrosis may be seen in cut section. The average size is about 5 cm in diameter, but growth to 15 cm in diameter and larger has been reported.[4] Most myxoma tumors appear to grow rapidly, but growth rates vary, and occasionally, tumor growth arrests spontaneously.[4] Weights range from 8 to 175 g, with a mean between 50 and 60 g.[8]

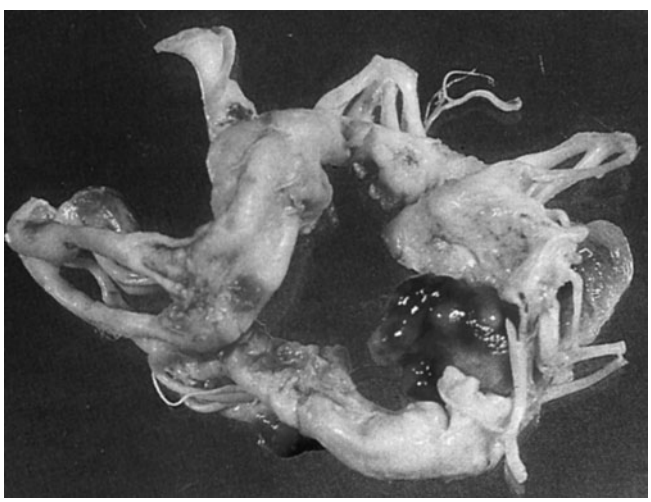

Figure 63-2. Left atrial myxoma arising from the posterior papillary muscle. *(Reproduced with permission from Hurst JW et al: Atlas of the Heart. New York, McGraw-Hill, 1988.)*

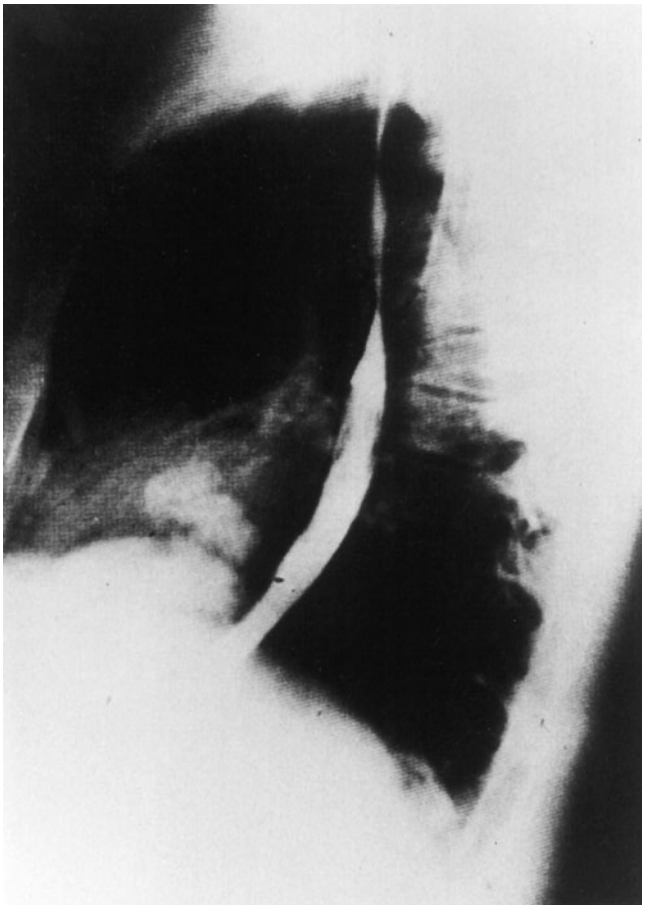

Figure 63-3. Calcified right atrial myxoma. *(Reproduced with permission from Hurst JW et al: Atlas of the Heart. New York, McGraw-Hill, 1988.)*

Histologically, myxomas are composed of polygonal-shaped cells and capillary channels within an acid mucopolysaccharide matrix[4] (Fig. 63-4). The cells appear singularly or in small clusters throughout the matrix, and mitoses are rare.[57] The matrix also contains a smattering of smooth muscle cells, reticulocytes, collagen, elastin fibers, and a few blood cells. Cyst, areas of hemorrhage, and foci of extramedullary hematopoiesis are present throughout the matrix.[49,56,58] Ten percent of the tumors have microscopic deposits of calcium and metastatic bone deposits, as well as sometimes glandular-like structures.[49,56] The base of the tumor contains a large artery and veins that connect with the subendocardium but do not extend deeply beyond the subendocardium in most cases.[49] We have seen a myxoma recently that on coronary angiography had a large feeding vessel and was suspected originally of being an

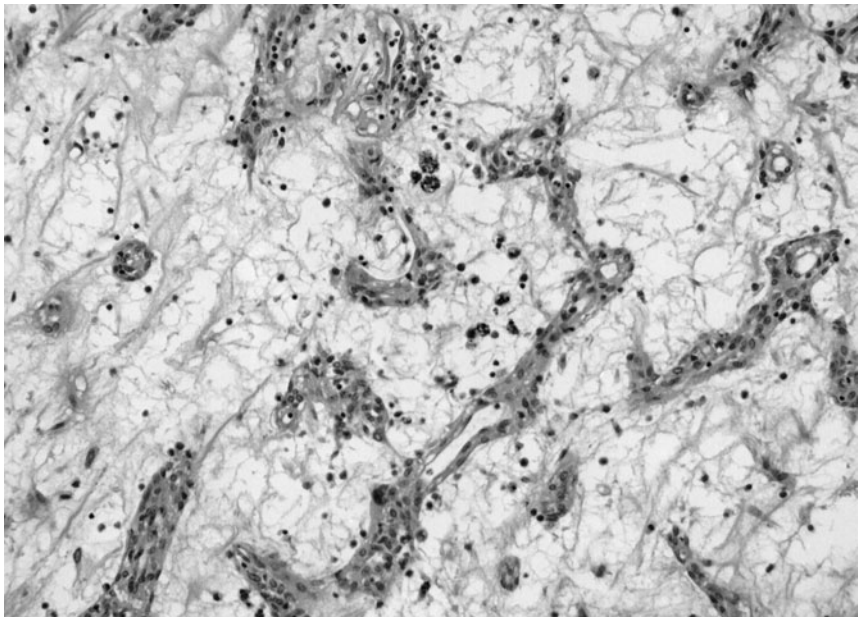

Figure 63-4. Typical microscopic appearance of atrial myxoma with nests of small stellate cells and blood vessels immersed in abundant acellular matrix rich in proteoglycans. These tumors often contain smooth muscle, areas of hemorrhage and calcification, hemosiderin-laden macrophages, and chronic inflammatory cells. Hematoxylin & eosin, ×200. (*Courtesy of Dr. G. G. Pietra.*)

angiosarcoma but on histology proved to be a typical benign myxoma. Myxomas tend to grow into the overlying cardiac cavity rather than into the surrounding myocardium. The tumor surface is covered by a monolayer of polygonal cells with interspersed primitive blood vessels.

Myxomas arise from the endocardium and are considered derivative of the subendocardial multipotential mesenchymal cell,[59,60] although origin from endocardial nervous tissue also has been suggested.[61] The multipotential mesenchymal cells are thought to be embryonic cells left behind during septation of the heart and are capable of differentiating into endothelial cells, smooth muscle cells, angioblasts, fibroblasts, myoblasts, and cartilage. This accounts for the occasional presence of hematopoietic tissue and bone in these tumors. There is no evidence that these tumors are of thrombotic origin, as was speculated formerly.[62]

Interestingly, myxomas have developed after cardiac trauma, including repair of atrial septal defects and transseptal puncture for paracutaneous dilatation of the mitral valve.

Clinical presentation

The classic triad of myxoma clinical presentation is intracardiac obstruction with congestive heart failure (67%), signs of embolization (29%), systemic or constitutional symptoms of fever (19%) and weight loss or fatigue (17%), and immunologic manifestations of myalgia, weakness, and arthralgia (5%), with almost all patients presenting with one or more of these symptoms.[31] Cardiac rhythm disturbances and infection occur less frequently.

CONSTITUTIONAL SYMPTOMS: Nearly all myxoma patients on careful questioning admit to a variety of constitutional symptoms that may include weight loss, fever, and lethargy. These complaints may be accompanied by laboratory abnormalities, including leukocytosis, elevated erythrocyte levels and sedimentation rate, hemolytic anemia, thrombocytopenia, and elevated C-reactive protein. Immunoelectrophoresis may reveal abnormal immunoglobulin levels with increased circulating IgG.[63] These symptoms often suggest an inflammatory autoimmune disease and are unrelated to the location and size of the tumor.[4]

The recent discovery of elevated levels of interleukin-6 in patients with myxoma has been linked to a variety of associated conditions, including lymphadenopathy, tumor metastasis, ventricular hypertrophy, and development of constitutional symptoms.[54,64–66] Other less frequent complaints include Raynaud phenomenon, arthralgias, myalgias, erythematous rash, and clubbing of the digits.[4,67,68]

Possible etiologies of such varied complaints and symptoms include tumor embolization with secondary myalgias and arthralgias and elevated immunoglobulin response.[69] Circulating antibody–tumor antigen complexes with complement activation also may play a role in the constitutional symptom complex.[70] More important, such symptom complexes tend to resolve following surgical resection of the tumor.[58,71,72]

OBSTRUCTION: Obstruction of blood flow in the heart is the most common cause of acute presenting symptoms. The nature of these symptoms is determined by which of the chambers is involved and the size of the tumor.

Myxomas in the left atrium tend to mimic mitral valvular heart disease. They produce dyspnea, which may be positional,[73] and other signs and symptoms of heart failure associated with elevated left atrial and pulmonary venous pressures. Clinically, mitral stenosis often is suspected and leads to echocardiography and diagnosis of myxoma. On occasion, large myxomas may interfere with mitral leaflet closure and produce mitral regurgitation, but this is uncommon.[4] Syncopal episodes occur in some patients and are thought to result from temporary occlusion of the mitral orifice.[46,73–75] Right atrial myxomas can produce a clinical picture of right-sided heart failure with signs and symptoms of venous hypertension, including hepatomegaly, ascites,

and dependent edema. The tumor simulates tricuspid valve stenosis by partially obstructing the valve orifice.[46,73–75] If a patent foramen ovale is present, right-to-left atrial shunting may occur with central cyanosis, and paradoxical embolization has been reported.[74,76,77]

Large ventricular myxomas may mimic ventricular outflow obstruction. The left ventricular myxoma may produce the equivalent of subaortic or aortic valvular stenosis,[77–79] whereas right ventricular myxomas can simulate right ventricular outflow track or pulmonic valve obstruction.

EMBOLIZATION: Systemic embolization is the second most common mode of presentation for patients with myxoma. It occurs in 30 to 40% of patients.[2,4,46,73,74] Because the majority of myxomas are left-sided, approximately 50% of embolic episodes affect the central nervous system owing to both intracranial and extracranial vascular obstruction. The neurologic deficits following embolization range from transient to permanent, but a high number do not resolve.[80] Specific central nervous system consequences include intracranial aneurysms, seizures, hemiparesis, and brain necrosis.[81–84] Retinal artery embolization with visual loss has occurred in some patients.[85,86]

Embolic material for cardiac myxoma has been found in iliac and femoral arteries, causing acute lower extremity ischemia.[87–89] Other sites of tumor embolization include abdominal viscera and the renal and coronary arteries.[90] Histologic examination of surgically removed peripheral myxoma that has embolized provides the diagnosis of an otherwise unsuspected tumor.[46,91,92]

Right-sided myxomatous emboli usually do not cause clinical manifestations but do obstruct pulmonary arteries and cause pulmonary hypertension and even death from acute obstruction.[4,77]

INFECTION: Infection arising in a myxoma is a rare complication and produces a clinical picture of infectious endocarditis,[91–95] and a number of bacterial pathogens and fungus forms[93] have been isolated.[96] Infection increases the likelihood of systemic embolization,[4] and infected myxoma warrants urgent surgical resection.

Diagnosis

CLINICAL EXAMINATION: Findings at the time of clinical assessment of a patient with cardiac myxoma vary according to the size, location, and mobility of the tumor. Left atrial myxomas may produce auscultatory findings similar to mitral stenosis, just as these tumors may mimic the symptoms of mitral disease. The well-described "tumor plop" is an early diagnostic sound heard and sometimes confused with a third heart sound. The diagnostic tumor plop occurs just after the opening snap of the mitral valve and is believed to be secondary to contact between the tumor and endocardial wall.[97,98] Of note, the murmur of cardiac myxoma may depend on its position, and this may aid in the auscultatory diagnosis. Left atrial myxomas that cause partial obstruction of left ventricular filling may result in elevated pulmonary vascular pressures with augmentation of the pulmonary component of the second heart sound.[99]

Right atrial myxomas may produce the same auscultatory findings as left atrial myxomas with the exception that they are best heard along the lower right sternal border rather than the cardiac apex. These include both systolic and diastolic murmurs and a tumor plop. In addition, right atrial hypertension may produce a large *a* wave in the jugular venous pulse and, when severe, may mimic superior vena caval syndrome. Similarly, elevated right atrial pressure can lead to right-to-left shunting across the patent foramen ovale. This may produce polycythemia, cyanosis, and clubbing of the digits. Lower body manifestations of venous hypertension are hepatomegaly, ascites, and peripheral edema.

CHEST RADIOGRAPH AND ELECTROCARDIOGRAM: The findings on chest roentgenogram, although not specific, may include generalized cardiomegaly, individual cardiac chamber enlargement, and pulmonary venous congestion. More specific occasional findings are density within the cardiac silhouette caused by calcification within the tumor (see Fig. 63-3). This finding occurs more often with right-sided myxomas[4]; however, the majority of our myxoma patients have normal chest roentgenograms.

ELECTROCARDIOGRAPHIC FINDINGS: Similar to plain-film imaging, nonspecific abnormalities are noted, including chamber enlargements, cardiomegaly, bundle-branch blocks, and axis deviation.[100] Fewer than 20% of patients have atrial fibrillation.[48] Evaluation of nonspecific electrocardiographic abnormalities occasionally leads to an incidental diagnosis of myxoma, but as with chest x-rays, most electrocardiograms are not helpful in establishing a diagnosis.

ECHOCARDIOGRAPHY: Cross-sectional echocardiography is the most useful test employed for the diagnosis and evaluation of myxoma. The sensitivity of two-dimensional (2-D) echocardiography for myxoma is 100%, and this imaging technique largely has supplanted angiocardiography.[101] However, coronary angiography usually is performed in patients over 40 years of age to rule out significant coronary arterial disease in a patient who has another indication for cardiac surgery. A transthoracic echocardiogram usually provides all the information for surgical resection, but transesophageal echocardiography (TEE) provides the best information concerning tumor size, location, mobility, and attachment.[102,103]

Transesophageal echocardiograms detect tumors as small as 1 to 3 mm in diameter.[104] Our practice is to obtain a transesophageal echocardiogram in the operating room before beginning the operation (Fig. 63-5). We particularly evaluate the posterior left atrial wall, atrial septum, and right atrium, which often are not well displayed on transthoracic examination, to exclude the possibility of biatrial multiple tumors. Additionally, operative TEE ensures a normal echocardiogram prior to leaving the operating room.

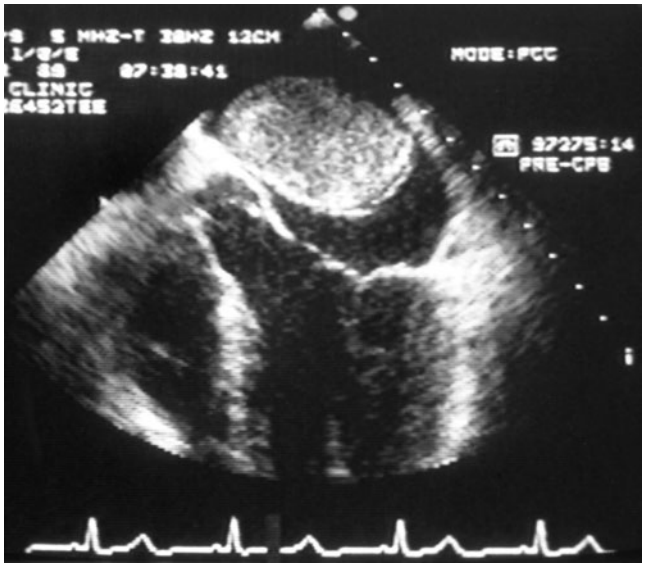

Figure 63-5. Transesophageal echocardiogram of large left atrial myxoma in patient presenting with symptoms of mitral valve disease. The tumor is attached to the interatrial septum above the normal mitral valve. (*Reproduced with permission from Hall RA, Anderson RP: Cardiac neoplasms, in Edmunds LH Jr (ed): Cardiac Surgery in the Adult. New York, McGraw-Hill, 1997; p. 1350.*)

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING: Although myxomas have been identified using computed tomography (CT),[100,105] this modality is most useful in malignant tumors of the heart because of its ability to demonstrate myocardial invasion and tumor involvement of adjacent structures.[100] Similarly, magnetic resonance imaging (MRI) has been employed in the diagnosis of myxomas and may yield a clear picture of tumor size, shape, and surface characteristics.[100,103,105,106] MRI is particularly useful in detecting intracardiac and pericardial extension and invasion of malignant secondary tumors and also is useful in the evaluation of ventricular masses that occasionally turn out to be myxoma. Both CT and MRI detect tumors as small as 0.5 to 1.0 cm and provide information regarding the composition of the tumor.[4] Neither CT nor MRI is needed for atrial myxomas if an adequate echocardiogram is available because the information from these studies is not likely to alter the surgical approach. The exception is the occasional right atrial myxoma that extends into one or both caval or tricuspid orifices. CT or MRI should be reserved for the situation in which the diagnosis or characterization of the tumor is unclear after complete echocardiographic evaluation.

Surgical management

Surgical resection is the only effective therapeutic option for patients with cardiac myxoma and should not be delayed because death from obstruction to flow within the heart or embolization may occur in as many as 8% of patients awaiting operation.[107,108] A median sternotomy approach with ascending aortic and bicaval cannulation usually is employed. Manipulation of the heart before initiation of cardiopulmonary bypass is minimized in deference to the known friability and embolic tendency of myxomas. For left atrial myxomas, the venae cavae are cannulated through the right atrial wall, with the inferior cannula placed close and laterally to the inferior vena cava–right atrial junction (Fig. 63-6). Caval snares are always used to allow opening of the right atrium, if necessary. If extensive exposure of the left atrium is needed or a malignant left atrial tumor is suspected, we mobilize and directly cannulate the superior vena cava, which allows it to be transected if necessary for additional

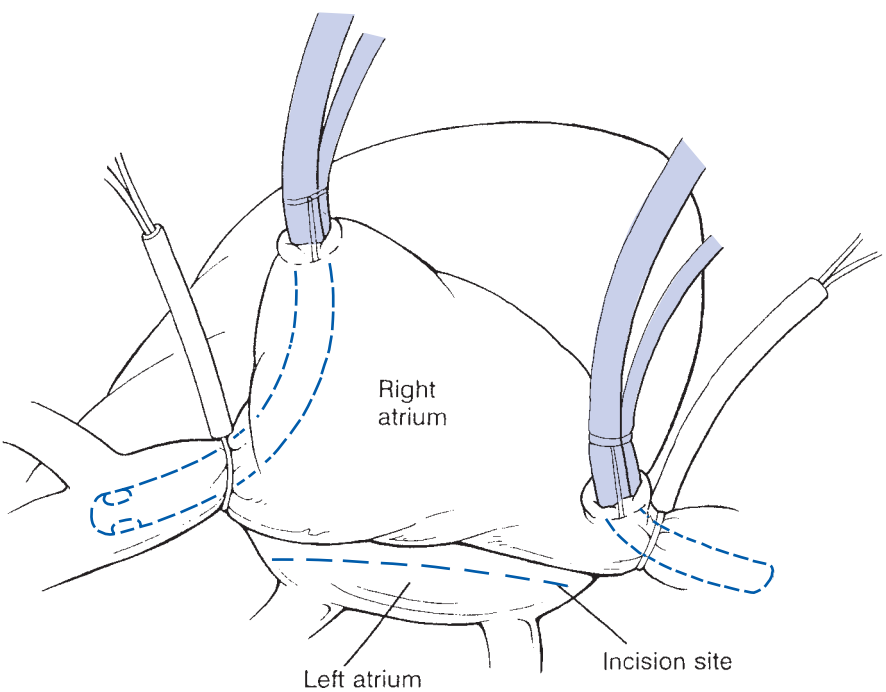

Figure 63-6. Standard venous cannulation for atrial myxomas and left arteriotomy site for left atrial myxoma.

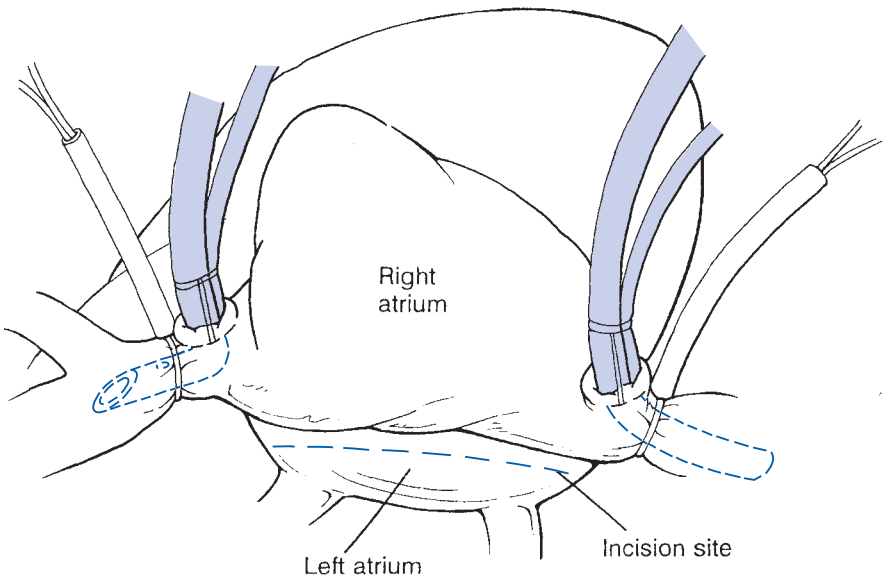

Figure 63-7. Superior vena cava cannula to allow increased right atrial exposure or division of superior vena cava for additional left atrial exposure.

exposure (Fig. 63-7). Body temperature is allowed to drift down, but there is no attempt to induce systemic hypothermia unless the need for reduced perfusion flow is anticipated. Modern cardioplegic techniques yield a quiet operative field and protect the myocardium from ischemic injury during aortic cross-clamping. Cardiopulmonary bypass is started, and the aorta is clamped prior to manipulation of the heart.

Exposure of left atrial myxomas is maximized by using several principles from mitral valve repair surgery. The surgeon desires the right side of the heart to rotate up and the left side of the heart to rotate down. Therefore, stay sutures are placed low on the pericardium on the right side, and no pericardial stay sutures are placed on the left prior to placing the chest retractor. This rotates the heart for optimal exposure of both the right and, particularly, the left atrium (Fig. 63-8). For left atrial tumors, the superior vena cava is mobilized extensively, as is the inferior vena cava–right atrial junction, allowing increased mobility and exposing the left atrial cavity. Left atrial myxomas can be

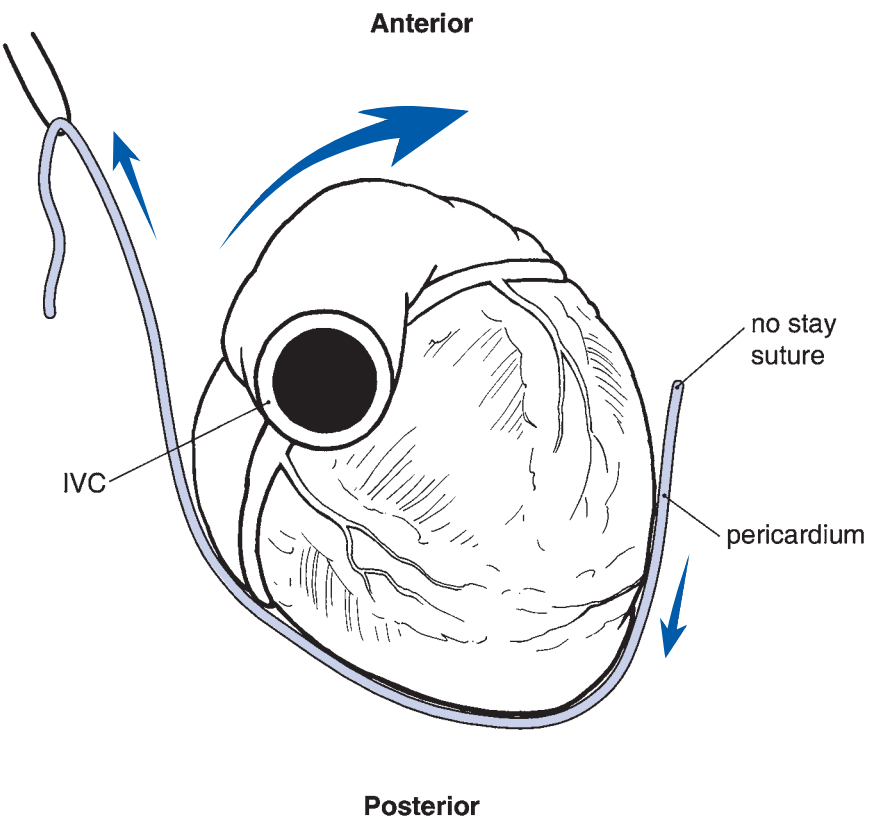

Figure 63-8. Rotation of the heart with pericardial stay sutures for left atrial exposure. IVC = inferior vena cava.

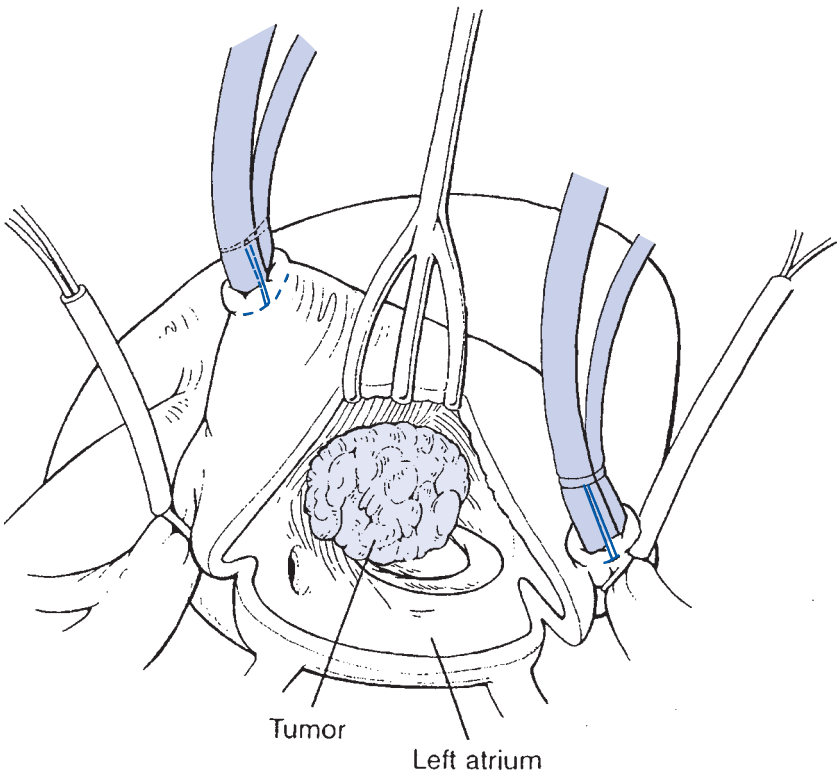

Figure 63-9. Left atriotomy and exposure of myxoma.

approached by an incision through the anterior wall of the left atrium anterior to the right pulmonary veins (Fig. 63-9). This incision can be extended behind both cavae for greater exposure (Figs. 63-10 and 63-11). Exposure and removal of large tumors attached to the interatrial septum may be aided by a second incision parallel to the first in the right atrium going posterior to the superior vena caval cannula and anterior to the inferior vena caval cannula. This biatrial incision allows easy removal of tumor attached to the fossa ovalis with full-thickness excision at the site of

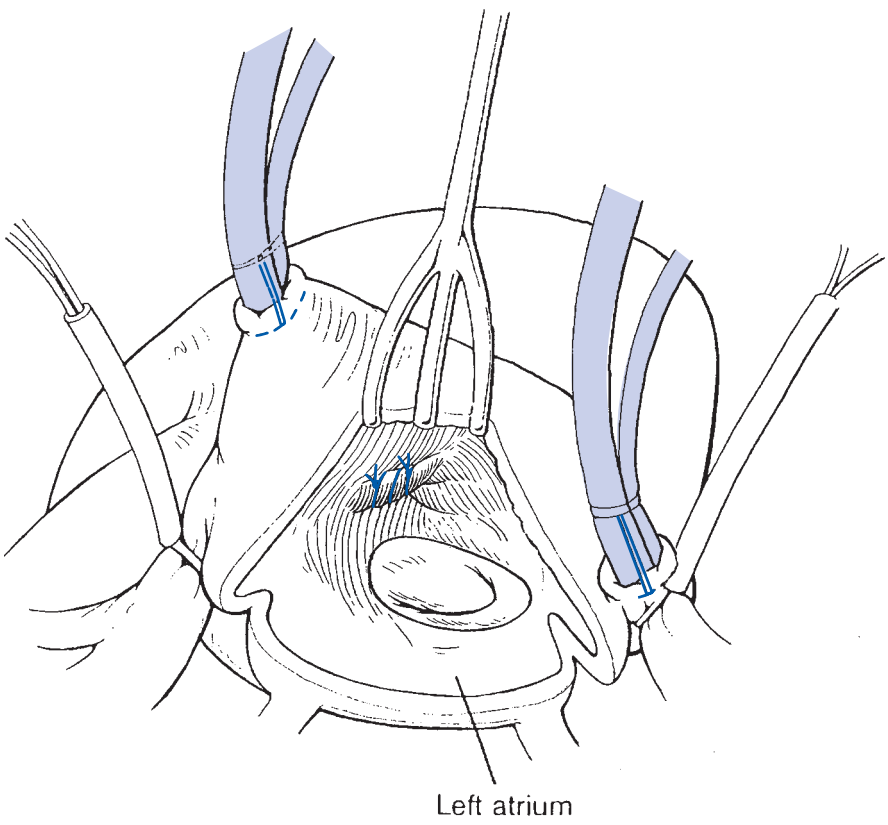

Figure 63-10. Repair of left atrial wall after removal of myxomas.

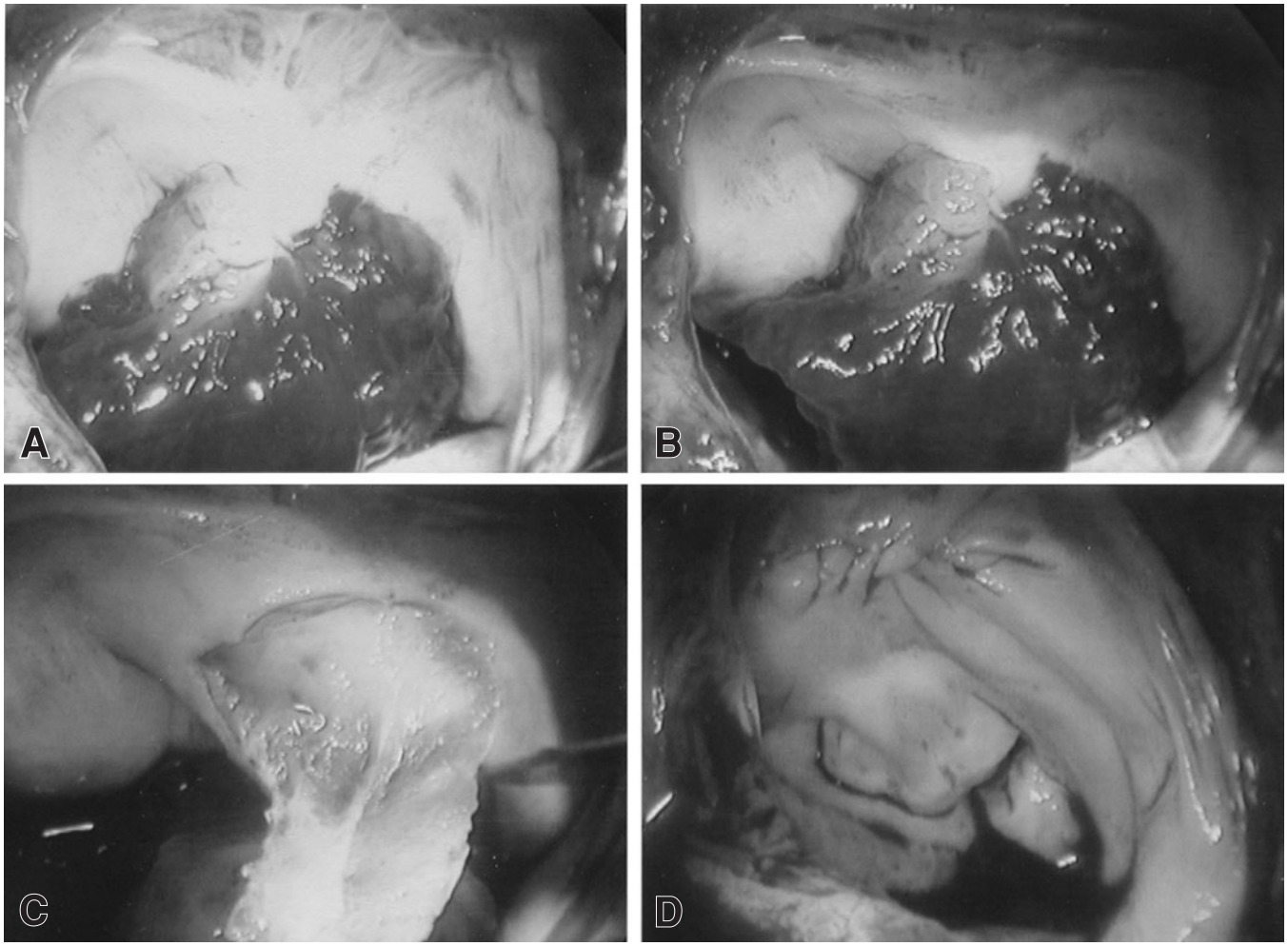

Figure 63-11. Photographs of left atrial myxoma removal and repair.

attachment and easy patch closure of the atrial septum if necessary.

Right atrial myxomas pose special venous cannulation problems, and intraoperative echocardiography may be of benefit in allowing safe cannulation. Both venae cavae may be cannulated directly. When low- or high-lying tumor pedicles preclude safe transatrial cannulation, cannulation of the jugular or femoral vein can provide venous drainage of the upper or lower body. In general, we always can cannulate the superior vena cava distal enough from the right atrium to allow adequate tumor resection, but occasionally femoral venous cannula drainage has been necessary for low-lying right atrial tumors encroaching on the inferior vena caval orifice. If the tumor is large or attached near both caval orifices, peripheral cannulation of both jugular and femoral veins may be used to initiate cardiopulmonary bypass and deep hypothermia. After the aorta is cross-clamped and the heart is arrested with antegrade cardioplegia, the right atrium may be opened widely for resection of the tumor and reconstruction of the atrium using pericardium or polytetrafluoroethylene during a period of circulatory arrest if this is needed for a dry field. Resection of large or critically placed right atrial myxomas often requires careful preoperative planning, intraoperative TEE, and special extracorporeal perfusion techniques to ensure complete removal of the tumor, protection of right atrial structures, and reconstruction of the atrium. Because myxomas rarely extend deep in the endocardium, it is not necessary to resect deeply around the conduction tissue. The tricuspid valve and the right atrium, as well as the left atrium and ventricle, should be inspected carefully for multicentric tumors in patients with right atrial myxoma, with or without familial myxoma. However, in the age of pre- and intraoperative TEE, it is unusual to find additional tumors not seen on echocardiography.

Regardless of the surgical approach, the ideal resection encompasses the tumor and a portion of the cardiac wall or interatrial septum to which it is attached. Whether excision of full-thickness wall is necessary or excision of only an endocardial attachment is sufficient to prevent recurrence is controversial. Our policy is to resect full thickness whenever possible. However, only partial-thickness resection of the area of tumor attachment has been performed when anatomically necessary without a noted increase in recurrence rate.[109,110]

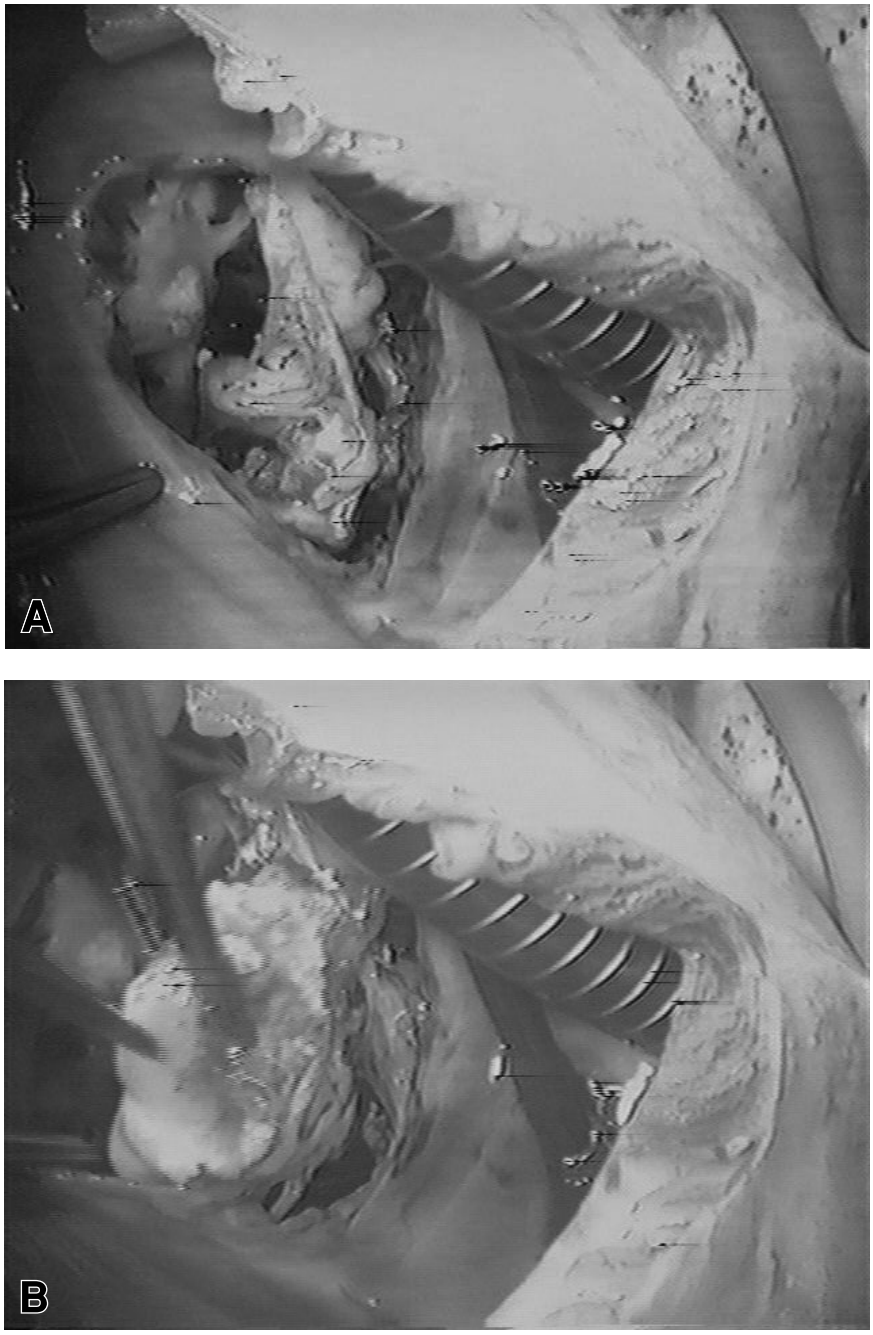

Figure 63-12. *A.* Takedown of atrial ventricular valve for ventricular exposure. *B.* Tumor exposure after valve takedown.

Ventricular myxomas usually are approached through the atrioventricular (AV) valve[111] or by detaching the anterior portion of the AV valve for exposure and resection and reattachment after resection (Fig. 63-12). Occasional small tumors in either outflow tract can be removed through the outflow valve.[111,112] If necessary, the tumor is excised through a direct incision into the ventricle, but this is unusual. It is not necessary to remove the full thickness of the ventricular wall because no recurrences have been reported with partial-thickness excisions. As with right atrial myxoma, the presence of ventricular myxoma prompts inspection for other tumors because of the high incidence of multiple tumors.

Every care should be taken to remove the tumor without fragmentation. Following tumor removal from the field, the area should be liberally irrigated, suctioned, and inspected for loose fragments. Whether blood removed from the field during tumor manipulation should be discarded or returned to the pump circuit is also controversial. There are rare instances of distant metastases from myxoma many years after tumor resection, and these reports raise the issue of potential intraoperative dissemination of tumor.[113,114] We use the cardiotomy suction during operation but use the wall suction during the brief time that the tumor is actually excised. We reason that tumor macroemboli entering the

profusion circuit will be filtered out in the cardiotomy reservoir. Considering the growth of the tumor within the bloodstream, its friable character would seem to pose no greater threat for distant metastases during tumor removal than it did during tumor development. The low malignant potential of the vast majority of myxomas and the rarity of metastasis further support this policy of retaining rather than discarding blood, and we believe that most cases of metastatic implantation of myxoma represent a preoperative embolic event.

MINIMALLY INVASIVE APPROACHES TO SURGICAL REMOVAL: Minimally invasive approaches are being applied with increasing frequency in all areas of cardiac surgery, and cardiac tumors are no exception. Experience is confined to benign tumors and is quite limited. Approaches have included right parasternal or partial sternotomy exposure with standard cardioplegic techniques,[115] right submammary incision with femoral-femoral bypass and nonclamped ventricular fibrillation,[116] and the right submammary port access method with antegrade cardioplegia and ascending aortic balloon occlusion.[117] Minimally invasive cardiac surgery may be used in a select group of patients with cardiac tumors. Thoracoscopic techniques have been used to aid in visualization and removal of ventricular fibroelastomas[118–120] (Fig. 63-13). There have been case reports of myxoma removal via thoracoscopy.[121] It is important to remember that use of a minimally invasive technique must not compromise complete surgical excision. Results in this limited number of selected patients have been good, but more experience and longer follow-up are needed before this can be recommended as a standard approach.

Results

Removal of atrial myxomas carries an operative mortality rate of 5% or less.[31] A review of 202 resections indicates that operative mortality is related to advanced age or disability and comorbid conditions.[113] Excision of ventricular myxomas carries a higher risk (approximately 10%), but the experience is small. Our experience over the last 15 years with 85 myxomas shows no operative or hospital mortality.

Recurrence of nonfamilial sporadic myxoma is approximately 1 to 4%.[4,109,110] It probably is even lower in patients with a normal DNA genotype. Many large series report no recurrent tumors.[109,122–125] The 20% of patients with sporadic myxoma and abnormal DNA have a recurrence rate estimated at between 12% and 40%.[4,62] The recurrence rate is highest in patients with familial complex myxomas, all of whom exhibit DNA mutation, and this is estimated to be about 22%.[4] Overall, recurrences are more common in younger patients. The disease-free interval averages about 4 years and can be as brief as 6 months.[109] Most recurrent myxomas occur within the heart, in the same or different cardiac chambers, and may be multiple.[29,46,126,127] The relationship of local recurrence to the adequacy of the original resection remains unsettled because sporadic tumors rarely recur even if full-thickness excision of the base is not done and because recurrent tumors often do not recur at the site of the original tumor.[109,128] Extracardiac recurrence after resection of tumor, presumably from embolization and subsequent tumor growth and local invasion, has been observed.[29,126–128] The biology of the tumor, dictated by gene expression rather than histology, may be the only reliable factor predicting recurrence. DNA testing of all patients with cardiac myxoma may prove to be the best predictor of the likelihood of recurrence.[129]

Uncertainty concerning the true malignant potential of myxomas has increased as reports that myxomas generally classified as "malignant" are found on subsequent review to be sarcomas with myxoid degeneration.[130] However, this issue also remains unsettled because of reports of metastatic growth of embolic myxoma fragments in the brain, arteries, soft tissue, and bones.[80,128,131–137] Symptomatic lesions of possible metastatic myxoma should be excised if possible.[80,131]

The extent to which patients should be subjected to long-term echocardiographic surveillance after myxoma resection is not standardized. It would seem prudent to closely follow patients who are treated initially for multicentric tumors, those whose tumors are removed from unusual locations in the heart, all tumors believed to have been incompletely resected, and all tumors found to have an abnormal DNA genotype. Patients undergoing resection of tumors thought to be myxomas but with malignant characteristics at pathologic examination should have long-term, careful follow-up.

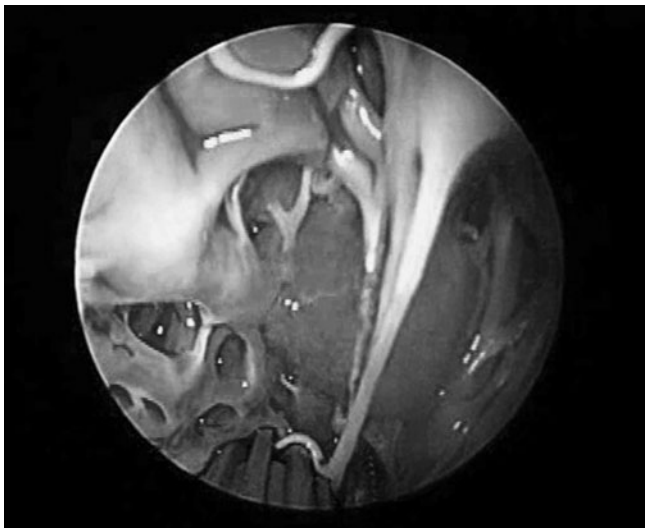

Figure 63-13. Thoracoscopic view of left atrial fibroelastoma.

Other Benign Cardiac Tumors

As shown in Table 63-2, myxomas comprise approximately 41% of benign cardiac tumors, with three other tumors (i.e., lipoma, papillary fibroelastoma, and rhabdomyoma) together contributing a similar proportion. A number of rarely encountered tumors account for the remainder.

Lipoma

Lipomas are well-encapsulated tumors consisting of mature fat cells that may occur anywhere in the heart but also are found in the pericardium, subendocardium, subepicardium, and intra-atrial septum.[2] They may occur at any age and have no sex predilection. Lipomas are slow growing and may attain considerable size before producing obstructive or arrhythmic symptoms. Many are asymptomatic and are discovered incidentally on routine chest roentgenogram, echocardiogram, or at surgery or autopsy.[138,139] Subepicardial and parietal lipomas tend to compress the heart and may be associated with pericardial effusion. Subendocardial tumors may produce chamber obstruction. The right atrium and left ventricle are the sites affected most often. Lipomas lying within the myocardium or septum can produce arrhythmias or conduction abnormalities.[140,141] Large tumors that produce severe symptoms should be resected. Smaller, asymptomatic tumors encountered unexpectedly during cardiac operation should be removed if excision can be performed without adding risk to the primary procedure. These tumors are not known to recur.

Lipomatous hypertrophy of the interatrial septum

Nonencapsulated hypertrophy of the fat within the atrial septum is known as *lipomatous hypertrophy.*[2] This abnormality is more common than cardiac lipoma and usually is encountered in elderly, obese, or female patients as an incidental finding during a variety of cardiac imaging procedures.[123] Various arrhythmias and conduction disturbances have been attributed to its presence.[124,141,142] The main problem is differentiation from a cardiac neoplasm when the lesion is discovered on echocardiography.[143] After the demonstration of a mass by echocardiography, the typical T1 and T2 signal intensity of fat on MRI usually can establish a diagnosis.[144,145] Arrhythmias and heart block are considered by some as indications for resection, but data are lacking as to the long-term benefits from resection.[146]

Papillary fibroelastoma of the heart valves

Papillary fibroelastomas are tumors that arise characteristically from the cardiac valves or adjacent endocardium.[147] Grossly, these tumors are described as resembling sea anemones with frondlike projections (Fig. 63-14). The AV and semilunar valves are affected with equal frequency. Papillary fibroelastomas formerly were thought to be innocuous because they were incidental findings at autopsy. It is now known that they are capable of producing obstruction of flow, particularly coronary ostial flow, and may embolize to the brain and produce stroke.[148–161] They are usually asymptomatic until a critical event occurs but now are found more often because of the more frequent use of echocardiography. Papillary fibroelastomas of the cardiac valve should be resected whenever diagnosed because of their known tendency to produce life-threatening complications. Valve repair rather than replacement should follow the resection of these benign tumors whenever technically feasible, using conservative margins of resection. Cytomegalovirus has been recovered in these tumors, suggesting the possibility of viral induction of the tumor and chronic viral endocarditis.[156]

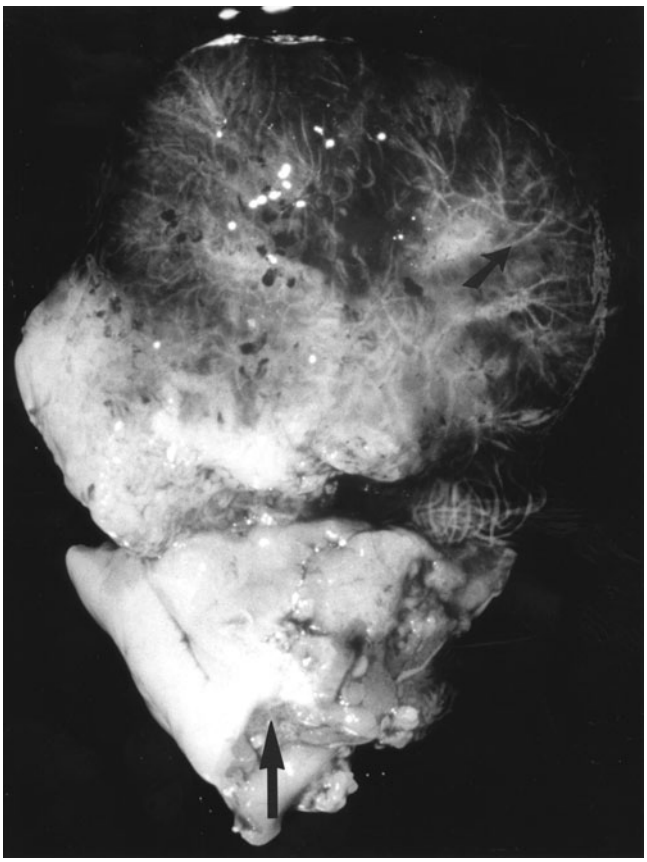

Figure 63-14. Papillary fibroelastoma of the tricuspid valve demonstrating delicate fronds.

Rhabdomyoma

Rhabdomyoma is the most frequently occurring cardiac tumor in children. It usually presents during the first few days after birth. It is thought to be a myocardial hamartoma rather than a true neoplasm.[162] Although rhabdomyoma appears sporadically, it is associated strongly with tuberous sclerosis, a hereditary disorder characterized by hamartomas in various organs, epilepsy, mental deficiency, and sebaceous adenomas. Fifty percent of patients with tuberous sclerosis have rhabdomyoma, but more than 50% of patients with rhabdomyoma have or will develop tuberous sclerosis.[163,164] The exceptional patient is one with a solitary, single rhabdomyoma who does not have or develop tuberous sclerosis.

Over 90% of rhabdomyomas are multiple and occur with approximately equal frequency in both ventricles.[165] The atrium is involved in fewer than 30% of patients. Pathologically, these tumors are firm, gray, and nodular and tend to project into the ventricular cavity. Micrographs show myocytes of twice normal size filled with glycogen and containing hyperchromatic nuclei and eosinophilic-staining

cytoplasmic granules.[2,166] Scattered bundles of myofibrils can be seen within cells by electron microscopy.[165]

The most common presentation is heart failure caused by tumor obstruction of cardiac chambers or valvular orifice flow. Clinical findings may mimic valvular or subvalvular stenosis. Arrhythmias, particularly ventricular tachycardia and sudden death, may be a presenting symptom.[166] Atrial tumors may produce atrial arrhythmias.[166] The diagnosis is suggested by clinical features of tuberous sclerosis and is made by echocardiography. Rarely, no intramyocardial tumor is found in a patient with ventricular arrhythmias, and the site of rhabdomyoma is located by electrophysiologic study.[166]

Early operation is recommended in patients who do not have tuberous sclerosis before 1 year of age.[125] The tumor usually is removed easily in early infancy, and some can be enucleated.[125] Unfortunately, symptomatic tumors often are both multiple and extensive, particularly in patients with tuberous sclerosis, who, unfortunately, have a dismal long-term outlook. In such circumstances, surgery offers little benefit.

Fibroma

Fibromas are the second most common benign cardiac tumor, with over 83% occurring in children. These tumors are solitary, occur exclusively within the ventricle and the ventricular septum, and affect the sexes equally. Fewer than 100 tumors have been reported, and most are diagnosed by age 2 years. These tumors are not associated with other disease, nor are they inherited. Fibromas are nonencapsulated, firm, nodular, gray-white tumors that can become bulky. They are composed of elongated fibroblasts in broad spiral bands and whirls mixed with collagen and elastin fibers. Calcium deposits or bone may occur within the tumor and occasionally are seen on roentgenography (Figs. 63-15 and 63-16).

Most fibromas produce symptoms through chamber obstruction, interference with contraction, or arrhythmias. Depending on size and location, such a tumor may interfere with valve function, obstruct flow paths, or cause

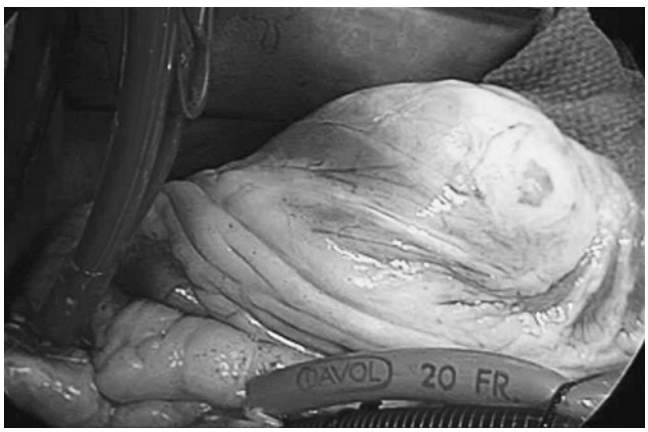

Figure 63-15. Left atrial fibroma.

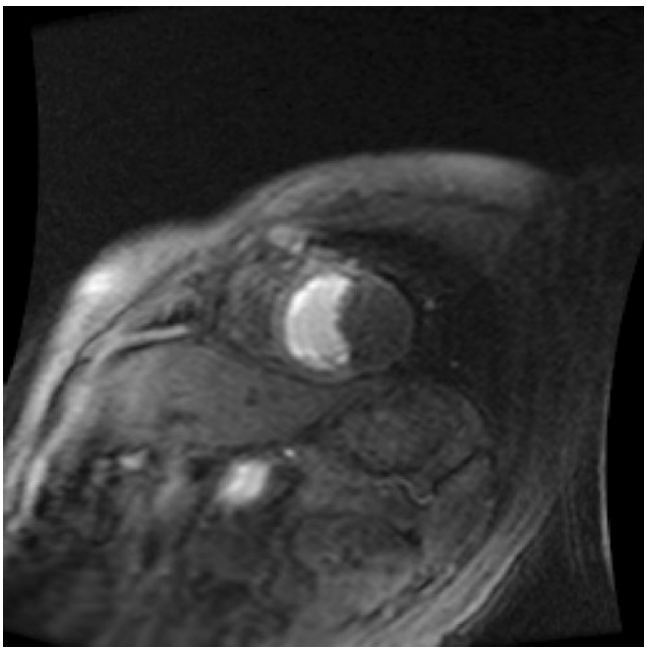

Figure 63-16. MRI of left ventricular fibroma.

sudden death from conduction disturbances in up to 25% of patients.[125] Intracardiac calcification on chest roentgenograms suggests the diagnosis, which is confirmed by echocardiogram.

Surgical excision is successful in some patients, particularly if the tumor is localized, does not involve vital structures, and can be enucleated.[125,167–169] However, it is not always possible to remove the tumor completely, and partial removal is only palliative, although some patients have survived many years.[125,168] Operative mortality may be high in infants. Most cases are in adolescents and adults.[125,167,168] Successful, complete excision is curative.[167,168] Children with extensive fibromas have been treated with cardiac transplantation.[169,170]

Mesothelioma of the AV node

Mesothelioma of the AV node, also termed *polycystic tumor, Purkinje tumor,* or *conduction tumor,* was mentioned in the pathologic classification of tumors. It is a relatively small, multicystic tumor that arises in proximity to the AV node and may extend upward into the interventricular septum and downward along the bundle of His.[2] Mesothelioma is associated with heart block, ventricular fibrillation,[171] and sudden death. Cardiac pacing alone does not prevent subsequent ventricular fibrillation. Surgical excision has been reported.[34]

Pheochromocytoma

Cardiac pheochromocytomas arise from chromaffin cells of the sympathetic nervous system and produce excess amounts of catecholamines, particularly norepinephrine. Approximately 90% of pheochromocytomas are in the adrenal glands. Fewer than 2% arise in the chest. Only 32 cardiac

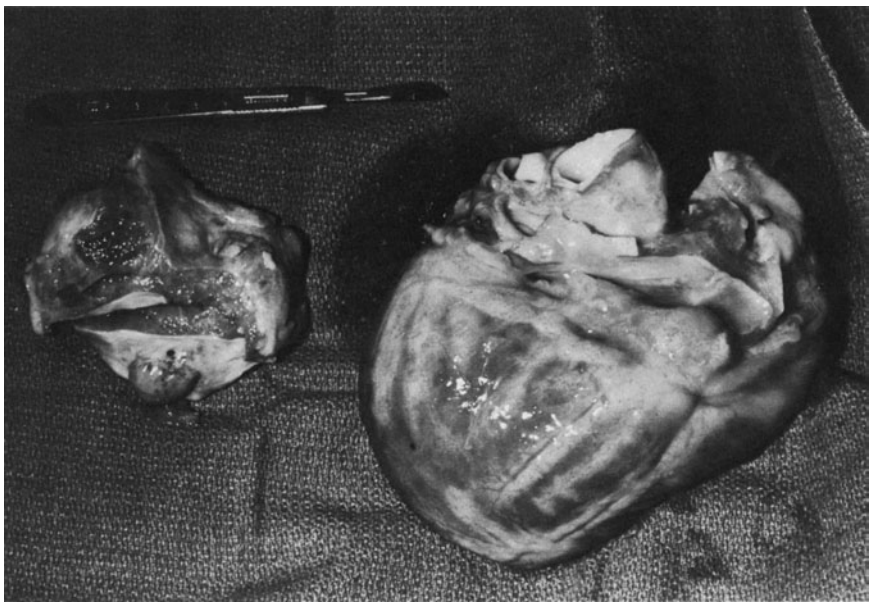

Figure 63-17. Excised left atrial pheochromocytoma and explanted heart prior to reimplantation.

pheochromocytomas had been reported by 1991.[172] The tumor predominantly affects young and middle-aged adults with an equal distribution between the sexes. Approximately 60% occur in the roof of the left atrium. The remainder involve the interatrial septum or anterior surface of the heart. The tumor is reddish brown, soft, lobular, and consists of nests of chromatin cells.

The patients usually present with symptoms of uncontrolled hypertension or are found to have elevated urinary catecholamines. The tumor usually is located by scintigraphy using [^{131}I]metaiodobenzylguanidine[173,174] and CT or MRI.[173,174] Cardiac catheterization with differential blood chamber sampling sometimes is necessary.[172] Because these tumors are vascular and may be near major coronary arteries, coronary arteriograms are advisable.

After the tumor is located, it should be removed using cardiopulmonary bypass with cardioplegic arrest. Patients require preanesthetic alpha and beta blockade and careful intraoperative and immediate postoperative monitoring. Most tumors are extremely vascular, and uncontrollable operative hemorrhage has occurred.[174] Resection may require removal of the atrial and/or ventricular wall or a segment of a major coronary artery.[172] Explantation of the heart to allow resection of a large left atrial pheochromocytoma has been attempted[175] (Fig. 63-17). Transplantation has been performed for nonresectable tumor. Complete excision produces cure.[168–170]

Paraganglioma

Paragangliomas are endocrine tumors that can secrete catecholamines. As a result, their presentation is often similar to that of pheochromocytomas. When found within the thoracic cavity, they are located most often in the posterior mediastinum. Paragangliomas typically present with atypical chest pain.[176,177] On echocardiography, they are often large and highly vascular tumors.[178] On cardiac catheterization, they may be intimately associated with the coronary arteries (Fig. 63-18). If they involve the left atrium, the technique of cardiac autotransplantation may be used to completely resect them[179] (Figs. 63-19 and 63-20).

Hemangioma

Hemangiomas of the heart are rare tumors (24 clinical cases reported), affect all ages, and may occur anywhere within the heart.[180,181] These are vascular tumors composed of capillaries or cavernous vascular channels. Patients usually develop dyspnea, occasional arrhythmias, or signs of right-sided heart failure.[182] Diagnosis is difficult, and chest roentgenography may be abnormal but is not specific. Echocardiography or cardiac catheterization usually but not always establishes a diagnosis of cardiac tumor by showing an intracavity filling defect.[183] CT and MRI should be done. Axial T2-weighted MRI should show a high signal mass owing to

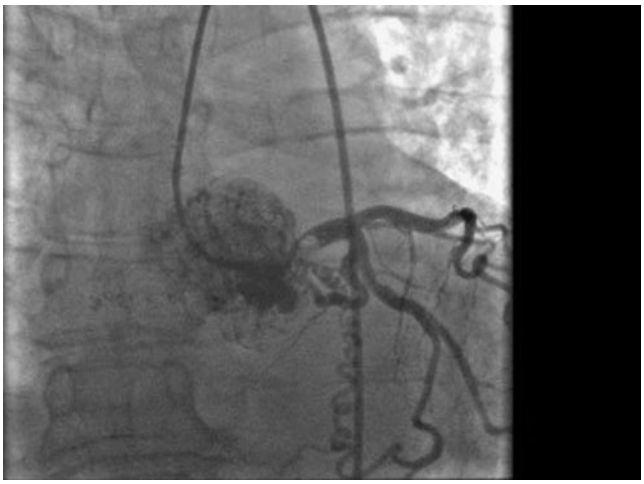

Figure 63-18. Paraganglioma blush of tumor.

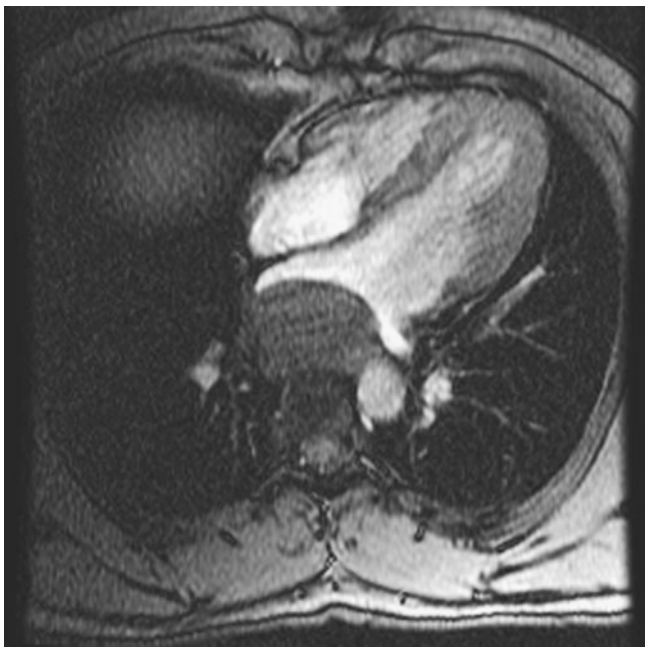

Figure 63-19. MRI of left atrial paraganglioma.

vascularity[184] (Fig. 63-21). Coronary angiography typically shows a tumor blush and maps the blood supply to the tumor.

The tumors can be resected in asymptomatic patients, and cardiopulmonary bypass is recommended. Meticulous ligation of feeding vessels is required to prevent postoperative residual arteriovenous fistulas or intracavity communications. Partial resections have produced long-term benefits.[180] Tumors rarely resolve spontaneously.[185]

Teratoma

Cardiac teratoma is a rare tumor that usually presents in infants and young children but has occurred in adults.[186]

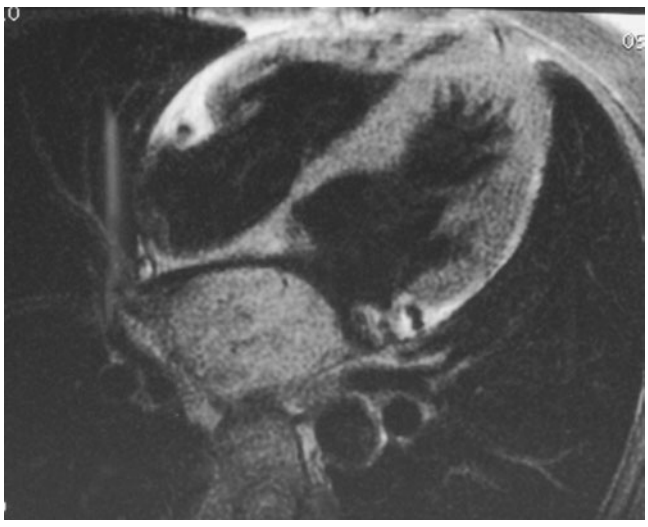

Figure 63-20. MRI of left atrial paraganglioma.

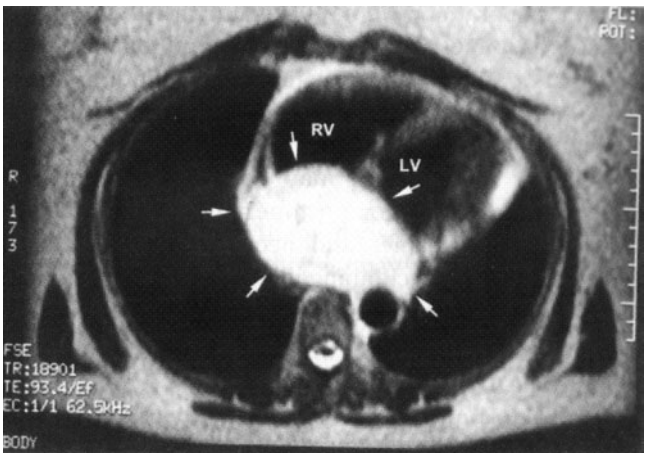

Figure 63-21. Axial T2-weighted magnetic resonance image showing high signal mass of left atrial hemangioma. (*Reproduced with permission from Lo JJ, Ramsay CN, Allen JW, et al: Left atrial cardiac hemangioma associated with shortness of breath and palpitations. Ann Thorac Surg 2002; 73:979.*)

About 80% of the tumors are benign, and the remainder have microscopic or clinically malignant cells.[187] These tumors are discovered by echocardiography after a variety of symptoms lead to cardiac or mediastinal evaluation. There is little experience with surgical removal, which should be possible with modern imaging and surgical technology.

Castleman tumor

Castleman disease is a poorly understood lymphoproliferative disorder. The disease was first described by Castleman and colleagues in 1956.[188] It typically presents as a solitary lesion in the mediastinum. The most common histologic type is hyaline vascular, which accounts for approximately 90% of cases and often behaves in a benign fashion. The more aggressive subgroups are the plasma and mixed-cell types, which have a more malignant behavior.[189,190] Patients may have a localized or multicentric disease with lymph node involvement, typically in the mediastinum. These tumors typically present as well-circumscribed masses.[191] There have been reports of Castleman disease with myocardial and coronary artery invasion. In these more aggressive cases, cardiac assist devices have been used as a bridge to recovery[192] (Figs. 63-22 and 63-23). CT imaging of the lesions reveals atypical or target-like enhancement that corresponds to various degrees of degeneration, necrosis, and fibrosis. Technetium-99m tetrofosmin and [^{123}I]beta-methyl-iodophenyl pentadecanoic acid (BMIPP) imaging may aid in the diagnosis. On BMIPP, these tumors show reduced uptake compared with the surrounding normal myocardium.[193,194] Complete surgical resection is considered curative.[195]

PRIMARY MALIGNANT TUMORS

Primary cardiac malignancy is very uncommon, with only 21 surgically treated cases noted in a 25-year surgical experience

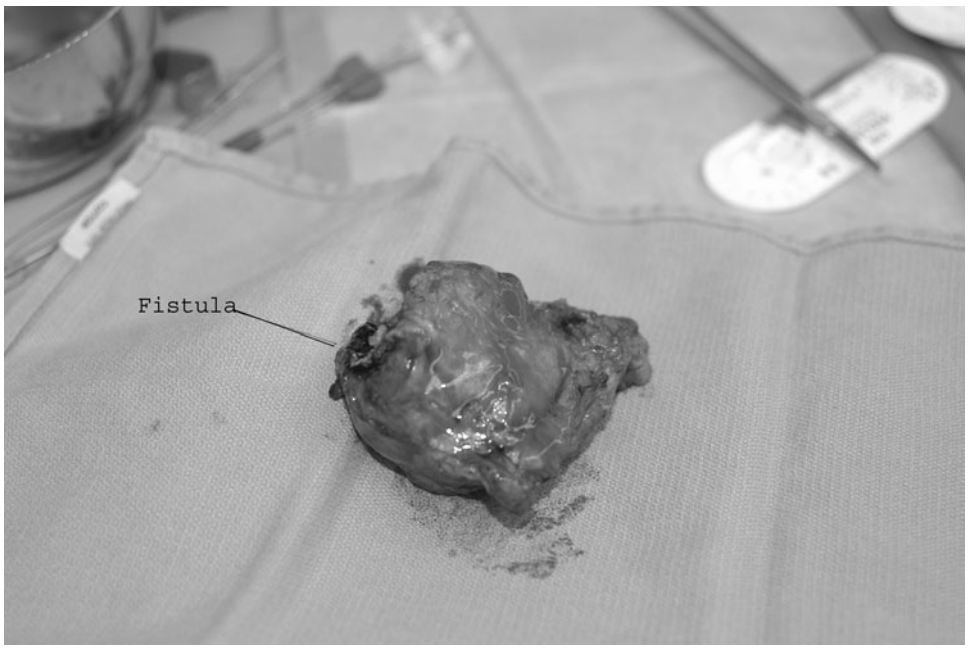

Figure 63-22. Castleman tumor showing fistula site.

from 1964 to 1969, combining the experience of two large institutions, the Texas Heart Institute and the M.D. Anderson Cancer Center in Houston.[196] Even in busy centers, primary cardiac malignancy continues to challenge the diagnostic ability and surgical skills of thoracic surgeons. Approximately 25% of primary cardiac tumors are malignant, and of these, about 75% are sarcomas. McAllister's survey of cardiac tumors found the most common to be angiosarcomas (31%), rhabdomyosarcomas (21%), malignant mesotheliomas (15%), and fibrosarcomas (11%)[2] (Table 63-4).

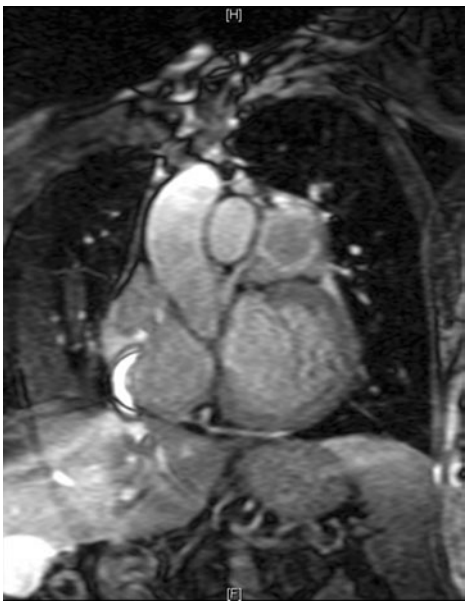

Figure 63-23. MRI of Castleman tumor.

Table 63–4.

Primary Malignant Cardiac Neoplasms in Adults

Tumor	Number	Percentage
Angiosarcoma	39	33
Rhabdomyosarcoma	24	21
Mesothelioma	19	16
Fibrosarcoma	13	11
Lymphoma	7	6
Osteosarcoma	5	4
Thymoma	4	3
Neurogenic sarcoma	3	2
Leiomyosarcoma	1	<1
Liposarcoma	1	<1
Synovial sarcoma	1	<1
Total	117	100

Source: Reproduced with permission from McAllister HA Jr, Fenoglio JJ Jr: Tumors of the cardiovascular system, in Atlas of Tumor Pathology. Washington DC, Armed Forces Institute of Pathology, 1978; fas. 15.

Table 63–5.

Symptoms of Primary Malignant Cardiac Tumors

	Number	Percentage
Dyspnea	13/21	61.9
Chest pain	6/21	28
Congestive heart failure	6/21	28
Palpitations	5/321	24
Fever	3/21	14
Myalgia	2/21	10

Source: Reproduced with permission from Murphy MC, Sweeney MS, Putnam JB Jr, et al: Surgical treatment of cardiac tumors: A 25-year experience. Ann Thorac Surg 1990; 49:612.

Primary malignant cardiac tumors arise sporadically, showing no inherited linkage. Although they may span the entire age spectrum, they usually occur in adults over 40 years of age. The patients usually present with symptoms of congestive heart failure, pleuritic chest pain, malaise, anorexia, and weight loss.[186,197] The most common symptom has been dyspnea[196] (Table 63-5). Some develop refractory arrhythmias, syncope, pericardial effusion, and tamponade.[196] The chest x-ray may be abnormal and even show a mass lesion, but the definite diagnosis usually is made with cardiac echocardiography.[197,198] We have seen an angiosarcoma of the right side of the heart that presented as multiple nodules on chest x-ray, and at thoracoscopy it was found to present multiple reddish lesions of the lung consistent with angiosarcoma. Subsequent cardiac echocardiography was used to confirm the diagnosis of a cardiac primary tumor. Right atrial lesions are more frequently malignant (usually angiosarcoma) than left-sided lesions (usually myxoma but, when malignant, often malignant fibrous histiocytoma). If malignancy is suspected, chest CT or MRI may suggest histology and provide detailed anatomy and help in staging and assessing resectability. The current status of positron-emission tomographic (PET) scans in evaluating these patients remains controversial. We perform cardiac catheterization on all patients over 40 years of age presenting with intracardiac masses and on all patients with large right atrial masses. Malignancy may be suggested and coronary involvement suspected by tumor blush (Fig. 63-24). This is not pathognomic because we have seen a large feeding vessel and tumor blush in a histologically confirmed myxoma.

Unfortunately, primary cardiac malignancy may grow to a large size prior to detection and involve portions of the heart not amenable to resection. Some of these patients have been considered for transplantation and will be discussed later. Otherwise, palliative medical therapy can be attempted with radiation therapy, although success in both symptom relief and longevity has been somewhat limited. Whether the tumor is primary or secondary, the decision to resect is based on tumor size and location and an absence of metastatic spread seen on complete evaluation. Unfortunately, most primary cardiac malignancies that have been referred to our center were considered to be benign initially and were resected incompletely at presentation. If malignancy is suspected or confirmed, and if the lesion appears anatomically resectable and there is no metastatic disease, then resection should be considered. If complete resection is possible, surgery provides better palliation and potentially can double

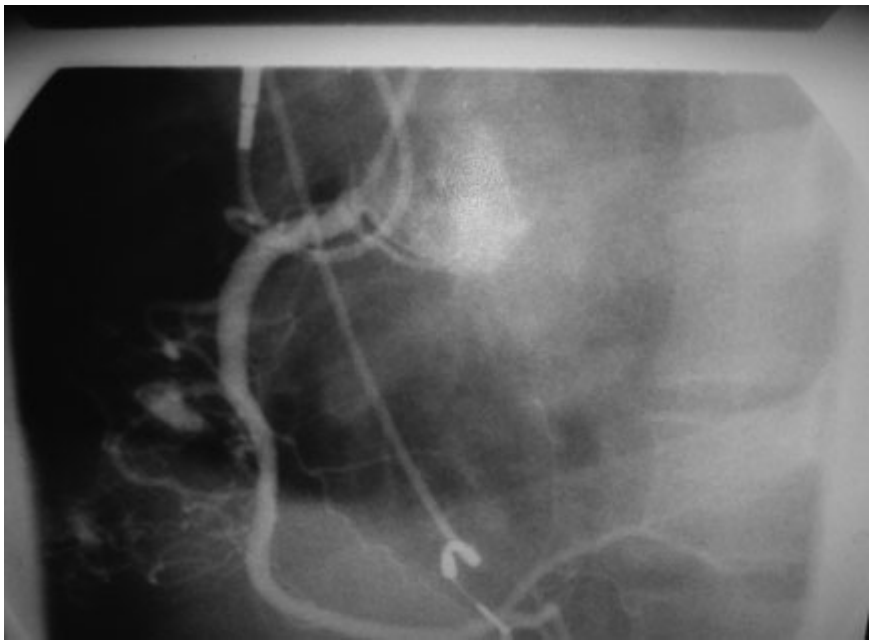

Figure 63-24. Tumor blush in right atrial sarcoma.

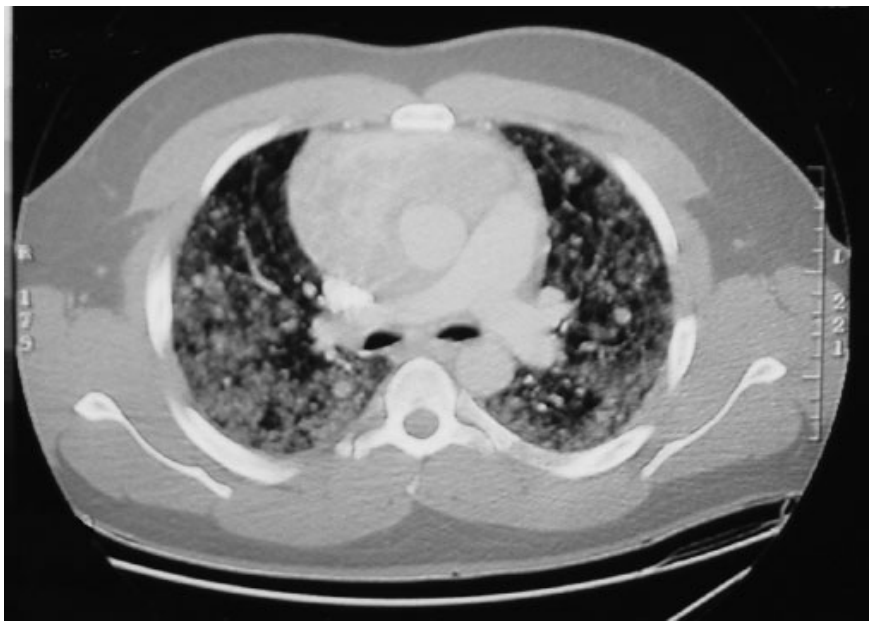

Figure 63-25. Angiosarcoma with extensive involvement of mediastinum.

survival.[199] After resection, we recommend adjuvant chemotherapy and believe that this will improve survival slightly[187,199,200] and add to our ability to treat this desperate disease. Complete resection will depend on the location of the tumor, the extent of involvement of the myocardium and/or fibrous skeleton of the heart, and histology.

Angiosarcoma

Angiosarcomas are two to three times more common in men than in women and have a predilection for the right side of the heart. Eighty percent arise in the right atrium.[197,201,202] These tumors tend to be bulky and aggressively invade adjacent structures, including the great veins, tricuspid valve, right ventricular free wall, interventricular septum, and right coronary artery[201] (Fig. 63-25). Obstruction and right-sided heart failure are not uncommon. Pathologic examination of resected specimens demonstrates anastomosing vascular channels lined with typical anaplastic epithelial cells. Unfortunately, most of these tumors have spread by the time of presentation, usually to the lung, liver, and brain.[197] Without resection, 90% of the patients are dead within 9 to 12 months of diagnosis despite radiation or chemotherapy.[32,197] We have seen carefully selected patients without evidence of spread on metastatic evaluation who have undergone complete surgical resection with subsequent chemotherapy (Fig. 63-26). Surgical resection may include the right atrium. In addition, right coronary bypass and even tricuspid valve repair or replacement may be undertaken (Figs. 63-27 and 63-28). We have had no hospital mortality in this small group, and the main problem remains metastasis rather than recurrence at the local site.

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma in adults. Its occurrence as a cardiac primary malignancy has been relatively recently accepted as a specific entity. It is characterized histologically by a mixture of spindle cells in a storiform pattern, polygonal cells resembling histiocytes, and malignant giant cells. The cell of origin is the fibroblast or histioblast.[198,204] It usually occurs in the left atrium and often mimics myxoma. In fact, every left atrial MFH referred to our institution has been previously incompletely resected when thought to represent a myxoma. The tendency to metastasize early is not as prominent as with angiosarcoma. Several reports exist documenting rapid symptomatic recurrence after incomplete resection despite chemotherapy. These patients often die of local cardiac disease prior to the development of metastases. We believe that if complete resection can be obtained (particularly if the malignant nature is recognized and complete resection can be done at the original operation) and adequate chemotherapy can be provided, we may improve survival in this otherwise dismal disease. Our group believes that incomplete resection is usually due to inadequate exposure of these broad-based tumors, which often extend to the anterior wall of the left atrium. Difficulty in exposing this posterior portion of the heart leads to inhibition of aggressive resection for clear margins and makes reconstruction difficult. We believe that these difficulties can be overcome by excising the heart and inverting it so that the posterior left atrium is now an anterior structure. This allows excellent visualization for aggressive resection and reconstruction done ex vivo, after which the heart is reimplanted (Fig. 63-29).

This was first attempted by Cooley in 1984 for a pheochromocytoma, and although it was accomplished technically, it was unsuccessful because of severe hemorrhage owing to the vascular nature of the tumor.[186] Our program first attempted this approach for MFH in 1998[204] (Fig. 63-30).

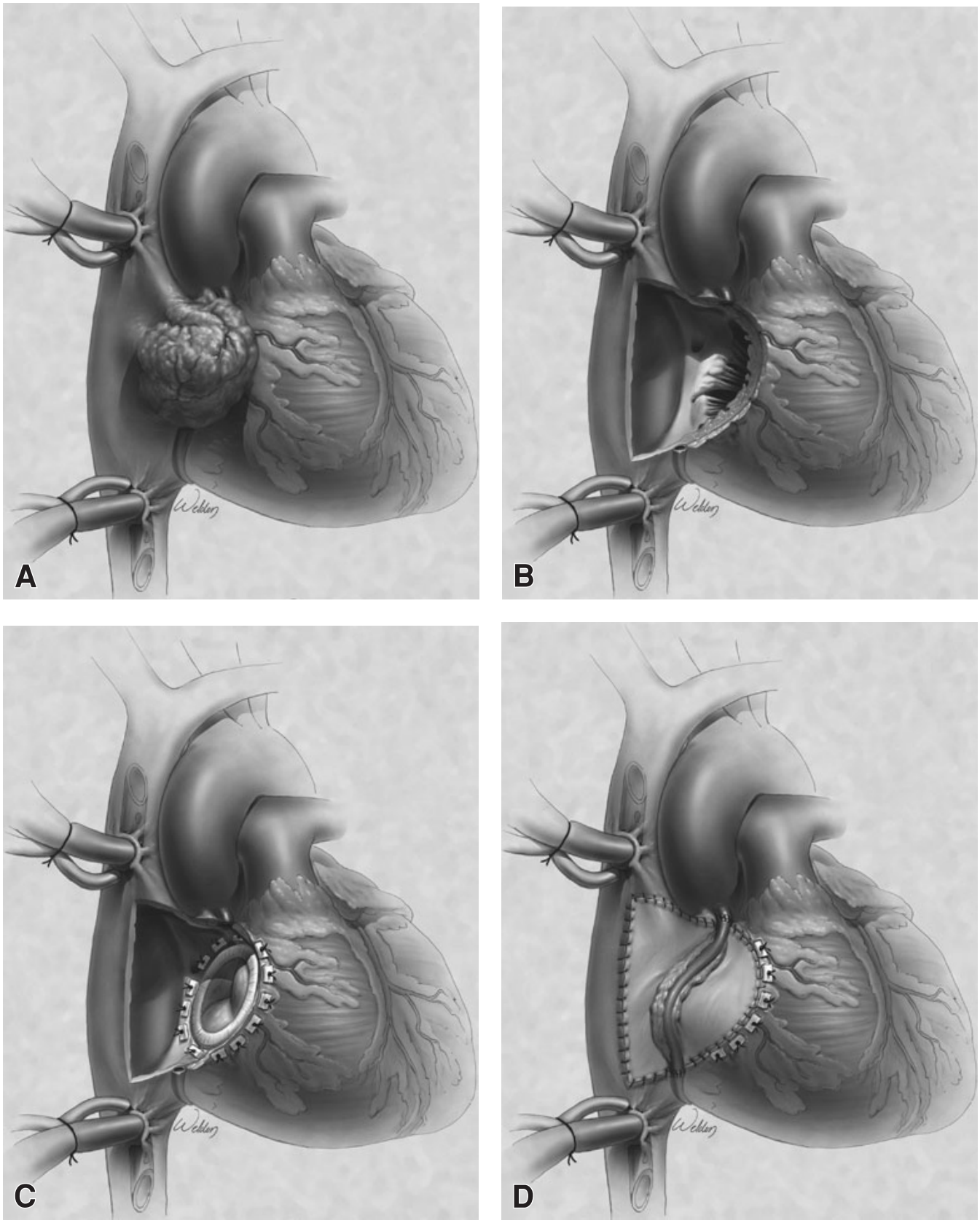

Figure 63-26. (A) Right atrial angiosarcoma involving right coronary artery and tricuspid valve. (B) Excision of tumor with right coronary artery and tricuspid valve. (C) Tricuspid valve replaced. (D) Completed repair using bovine pericardium. (*Copyright 2002, Baylor College of Medicine.*)

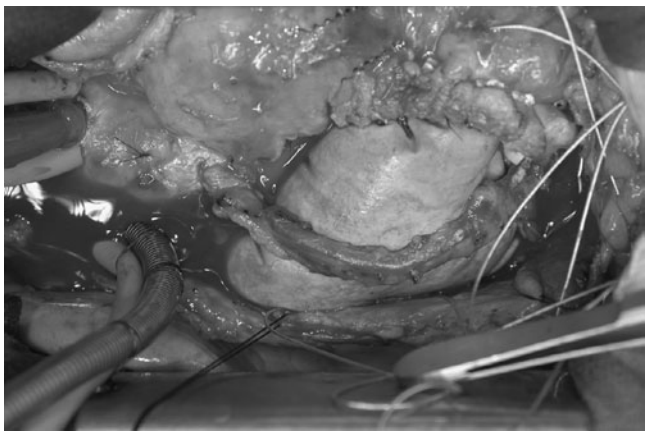

Figure 63-27. Right atrial angiosarcoma (final repair).

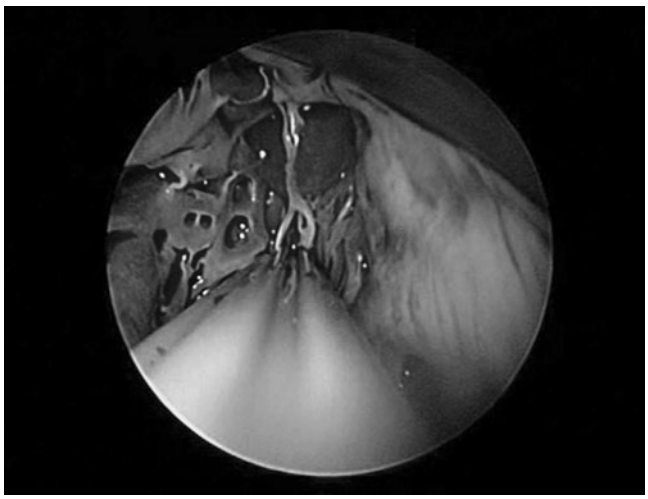

Figure 63-28. Thoracoscopic view of left atrial fibroelastoma.

We have performed 14 of these autotransplant procedures with no operative or hospital mortality. Seven patients have died of metastatic disease without local recurrence, and six are alive. Our longest survivor lived for 6 years and died of local recurrence and metastatic disease. All patients were given adjuvant chemotherapy. This has proven to be an efficacious technique at local control with a low mortality in our hands, but metastasis is still common and strongly suggests that further improvements in survival will require more effective, biologically based systemic therapy.

Rhabdomyosarcoma

Rhabdomyosarcomas do not evolve from rhabdomyomas and occur equally in the sexes. The tumors are multicentric in 60% of patients and arise from either ventricle. These tumors frequently invade cardiac valves or interfere with valve function because of their intracavitary bulk. Microscopically, tumor cells demonstrate pleomorphic nuclei and spidery, wispy, streaming eosinophilic cytoplasm, usually in a muscle-like pattern (Fig. 63-31).

The tumors are aggressive and may invade pericardium. Surgical excision of small tumors may be rational, but local and distant metastases and poor response to radiation or chemotherapy limit survival to less than 12 months in most of these patients.[167,186,187,199,205,206]

Other Sarcomas and Mesenchymal-Origin Tumors

McAllister and Fenoglio found that malignant mesotheliomas arising from the heart or pericardium and not from the surrounding pleura were the third most common malignant cardiac tumors and that fibrosarcomas were fourth.[2] However, in the two decades since their work, clinicians have

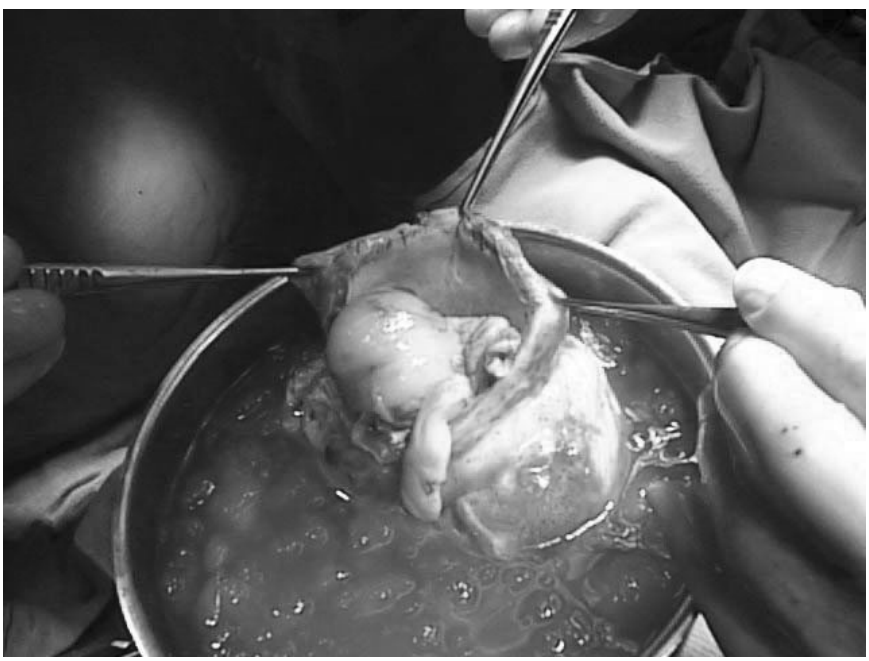

Figure 63-29. Ex vivo heart showing large sarcoma arising from the anterior left atrial wall.

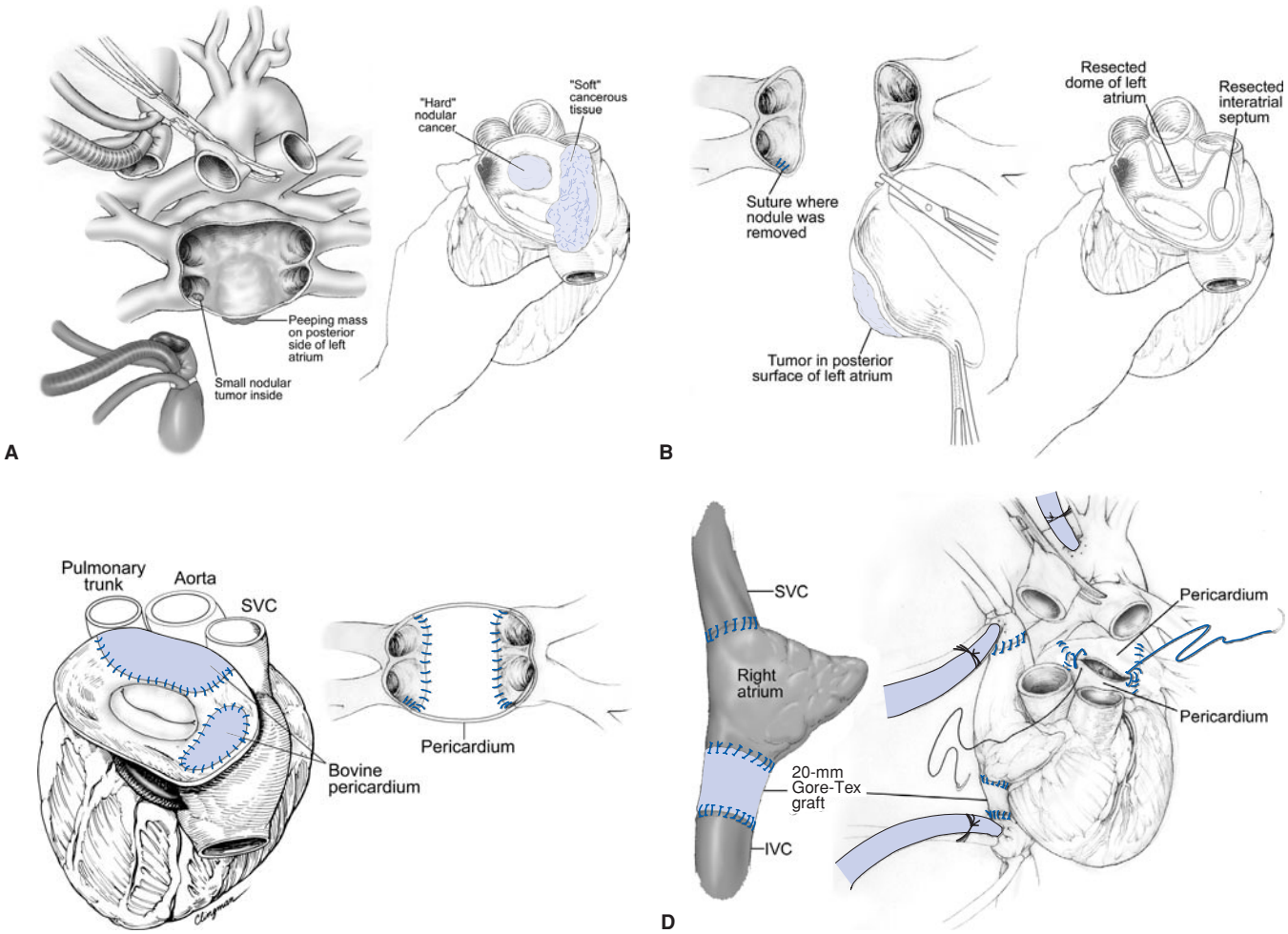

Figure 63-30. (A) Explanation of the heart for exposure of extensive left atrial sarcoma. (B) Resection of left atrial sarcoma. (C) Reconstruction of the heart with bovine pericardium after tumor resection. (D) Reimplantation of the heart using a 20-mm polytetrafluoroethylene graft between the inferior vena cava (IVC) and right atrium. SVC = superior vena cava.

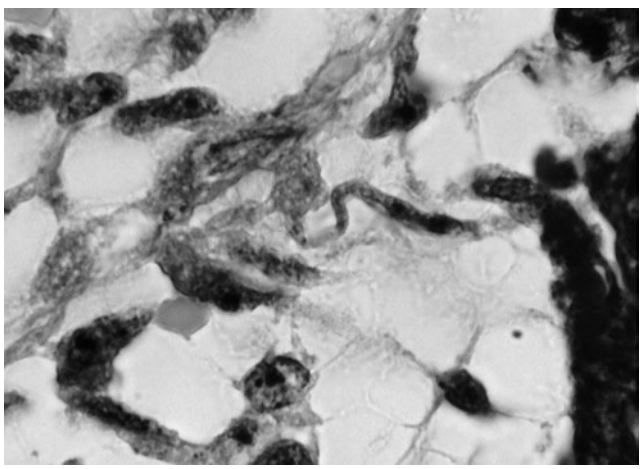

Figure 63-31. Representative microphotograph of rhabdomyosarcoma showing loosely elongated rhabdomyoblasts with distinct angulation of the muscle fibers and undifferentiated tumor cells with plump nuclei and prominent nucleoli. Masson's trichome, ×800. (*Courtesy of Dr. G. G. Pietra.*)

rarely encountered these tumors. This apparent decrease in incidence may be related to changes in histologic criteria for classifying primary malignant neoplasms since their study.[5,180,187,196–200,206–208]

The histology of these tumors can be ambiguous and difficult. These neoplasms can resemble other sarcomas, and some might be deemed fibrous histiocytomas today. The behavior of these tumors is more important, and as with other cardiac sarcomas, resection of small tumors in the absence of known metastasis perhaps is justified, but data are scarce.[32,196,199,206] This being said, it is important to rule out more diffuse thoracic involvement with mesothelioma before considering resection of an isolated cardiac or pericardial mesothelioma. A PET scan may be considered, and any suspicious pleural thickening or effusion should be evaluated carefully both radiographically and histologically.

Myosarcoma, liposarcoma, osteosarcoma, chondromyxosarcoma, plasmacytoma, and carcinosarcoma arising from the heart all have been reported,[125,208–211] but by the time diagnosis is made, only palliative therapy usually can be

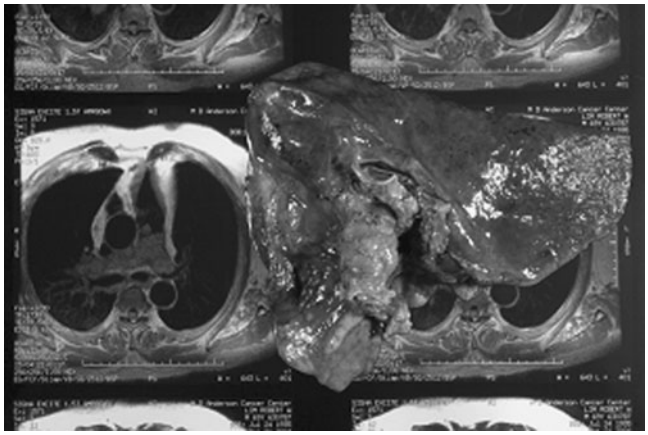

Figure 63-32. Pulmonary artery sarcoma.

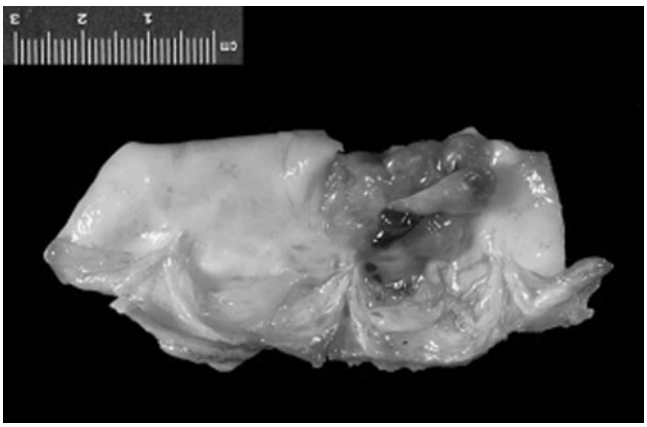

Figure 63-33. Pulmonary artery angiosarcoma showing valve involved.

offered, and surgery is indicated only occasionally. Regardless of therapy, it is unusual for patients with these diagnoses to survive more than a year.

Lymphomas

Lymphomas may arise from the heart, although this is rare.[212] Most of these tumors respond to radiation and chemotherapy. Even when complete resection is not possible, and incomplete resection is performed to relieve acute obstructive systems, radiation and chemotherapy have allowed for up to 3-year survival in selected patients.

Pulmonary Artery Sarcomas

Most pulmonary artery sarcomas are classified as angiosarcomas when a specific diagnosis has been possible. The most frequent presenting symptom is shortness of breath and peripheral edema from concomitant right-sided heart failure. The diagnostic modalities of choice for pulmonary artery sarcomas are chest CT or MRI (Fig. 63-32).

Surgical resection has been used both to improve functional status and for debulking prior to initiation of chemotherapy. Chemotherapy and radiotherapy are ineffective in the rapid relief of functional pulmonary artery obstruction caused by these tumors. These tumors usually are discovered after they have grown to considerable size (Fig. 63-33). Smaller tumors usually are clinically silent but may be discovered at the time of pulmonary artery endarterectomy for what is thought to be a case of chronic pulmonary emboli. Resection often requires replacement of a portion of the pulmonary root and branch pulmonary arteries using pulmonary homografts. Pneumonectomy may be required to resect the tumor completely. We have data on 5 patients with pulmonary artery sarcoma, 3 of whom required concomitant pneumonectomy. There were no in-hospital or 30-day deaths, and all patients were discharged home. Our longest survivor currently has lived 42 months and has no known disease. In all cases, adjuvant chemotherapy is used, even in the face of clear surgical margins.

Heart Transplantation

Malignant primary cardiac tumors may grow to a large size prior to detection. Additionally, extensive myocardial involvement or location affecting the fibrous trigone of the heart may make complete resection impossible. Because complete resection yields better results than incomplete resection,[199] orthotopic cardiac transplantation has been considered as a treatment option in some patients. Reports of transplantation for a number of cardiac tumors, including sarcoma,[213–215] pheochromocytoma,[216] lymphoma,[217] fibroma,[170] and myxoma,[218] have appeared. However, the long-term results are uncertain because some patients die from recurrent metastatic disease despite transplantation.[216,217,219] As of 2000, 28 patients had been reported who had undergone orthotopic transplantation for primary cardiac tumors, and of these, 21 had malignant tumors.[219] The mean survival for patients with primary cardiac malignancy was 12 months. Although technically feasible in some cases, orthotopic transplantation is hindered by a scarcity of donor organs, coupled with an extensive recipient list of patients without cancer. In addition, the large size of the tumor when diagnosed often necessitates rapid intervention for progressive congestive heart failure. Finally, the morbidity and mortality involved with immunosuppression, as well as the unknown effect of immunosuppression on any remaining malignancy, should be considered. For these reasons, orthotopic cardiac transplantation for primary cardiac tumor remains controversial and should be considered carefully on a case-by-case basis by experienced transplant and tumor boards. In most cases, orthotopic transplantation should be reserved for unresectable benign tumors, such as cardiac fibroma.

SECONDARY METASTATIC TUMORS

Approximately 10% of metastatic tumors eventually reach the heart or pericardium, and almost every type of malignant tumor has been known to do so.[2,5,9,220] Secondary

Table 63–6.

Metastatic Cardiac Disease

Tumor	Total (no.)	Cardiac (%)	Pericardial (%)
Leukemia	420	53.9	22.4
Melanoma	59	34.0	23.7
Lung ca	402	10.2	15.7
Sarcoma	207	9.2	9.2
Breast ca	289	8.3	11.8
Esophageal ca	65	7.7	7.7
Ovarian ca	115	5.7	7.0
Kidney ca	95	5.3	0.0
Gastric ca	3.8	3.6	3.2
Prostate ca	186	2.7	1.0
Colon ca	214	0.9	2.8
Lymphoma	75	—	14.6

Source: Reproduced with permission from Perry, MC: Cardiac metastasis, in Kapoor AS (ed): Cancer and the Heart. New York, Springer-Verlag Publishers, 1986.

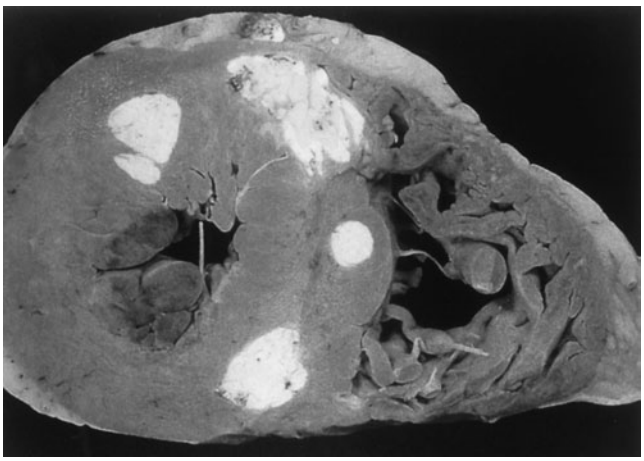

Figure 63-34. Hematogenous metastases within the myocardium of a patient with renal cell cancer. (*Reproduced with permission from Hurst JW et al: Atlas of the Heart. New York, McGraw-Hill, 1988.*)

neoplasms are 20 to 40 times more common than primary cardiac malignancies.[4,221] Up to 50% of patients with leukemia develop cardiac lesions.[5] Other cancers that commonly involve the heart include breast and lung cancers, lymphoma, melanoma, and various sarcomas.[2,222,223] Metastases involving the pericardium, epicardium, myocardium, and endocardium roughly follow that order of frequency[2,9] as well (Table 63-6).

The most common means of spread, particularly for melanoma, sarcoma, and bronchogenic carcinoma, is hematogenous and ultimately via coronary arteries. In addition, metastasis can reach the heart through lymphatic channels; through direct extension from adjacent lung, breast, esophageal, and thymic tumors; and from the subdiaphragmatic vena cava. The pericardium is involved most often by direct extension of thoracic cancer; the heart is the target of hematologous and/or retrograde lymphatic metastasis.[5] Cardiac metastases rarely are solitary and nearly always produce multiple microscopic nests and discrete nodules of tumor cells[2,5,9] (Fig. 63-34). Cardiac metastases produce clinical symptoms in only about 10% of afflicted patients.[5,224,225] The most common symptom is pericardial effusion or cardiac tamponade. Occasionally, patients develop refractory arrhythmias or congestive heart failure. Chest radiographs and electrocardiograms tend to show nonspecific changes, but echocardiography is particularly useful for diagnosis of pericardial effusion, irregular pericardial thickening, or intracavity masses interfering with blood flow.

Surgical therapy is limited to relief of recurrent pericardial effusions or, occasionally, cardiac tamponade. In most instances, these patients have widespread disease with limited life expectancies. Surgical therapy is directed at providing symptomatic palliation with minimal patient discomfort and hospital stay. This is most readily accomplished via subxiphoid pericardiotomy, which can be accomplished under local anesthesia if necessary with reliable relief of symptoms, a recurrence rate of about 3%, and little mortality.[223] Alternatively, a large pericardial window in the left pleural space can be created using thoracoscopy, but we would recommend this only under unusual circumstances.[226] This can be accomplished with minimal patient discomfort but does require general anesthesia with single-lung ventilation and may be poorly tolerated by patients with hemodynamic deterioration secondary to large effusions.

RIGHT ATRIAL EXTENSION OF SUBDIAPHRAGMATIC TUMORS

Abdominal and pelvic tumors on occasion may grow in a cephalad direction via the inferior vena cava to reach the right atrium. Subdiaphragmatic tumors are frequently renal carcinomas, although hepatic, adrenal, and uterine tumors occasionally have exhibited this behavior. Up to 10% of renal cell carcinomas invade the inferior vena cava,

and nearly 40% of these reach the right atrium.[227] Radiation and chemotherapy are not effective in relieving the obstruction of blood flow. If the kidney can be fully removed, as well as the tail of tumor thrombus, survival can approach 75% at 5 years.[125,229]

Renal cell tumors with atrial extension typically are resected with abdominal dissection to ensure resectability of the renal tumor. Initially, we performed a concomitant median sternotomy and often used cardiopulmonary bypass with hypothermic circulatory arrest when treating these patients. However, we have changed our approach and now work closely with our liver transplant surgeons who have extensive experience in the area of the retrohepatic vena cava. We have found that we can expose the vena cava up to the right atrium through an abdominal incision. With ligation of the arterial inflow, the tumor tail often shrinks below the diaphragm, and in almost all circumstances, this can be removed without the use of cardiopulmonary bypass. Occasionally venovenous bypass as used in hepatic transplantation is necessary to occlude inflow through the inferior vena cava, but this is unusual. If the tumor is too extensive for this maneuver, then median sternotomy is performed, and cardiopulmonary bypass with hypothermic circulatory arrest can be used to remove the tumor from the cardiac chambers down into the inferior vena cava. Perfusion can be restarted, followed by removal of the rest of the tumor. Although it leads to adequate exposure, significant problems with coagulopathy are often apparent after cardiopulmonary bypass and profound hypothermia.

A 5-year survival rate of 75% has been achieved following nephrectomy with resection of right atrial tumor extension.[228,229] Other subdiaphragmatic tumors with atrial extension that have been resected successfully include hepatic and adrenal carcinoma, as well gynecologic tumors.[230–234]

MOLECULAR- AND BIOLOGIC-BASED DIAGNOSIS AND THERAPY FOR CARDIAC TUMORS

This is an exciting time for investigators involved in the search for novel therapies for tumors such as many of those discussed in this chapter. A "new biology" is being developed in laboratories around the world working in these areas, and this is supplanted by the knowledge that is being obtained from the concerted Human Genome Project and the subsequent development of proteomics.[235] It is incumbent on the thoracic surgeon involved in the care of patients with cardiac tumors to have some degree of familiarity with the terms and promise of these advances because significant additional improvement in survival of many of these patients is unlikely to result from further advances in surgical technique.

Interestingly, many sarcomas demonstrate reproducible translocations that allow for the production of novel chimeric genes that may code for a variety of fusion proteins. Many of these proteins have been found to engender cellular phenotypic malignant changes, resistance to apoptosis, and unfettered growth.[236] Although not associated with cardiac involvement, the fusion proteins EWS-FL11 and EWS-ERG are noted in Ewing's sarcoma. When full-length antisense oligonucleotide constructs are used to target the mRNA of these proteins, protein expression is downregulated, and an eightfold increase in apoptosis sensitivity is noted.[227] These fusion proteins have been noted in some forms of rhabdomyosarcoma, and the most common is PAX3-FKHR. This oncoprotein combines components of two strong transcriptional activators and may increase the production of the downstream antiapoptotic protein BCL-XL. Antisense oligonucleotides directed at this oncoprotein mRNA have led to apoptosis in rhabdomyosarcoma cells.[237,238] Similarly, in our laboratory we have demonstrated that antisense oligonucleotides directed at the mRNA of the downstream antiapoptotic protein BCL-XL in mesothelioma can induce apoptotic cellular death and engender chemosensitivity.[239] A similar translocation and fusion protein have been noted in fibrosarcoma. This translocation [t(12;15)(p13q25)] brings together genes from chromosomes 12 and 15, which combines a transcription factor with a tyrosine kinase receptor. The resulting fusion protein is a tyrosine kinase that has oncogenic potential.[240] Reproducible translocations and fusion proteins with downstream effectors of malignant behavior have not been described for angiosarcoma, but they are actively being sought. Antisense treatment has been maligned in the past owing to problems with both delivery and stability of therapeutic constructs. However, sophisticated biochemical alteration of these molecules has improved stability, and two recent solid tumor trials using antisense therapy for salvage have demonstrated positive results.[241,242] Additional methods of delivering antisense to tumor cells, including viral vector delivery, have been developed. Finally, in addition to antisense methods, small molecule inhibition of many of these fusion proteins should be possible.

Angiosarcoma is an obvious target for therapies based on antiangiogenesis. The weak antiangiogenic properties of interferon-alfa are presumed to be the mechanism that accounts for responses to this agent in this tumor.[243] Multiple new antiangiogenic agents are being evaluated currently in phase I and II trials, and a number of noncardiac angiosarcoma patients have been treated at our institution on this basis. We have noted several to develop stabilized disease, but no definitive data are yet published. Certainly, the use of these agents in these vascular-origin tumors is theoretically attractive.

Viral vector–mediated gene therapy has been evaluated for various sarcomas in the preclinical setting. A number of potential targets exist for these sorts of therapies. Although *p53* is not commonly mutated or absent, *mdm-2* is often overexpressed in many sarcomas, including angiosarcoma. This gene is a known oncogene that is able to directly

induce cellular transformation. Importantly, when overexpressed, it binds to and inhibits *p53* activity, even though expression of *p53* may appear normal. Overexpression of *mdm-2* also has been associated with VEGF overproduction and angiogenesis.[243,244] Preclinical studies of adenoviral vector *p53* transduction of sarcoma in SCID mice have demonstrated growth delay, tumor regression, and decreases in VEGF expression.[245] Many other targets for this approach, including inhibition of NF-κB expression using an adenoviral-dominant negative Iκ-Bα construct and prodrug-mediated gene therapy using a doxorubicin prodrug and adenoviral transfer of a metabolizing enzyme in sarcoma cells, have been shown to be effective.[230,231] Unfortunately, the application of viral-mediated gene therapy paradigms to this tumor suffers the same problems of targeting, transgene expression durability, and immune response that are problematic for the field in general.

In regard to molecular diagnosis, there are no reproducible familial patterns for development of most malignant tumors. However, familial cardiac myxoma, rhabdomyoma, and fibroma may exhibit reproducible genetic abnormalities that lend themselves to the development of genetic testing to identify individuals at risk. Familial myxoma syndrome, or Carney complex, has been associated with mutations in the 17q24 gene *PRKAR1α* that codes for the R1α regulatory subunit of cAMP-dependent protein kinase A (PKA).[248] Although not widely available, genetic diagnosis of this syndrome is now technically achievable.[249] Reproducible mutations in the *TSC-1* and *TSC-2* genes in patients with tuberous sclerosis and cardiac rhabdomyoma, as well as mutations in the *PTC* gene of patients with the Gorlin syndrome and cardiac fibroma, have been noted.[250–252] It is hoped that in the near future we will be able to predict who is at particular risk for these and other cardiac tumors. This could allow for more intense surveillance, earlier detection, and a higher rate of surgical or multimodality cure for these patients.

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PART

VIII

Transplant and Circulatory Support

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CHAPTER 64

Immunobiology of Heart and Heart-Lung Transplantation

Bartley P. Griffith • Michel Haddad • Robert S. Poston

The purpose of this chapter is to introduce the immune biology of heart and lung transplantation to the surgeon with the hope that it will provide a better understanding of the complex events that occur outside the operating room and give the subsequent strategies of immunosuppression a clear rationale. This work differs from the more usual approach in the thoracic surgical textbook, which typically lists established classification systems used for diagnosing various grades of rejection and reiterates the results of various conventional immunosuppression therapies generally already well known to the reader. It has been a challenge to distill the more germane aspects of the molecular events surrounding the allogeneic response in a way that those events can be better understood by those heart and lung transplant surgeons not intimately involved in the field of immunology. It is hoped that transplant recipients will benefit if the fundamentals presented here can be understood and made useful by clinicians.

THE MAJOR HISTOCOMPATIBILITY COMPLEX

An allogeneic organ is one that is transferred from one individual to another of the same species but with a different genetic repertoire. A donor heart or lung is immunologically incompatible with the host tissues, and an immunologic reaction or alloresponse is directed against donor proteins (antigens) located on the surface of endothelial, mesenchymal, and epithelial cells of the allograft. Both major and minor surface proteins contribute to eliciting such an allogeneic response.

The major histocompatibility complex (MHC) proteins are produced by multiple polymorphic genes whose glycoprotein products, the MHC proteins, are expressed on the surfaces of cells. These protein products, along with the ABO blood antigens, are the principal determinants of whether an organ is deemed as self or nonself and hence are the primary targets of the immune response to allografts. The MHC proteins, which are called *human leukocyte antigens* (HLAs) in humans, guide the development of T lymphocytes to have a low affinity to self and to use the reaction to self as a way in which foreign peptides are recognized (MHC restriction). The genes that express HLAs are among the most variable (or have the largest number of polymorphisms) in the human genome.

The HLA gene complex encodes two main classes of HLAs. Class I HLA molecules include types A, B, and C, which are cellular antigens that exist in most cells and stimulate cytotoxic T lymphocytes that express the cell surface receptor CD8 (Fig. 64-1). In addition, the HLA gene complex encodes HLA class II molecules, which also include three types, DP, DQ, and DR. These are expressed on antigen-presenting cells such as B cells and helper T lymphocytes that express the CD4 surface receptor.

At least 20 definable loci, or *alleles*, at HLA-A, 40 at HLA-B, and 10 at HLA-DR[1] have been identified that are inherited as a unit called the *haplotype*. With two possible alleles at each HLA-A, HLA-B, and HLA-DR loci, one being maternal and one paternal, an antigen *mismatch* is possible for 0 through 6 antigens. Because of their proximity on chromosome 6, the alleles for HLA-C, HLA-DQ, and HLA-DP are predictably inherited as extended haplotypes with HLA-A, HLA-B, and HLA-DR in a defined donor population (i.e., linkage disequilibrium). Tissue compatibility for transplantation traditionally has required only HLA-A, HLA-B, and HLA-DR typing and preferably compatibility as well. Only in unusual cases, such as bone marrow transplant procedures that draw donors from a worldwide registry, have there been clinically important mismatches of the other HLA alleles.[2] Although either serology or DNA sequencing is used for typing, recent data suggest that a serologic (i.e., antigen) mismatch has a greater effect on outcome than a DNA (i.e., allele) mismatch.[3]

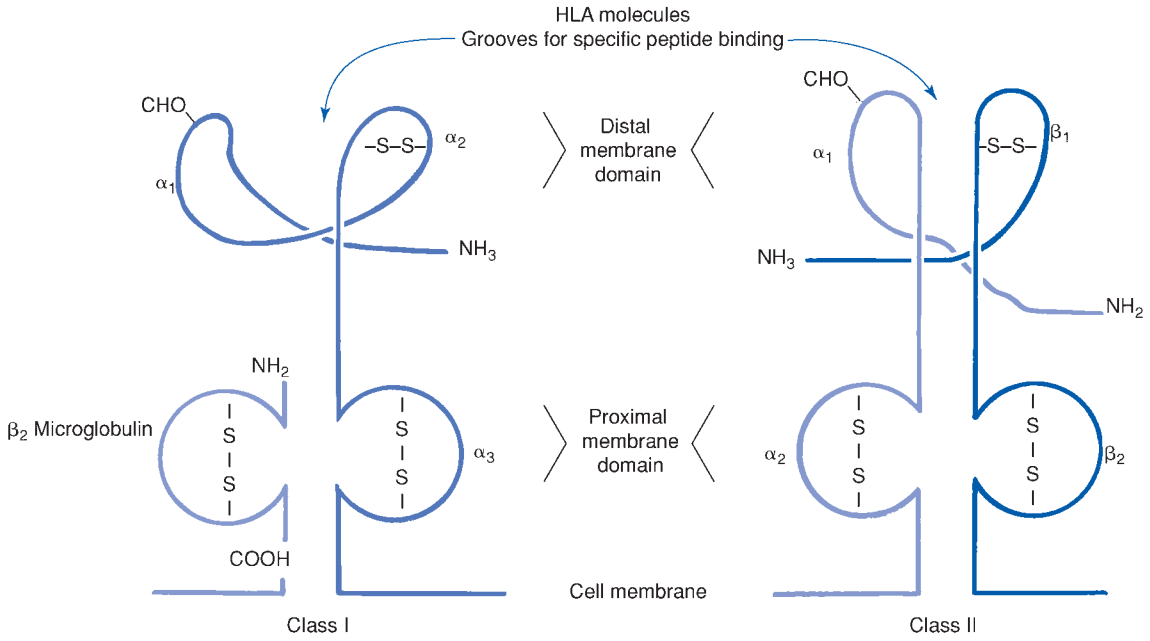

Figure 64-1. Class I and II HLA molecules are made up of polypeptide chains with intrachain disulfide bonds. The α_1 and α_2 distal domains of class I and the α_1 and β_1 domains of class II make up the peptide binding site for alloantigen. *(Adapted with permission from Parham M, in Haber E (ed): Immunobiology of Transplantation Molecular Cardiovascular Medicines. New York, Scientific American Press, 1995.)*

In heart and lung transplantation, several single-institution studies examining the effect of HLA matching on outcome have found an association between the degree of serologic HLA-DR matching and actuarial graft survival at 1, 5, and 10 years. In general, an association was not present for HLA-A and HLA-B matching. In fact, in a report from the Texas Heart Institute, Kerman and colleagues reviewed 448 heart transplants[4] and found an inverse relationship between HLA-A and HLA-B mismatches and death from cardiac allograft vasculopathy!

Most studies draw from a system of random allocation of donor organs, resulting in fewer than 8% of closely matched donor-recipient pairs (defined as 0, 1, or 2 mismatches). Given this low frequency, an adequate pool of closely matched pairs for comparison to recipients that are mismatched at multiple loci with the donor is made possible only by a multi-institutional study of significant size. Two cardiac transplantation registries have fulfilled this size requirement and verified the relationship between HLA matching and acute graft survival: the Collaborative Transplant Study,[5] with 8331 recipients, and the United Network for Organ Sharing/International Society for Heart-Lung Transplantation (UNOS/ISHLT) Registry,[6] with 10,752 recipients. In the Collaborative Transplant Study, 128 patients (1.5%) with either 0 or 1 combined HLA-A, HLA-B, or HLA-DR mismatches were compared with those with 2 mismatches and 3 to 6 mismatches. Mean rates of survival at 3 years were a striking 83%, 76%, and 71%, respectively. Multifactorial regression analysis further established that HLA matching had a strong independent effect on graft survival, with the most pronounced effect at 6 months. While the timing might suggest a predominant role for acute rejection, only graft survival and not rejection rates were reported.

The UNOS/ISHLT Registry investigators also found a progressive reduction in risk for greater donor-recipient HLA matching. Unlike the Collaborative Transplant Study, however, data obtained from this registry are derived from a database whose use is compulsory for all transplant centers in the United States and subject to auditing and verification. Follow-up in this patient population was found to be virtually complete. The primary benefit of matching appeared to be at the HLA-A and HLA-DR loci with no independent effect of matching at the HLA-B locus. However, these retrospective data, similar to the previous study, were based on serologic methods of tissue typing that are less accurate than current DNA techniques. Again, the effect of HLA matching was greatest at 6 months, with the survival curves between matched and mismatched patients becoming parallel at later time points. Considering the results of these two registry studies in light of prior work,[7] HLA matching is unlikely to influence chronic graft rejection. Larger numbers of well-matched transplants studied at a prolonged follow-up are needed to investigate the influence of HLA matching on chronic rejection.

Data demonstrating the effect of HLA matching on outcomes in heart-lung and lung transplantation are sparse.

In one study from the University of Pittsburgh, 74 single- and double-lung transplant recipients were analyzed, and a strong effect of HLA-DR matching on 6-month graft survival was evident (100% versus 75% versus 56% for 0, 1, and 2 HLA-DR mismatches, respectively).[8] Combining HLA-A, HLA-B, and HLA-DR mismatches showed 100% survival for 0 to 2 mismatches, 78% for 3 to 4, and 58% for 5 to 6. The Collaborative Transplant Study showed a trend toward improved survival for well-matched grafts in both heart-lung and lung recipients, but this did not reach statistical significance (1176 patients enrolled in the lung transplant group and 640 in the heart-lung group).[5] The UNOS/ISHLT Registry data also showed a less impressive effect of matching on lung allograft outcome. A significant reduction in risk with any degree of HLA matching was seen, but there was no progressive improvement with increasing levels of matching.

These data support the conclusion that HLA matching confers an important benefit after heart transplantation and probably after heart-lung and lung transplantation. The conventional wisdom that deems prospective HLA matching to be logistically unfeasible in thoracic organ transplantation may be changing. The former requirement of HLA typing using serologic methods for donor splenic tissue retrieved during procurement did not provide sufficient time for prospective typing given that heart and lung allografts tolerate only 4 to 6 hours of ischemia time. This formidable restriction has been overcome by the use of polymerase chain reaction (PCR)–based HLA typing on peripheral blood lymphocytes prior to the procurement procedure. Future advances in our current preservation methods such as the use of continuous, warm, sanguineous perfusion of the ex vivo cardiac allograft[9] will permit procurements from longer distances, a certain requirement of an organ allocation system that takes into consideration HLA matching.

Some groups have, in fact, reported impressive advances in achieving prospective HLA matching. One is the Harefield group, which recently reported that within their donor allocation zone, HLA typing was available before organ retrieval in 69% of cases performed in 1994. Based on outcome data from their institution, this group has focused on HLA-DR matching only and has seen an increase in prospective matching from 5 to 25% of transplants in a recent 1-year time period and a reduction in acute rejection in those matched. However, widespread adoption of cardiac HLA matching has been hindered by continued limitations. A benefit on early cardiac allograft survival was seen mainly for those with more than three antigen matches, an infrequent event (fewer than 8% of cases) in the current system of random allocation of donor organs. Increasing this frequency of close matches via prospective matching would require significantly prolonged ischemia and waiting-list times for the donor organ and transplant candidate, respectively. Given current methods of organ preservation, limited organ supplies, and the high recipient waiting-list mortality, such a requirement would seem unacceptable in light of the modest impact on acute organ survival and lack of evidence supporting an effect on long-term graft outcome and chronic rejection.

ANTIGEN PROCESSING/AFFERENT RESPONSE

HLA class I and class II molecules are not uniformly expressed on the same cells. HLA expression is low at baseline in human donor hearts and lungs but can be found to stain prominently for both classes in response to inflammatory stimuli (Fig. 64-2). After transplantation, class I molecules present protein products produced from the endogenous breakdown of their own MHC protein to previously activated CD8± cytotoxic lymphocytes (CTLs) (Fig. 64-3). Class I molecules are found on the surfaces of all cells except the erythrocyte, which incidentally protects a malaria-infected red blood cell from cytotoxic (CD8±) T-lymphocyte surveillance. Class II expression is found constitutively on the professional *antigen-presenting cells* (APCs) such as dendritic cells, B lymphocytes, macrophages, and thymic epithelium. It is also induced on other cell types by cytokines such as interferon (INF), which is produced as part of the alloimmune response. Originating either from the donor organ (i.e., passenger cells) or from the host, these APCs internalize, process, and present shed fragments of donor proteins on class II molecules (see Fig. 64-3). The allogenic class II molecule and bound peptide exclusively react with a large number of CD4± T cells (perhaps 1%) in a process called the *direct* or *allorestricted pathway.*[10,11]

The direct recognition of a few allogenic donor class II and I MHC epitopes by host CD4 and CD8 cells soon draws other epitopes into the response as a result of a general upregulation of antigen processing and presentation.[12] This process, called *epitope spreading,* is a potent initiator of cell-mediated rejection when accompanied by costimulatory signals

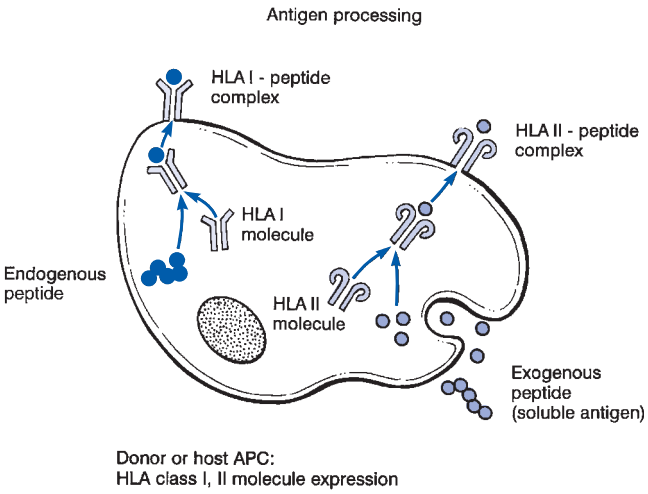

Figure 64-2. Donor antigen derives from either the endogenous pathway or the exogenous pathway.

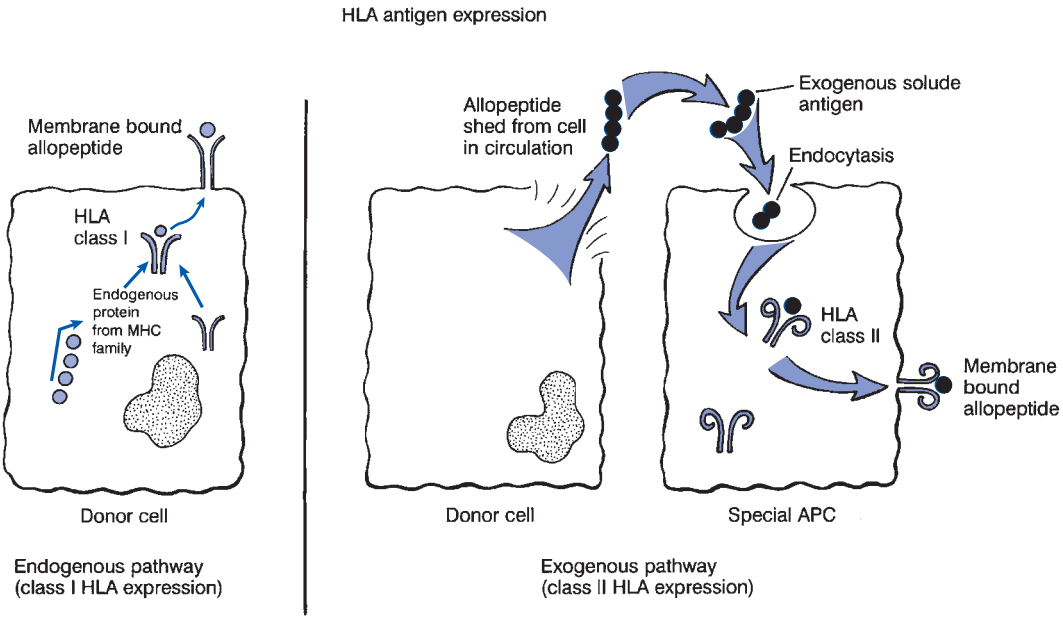

Figure 64-3. Generally, HLA class I molecules bind protein fragments of donor MHC protein produced from endogenous cellular processes. Allopeptides from MHC donor cell membrane fragments are brought into special APCs that process and bind them to HLA class II molecules for presentation to host T cells.

generated by the interaction of certain cell surface proteins on APCs and T cells (Fig. 64-4). The indirect or self-restricted pathway is the physiologic mechanism of T-cell immune recognition. In this pathway, host-derived APCs process exogenous allo-MHC fragments and bind them to host class II and I MHC molecules for presentation to host T cells. The exact role for the indirect alloresponse in transplantation is not well characterized, but it is believed to be a significant contributor to late and chronic rejection when donor APCs eventually are replaced by those of the host.[13] Its role in chronic rejection is supported by the observation that T cells from patients with chronically rejected renal, cardiac, and lung transplants show evidence of indirect, but not direct, reactivity to presented donor HLA allopeptides.[14] Indirect alloresponses may be especially important in xenograft responses, in which recipient T cells and donor APCs cannot make efficient contact with each other. On the other hand, indirect antigen presentation in the absence of costimulation has been proposed as one of the mechanisms of tolerance, which is thought to explain the immunosuppressive effects of blood transfusions.

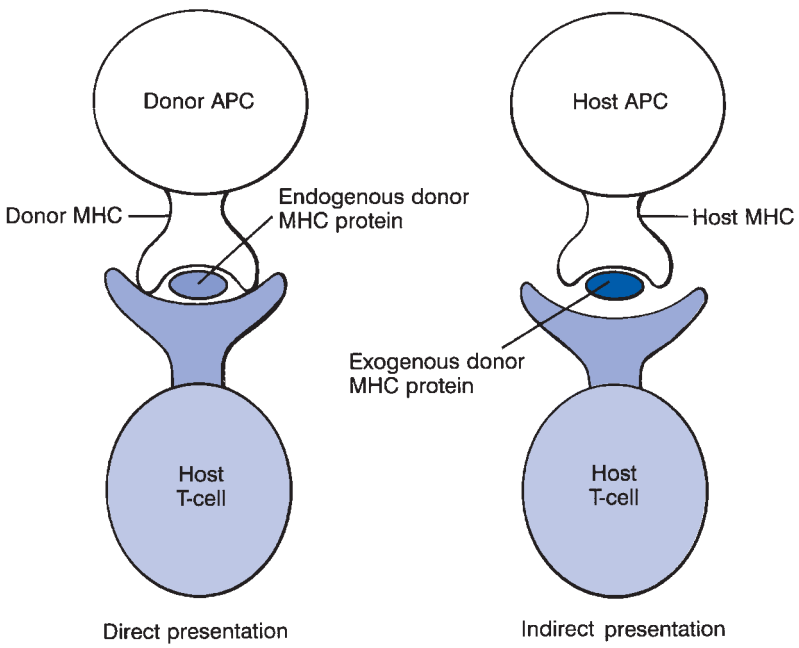

Figure 64-4. Host T lymphocytes can respond to alloantigens by the direct or indirect pathway. On direct presentation, donor cells bind endogenous MHC protein to donor MHC molecules (allorestricted). In the direct path, host cells respond to processed donor MHC peptide bound to host MHC (self-restricted). The direct pathway can stimulate many T cells and is responsible for most acute rejections, whereas fewer T cells respond to the small foreign peptide presented in host MHC molecule. The indirect pathway has been implicated as an important part of the late chronic rejection process when host APCs replace those of the donor within the allograft.

The direct and indirect pathways likely have differential sensitivities to immunosuppressive drugs.

CD4 cells elaborate various cytokines that amplify the generalized inflammatory response. Two different mature CD4 cells have been characterized: TH1 cells, which secrete interferon (INF) and interleukin 2 (IL-2) and stimulate cellular immunity, and TH2 cells, which secrete IL-4 and IL-10 and stimulate B lymphocytes to produce antibodies. Because TH1 and TH2 cells are known to mutually suppress each other's subsets, the TH2 cells have been implicated in tolerance against cell-mediated rejection.[15] While mechanisms are evolving, it appears that the TH1 cells arise in regional lymph nodes following class II presentation on macrophages and mature dendritic cells (DCs). Mature DCs are the most effective APCs at activating naive T cells because they express high levels of HLA, intercellular adhesion, and costimulatory molecules. TH2 cells arise from class II presentation by B lymphocytes or immature DCs, cells that are capable of presenting antigen but that provide low levels of costimulation.[16]

Only mature DCs provide the appropriate costimulatory signal for the conversion of naive CD8 T cells to activated cytotoxic lymphocytes (CTLs). In addition, this process typically requires exogenous IL-2 from CD4 "helper" T cells. A more stringent requirement for stimulation of CD8± versus CD4± T cells ensures that CTLs are formed only when evidence of their need is unambiguous.[1]

EFFERENT ALLORESPONSE

After recognizing a heart or lung allograft as foreign, the immune system unleashes cellular and humoral (antibody) attacks (Fig. 64-5). The efferent response usually begins when activated CD4 cells secrete various cytokines that drive the inflammatory response.[17] IL-2 increases the expression of its own receptors (IL-2Rs) on CD4 cells, driving the proliferation and further differentiation of CD4 cells. The activated CD4 cells secrete additional lymphokines, including INF, which along with IL-2 stimulates the activated CTLs to bind to the allograft cells presenting donor MHC protein molecules. The CTLs proliferate and specifically kill the allotarget by at least two mechanisms.[18] In the presence of Ca^{2+}, the protein perforin polymerizes onto the target cell and causes 16- to 20-nm pores to open in the cell membrane, resulting in osmotic collapse. The other likely method is by stimulation of apoptosis (programmed cell death) by interaction of the lymphocyte Fasligand with the APO-1/Fas receptor of the target cell. Second messengers are elicited that activate endonucleases and proteases to cause fragmentation of DNA and T-cell dissolution. Tissues that appear to have an immune privilege, such as the testis, eye, brain, and some tumors, use this Fas/Fas-L apoptotic pathway to destroy autoreactive lymphocytes. This pathway is being exploited for the development of tolerance to allogenic tissues in experimental models.[19]

Graft ischemia and reperfusion provoke a nonspecific immune response involving neutrophils and macrophages. Through the production of cytokines such as INF and tumor necrosis factor (TNF), these cells upregulate costimulatory and MHC class I and II molecules, thereby enhancing immunogenicity and T-cell recruitment to the graft. Macrophages also release IL-1, which promotes a positive-feedback cycle by driving IL-2 production by T cells. Through this mechanism, a significant bout of reperfusion injury (RI) has been shown clinically to increase the incidence of acute rejection.[20] In addition, by activating the coronary endothelium and initiating smooth muscle cell proliferation, RI has been hypothesized to be an important contributor to chronic allograft vasculopathy.[21] Inhibition of RI has been shown to reduce this vasculopathy both experimentally[22] and clinically.[23]

On the other hand, recent data suggest that host reparative responses may mitigate the immunogenic effects of RI. By analyzing female cardiac allografts transplanted into male recipients, Quaini and colleagues documented the migration of host stem cells that matured into myocytes, endothelium, and capillaries in the donor hearts as soon as 4 days posttransplantation.[24] With the discovery of this capacity for rapid formation of an organ chimera with up to 20% mature host-derived tissue, it is hypothesized that RI actually may result in a reduction rather than enhancement of allograft immunogenicity. The overall effect of RI on the allograft likely depends on which pathway plays a greater role in any given donor-recipient pair, illustrating an important future area for investigation.

The humoral response begins as host and B cells are drawn into the alloresponse by the lymphokines and by their own class I and II cell receptor engagement with the donor cells. The activated B cells evolve into plasma cells that produce allospecific antibodies against the donor class I and II HLA molecules and engage the complement cascade.

T-CELL LYMPHOCYTE MATURATION AND ALLOACTIVATION

Recognition of antigens belonging to the body versus antigens that are foreign begins in the thymus. A very large number of T cells with variable TCR protein sequences are formed in the thymus. These receptors, similar to antibodies produced by B cells, recognize specific peptide sequences. However, unlike antibodies, the TCRs cannot be released from the cell membrane and require an association with five invariant polyproteins collectively called the *CD3 complex*. The TCRs cannot recognize free antigen but are restricted by the HLA molecule with which they interact. Genes responsible for the TCRs randomly rearrange within the thymus to provide an astonishing array ($\sim 10^{16}$) of potential binding sites necessary for diversity. Immature T cells are selected to survive in the thymus based on whether and how strongly their TCRs bind the body's own HLA class I and II molecules expressed on the thymic

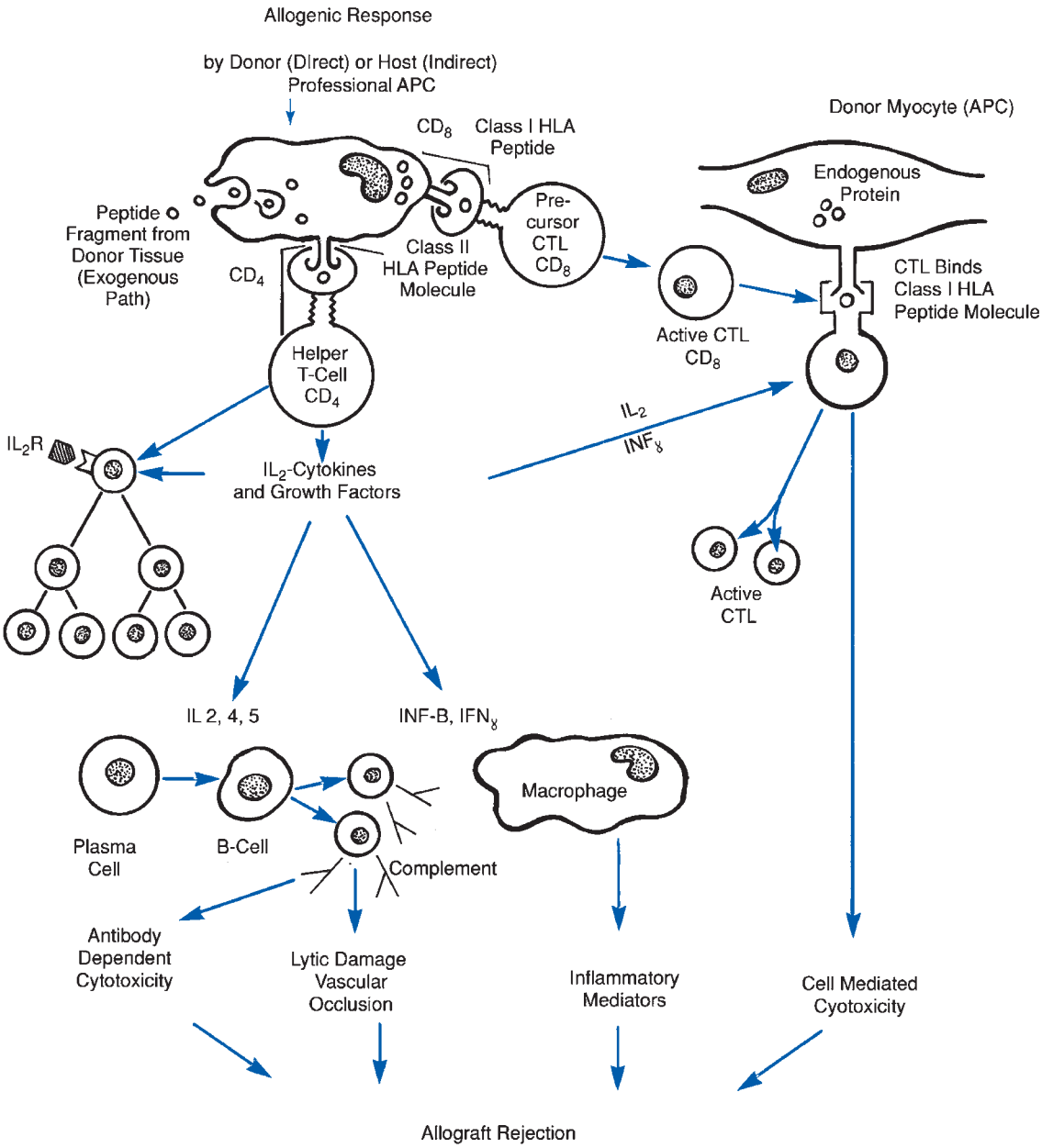

Figure 64-5. The alloresponse is a complicated cellular and humoral process that generally begins when a CD4 cell recognizes a class II donor HLA molecule–peptide complex presented on a donor heart or lung APC (direct path) and a precursor CTL cell of CD8 lineage binds to a class I donor molecule. The CD4 proliferates and produces IL-2 that drives the process further. The activated CTL cells seek class I donor-specific targets and are stimulated by IL-2 and INF to kill targets. These CTL CD8 cells are responsible primarily for destruction of the allograft. Antibodies are produced selectively by B cells and draw inflammatory cells to the targets by antibody-dependent cytotoxicity. Complement is also activated by the humoral arm and initiates lytic changes and thrombosis in the allograft. Other inflammatory cytokines attract polymorphonuclear cells into the response, and TNF and INF mix to activate macrophages.

epithelium (Fig. 64-6). This leads to the differentiation and selection of T cells that recognize self molecules from nonself sequences. T cells that have receptors that interact with the body's own HLA antigens are selected out, leaving the cells that recognize all other nonself HLA sequences. It is believed that when T cells react too strongly or too weakly to HLA molecules in the thymus, they are negatively selected and die by apotosis or DNA fragmentation to prevent the establishment of autoreactive T-cell clones that would be detrimental to the body. In fact, 95% of the thymocytes do not survive this selection. The importance of the thymus is illustrated when it fails to develop in DiGeorge syndrome. This disease results in an increased risk for a wide range of opportunistic infections that is reversed by thymic transplantation.[25]

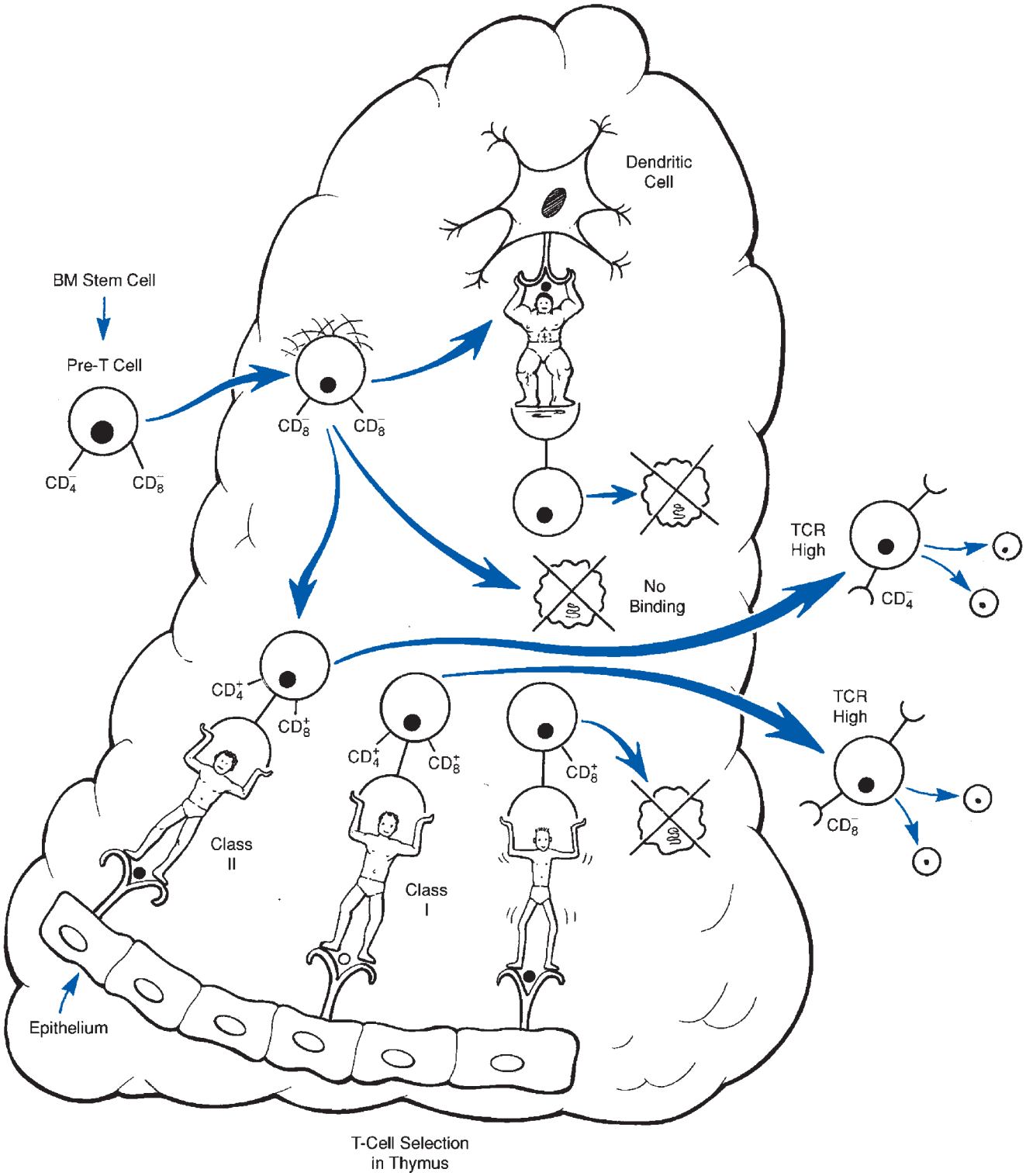

Figure 64-6. T cells enter the thymus from the bone marrow, where they differentiate and assemble diverse TCRs that cause the cells to be pl or mi selected, based on their usefulness. Diversity is based on rearrangement of genes responsible for variable portions of the chains that form the TCR heterodimer. When the TCR is pl selected on a class I HLA molecule, CD8 will form part of the receptor complex, and when a class II molecule is involved, then CD4 will form.

T cells are said to be naive until they are exposed to specific antigens in the periphery. When the TCR expressed on a T-helper lymphocyte engages its specific membrane-bound MHC (HLA) molecule on an APC, a series of reactions occurs in the cell, leading to a rise in intracellular calcium (Fig. 64-7). The Ca^{2+} influx results in the accumulation of calcineurin, which, in turn, removes a phosphate from the nuclear factor for activation of T cells (NFAT-P).[26] NFAT then can enter the nucleus, where it promotes transcription of the cytokine IL-2. IL-2 prompts the appearance of IL-2 receptors (IL-2Rs) on the surfaces of T cells with which it reacts (autostimulation), prompting proliferation and differentiation of the lymphocytes and enabling them to interact with B cells and cytotoxic T cells. While the TCR/CD3-dependent signal is necessary, it alone is not sufficient to activate quiescent T cells. Full activation requires a second or costimulatory signal provided by physical contact between various T-cell surface proteins known as *integrins* and their ligands on the APC surface.[27] The molecules on the surfaces of T cells that form an "immunologic synapse" with costimulatory molecules on APCs include CD28, whose ligand is B7; CD154, which binds to CD40; CD2, the ligand for CD58 (LFA-3); and LFA-1, the ligand for ICAM-1. CD8 and CD4 receptors also assist in the binding of the T cell to its MHC peptide of class I or class II specificity and modify the TCR signal (see Fig. 64-7). T cells that have been activated express CTLA-4, which may act as a competitive inhibitor of CD28, thereby blocking the generation of costimulatory signals.[28] Inhibition of costimulation using monoclonal antibodies against ICAM,[29] CD40L,[30] and CD28[31] has generated donor-specific tolerance in preclinical transplantation models. Stimulation of alloresponsive T cells in the absence of costimulation seems to be a central feature in this form of tolerance because the addition of less specific immunosuppressive medications such as FK506 or corticosteroids inhibits its development. Other T-cell integrins combine with matrix molecules of the allograft that are exposed during inflammation, including fibronectin, lamenin, fibrinogen, and vitronectin. These sites link the immune response to the organizing framework of all tissues and provide further evidence of the connection between early graft injury and chronic rejection. Another family of cell adhesion molecules called *selectins* has been identified on the endothelium and assists in the first contact of leukocytes, macrophages, and platelets with the donor organ by inducing rolling, sticking, and finally, transepithelial migration. The selectins are upregulated by the inflammatory cytokines IL-1, INF, and TNF that are elaborated from immune cells during the alloresponse.

REJECTION OF HEART AND LUNGS

Hyperacute Rejection

Hyperacute rejection (HAR) is said to occur when edema, hemorrhage, and thrombosis are noted shortly following reperfusion of the graft. This process involves preformed antibodies that immediately bind to the endothelium of blood vessels in the graft, leading to activation of the complement and coagulation cascades. These antibodies bind to oligosaccharide antigens of the ABO blood group and xenoreactive antigens that are similar to those found on numerous endemic bacteria, protozoa, and viruses. The cross-reactivity of antibodies directed against these endemic microbes is likely to be responsible for the preexisting natural antibodies that cause HAR after transplantation with either ABO-incompatible or xenogenic organs. Because the titer and avidity of preformed antibodies against the blood group antigens in newborn infants is low, ABO-incompatible cardiac allografts have shown greater success in these patients.[32] HAR also occurs from antibodies directed against nonself HLA antigens, especially in patients with a prior history of exposure to allogenic HLA through blood transfusions or pregnancies. Mechanical support with a ventricular assist device is also a strong risk factor for development of anti-HLA antibodies, which can be alleviated in part by the use of leukocyte-depleted cytomegalovirus (CMV)–negative blood transfusions.[33]

Although anti–class I antibodies (Abs) are more destructive of the graft endothelial cells, class II HLAs are expressed on graft vasculature during periods of inflammation and also can provoke HAR when bound by anti–HLA class II Abs following allotransplantation. Although HAR can be treated by cobra venom factor to deplete complement,[34] it is best prevented during allotransplantation by avoiding blood group disparities and identifying preexisting antibodies to HLA antigens, as will be discussed in the next section.

Despite their high endothelial avidity, neither the pre- nor the posttransplant presence of anti-HLA antibodies guarantees HAR. By using an aggressive perioperative regimen of plasmapheresis, intravenous immunoglobulin (IVIG), and Cytoxan, patients have successfully avoided HAR after transplantation despite a positive prospective crossmatch, as will be discussed below.[35] Antidonor HLA antibodies have developed in some patients after transplant despite a negative prospective crossmatch. Titers may rise as early as 3 to 4 days after transplantation, which implies a secondary antibody response with undetectable levels of preformed anti-HLA antibodies from prior exposures. Although a process known as *accelerated acellular rejection* occurs in a few, the induction of a protective phenotype (e.g., bcl-x_L, bcl-2, and A20) inhibits endothelial activation and prevents vascular injury in the vast majority of cases.[36]

Acute Rejection

Acute rejection involves both cellular and humoral immunity and is most common within weeks to months after transplantation. Although late acute episodes can occur, they often do so in the setting of a change in the balance of the immunosuppression regimen versus host immunity. A decrease in the blood level of immunosuppressant either by prescription drug interaction, poor compliance, or an upregulation in alloreactivity owing to viral infection can cause a late allorejection. Myocardial and pulmonary parenchymal infiltration by lymphocytes on endomyocardial or pulmonary biopsy is the

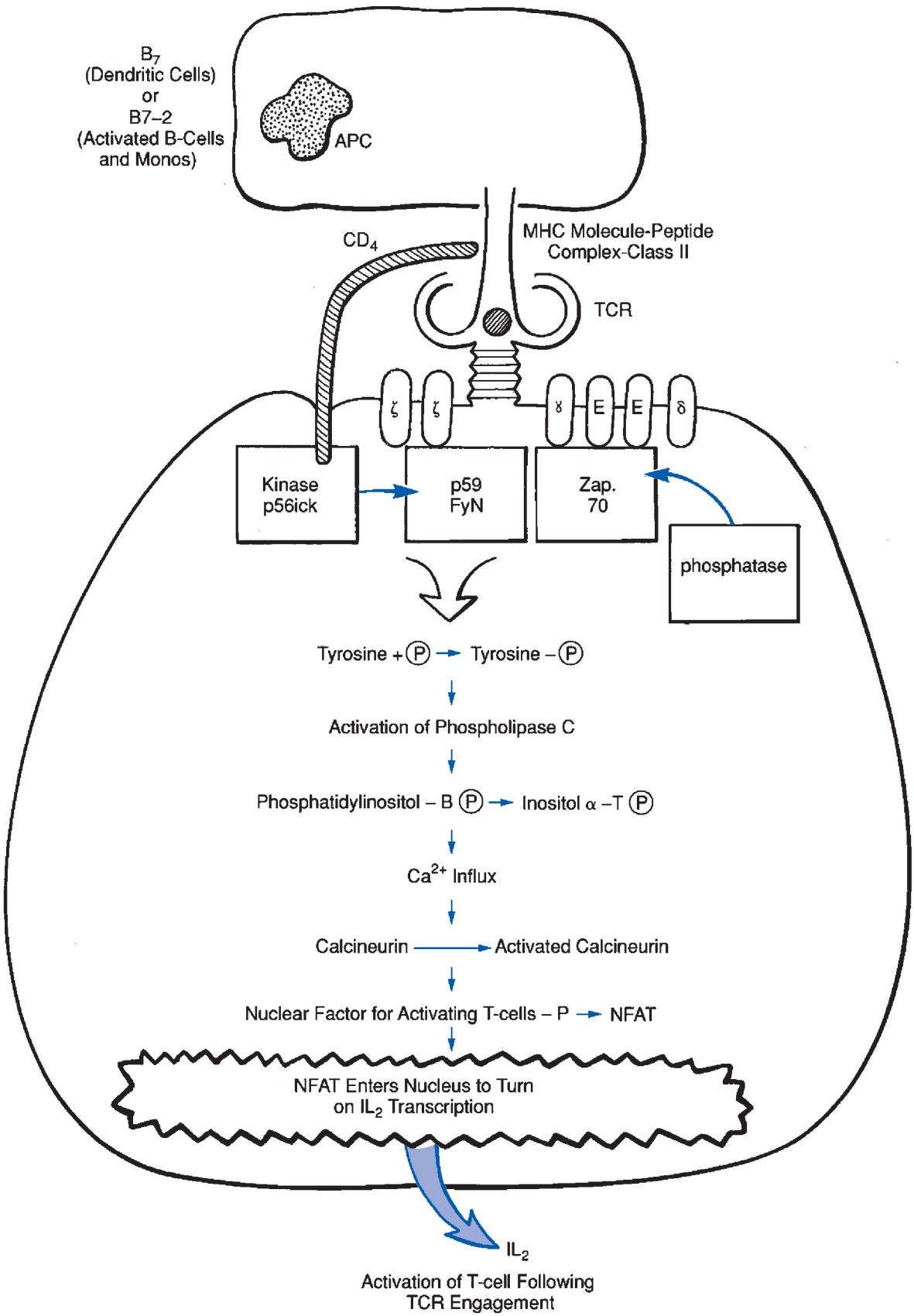

Figure 64-7. CD4 cell's TCR has engaged its specific MHC class II molecule and bound allopeptide. The TCR complex initiates cytotoxic signal transduction that enables a Ca^{2+} influx activation of calcineurin nuclear factor for activating T cells, loses phosphate, and enters the nucleus to begin the promotor sequence to activate the IL-2 gene. *(Adapted with permission from Parham M, in Haber E (ed): Immunobiology of Transplantation Molecular Cardiovascular Medicines. New York, Scientific American Press, 1995.)*

Table 64–1.

New ISHLT Morphologic Grading of Acute Rejection

Heart		Lung	
Grade 1a	Focal aggregates of perivascular activated lymphocytes; rarely interstitial foci	Grade 1	Minimal perivascular and interstitial mononuclear infiltrates*
Grade 1b	Diffuse but sparse interstitial foci; activated lymphocytes	Grade 2	Mild perivascular and interstitial mononuclear infiltrates*
Grade 2	One focus of perimyocytic-activated lymphocytes with myocyte damage	Grade 3	Moderate perivascular and interstitial mononuclear infiltrates*
Grade 3a	Multifocal areas of myocyte damage caused by activated lymphocytes and eosinophils	Grade 4	Severe perivascular and interstitial mononuclear infiltrates*
Grade 3b	Borderline severe rejection		
Grade 4	Diffuse mixed (eosinophils, often neutrophils) infiltrate with vasculitis, hemorrhage, and myocyte necrosis		

**Without lymphocytic bronchitis or bronchiolitis.*

finding that supports the presence of acute rejection. The presence of cellular necrosis implies a higher rejection grade (Table 64-1). Nonhistologic modalities for diagnosing this condition, including measurement of hemodynamic parameters, echocardiograms, radionuclide scanning, and magnetic resonance imaging, have shown good correlation with established high-grade rejections but have not demonstrated sufficient predictive values. Severe acute rejection episodes have been noted in patients with normal echocardiograms. However, the existence of ventricular dysfunction or hemodynamic compromise should raise the suspicion of rejection.

Acute vascular rejection has been used primarily after cardiac transplantation to refer to depositions of immunoglobulin and complement within the walls of the coronary artery.[37] Although it has been proposed that this is a common form of acute rejection that can lead to allograft ischemia and dysfunction, many physicians believe that the deposits are nonspecific and more related to endothelial injury from ischemia. Enhanced perioperative immunosuppression, such as the use of polyclonal antithymoglobulins or the monoclonal anti-CD3 antibody (OKT3) for induction immunosuppression, can protract the healing phase of ischemic myocardial injury and confuse the histologic diagnosis of ischemic injury versus acute rejection.[38] This condition has been found, however, to account for many cases of allograft dysfunction in the presence of "normal" myocardial biopsies without cytolysis long after allograft implantation. The diagnosis was made on further evaluation of blood vessels on biopsy samples including the presence of C4d antibody deposits on endothelial cells with or without thrombosis or cell necrosis. Although some physicians advocate aggressive therapy when there is a suspicion, some will not treat with increased immunotherapy unless there is significant allograft dysfunction.

Chronic Rejection of the Heart

This process account for most cases of graft loss after the first year following transplantation. Although chronic, persistent cell-mediated rejection causes progressive myocardial fibrosis and dysfunction, the term *chronic allograft vasculopathy* (AV) takes into consideration the role of multiple nonimmune factors in the etiology of this process. AV to various degrees has a prevalence of at least 40 to 60% within 5 years of transplantation.[39] This obstructive process can progress to near-complete occlusion of the coronary arteries causing micro- and macroinfarction (Figs. 64-8 and 64-9) and is the leading cause

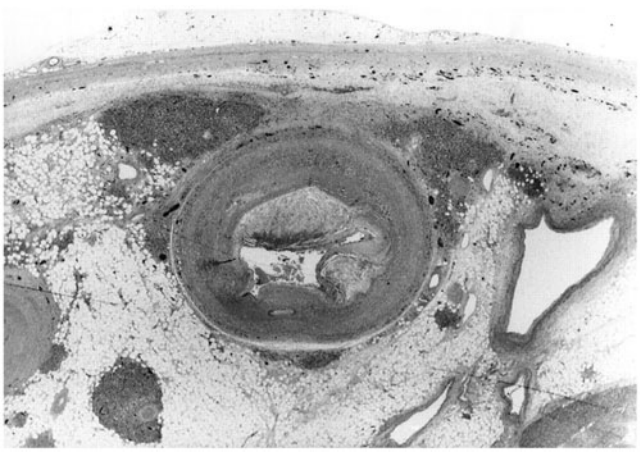

Figure 64-8. Obliterative arteriopathy, or chronic allograft vasculopathy (CAV), results in concentric narrowing of the epicardial coronary arteries and their large intramyocardial branches. This section was taken from an explanted cardiac allograft resected at the time of retransplantation for chronic rejection. Note the fibrointimal hyperplasia and adventitial and mural inflammation.

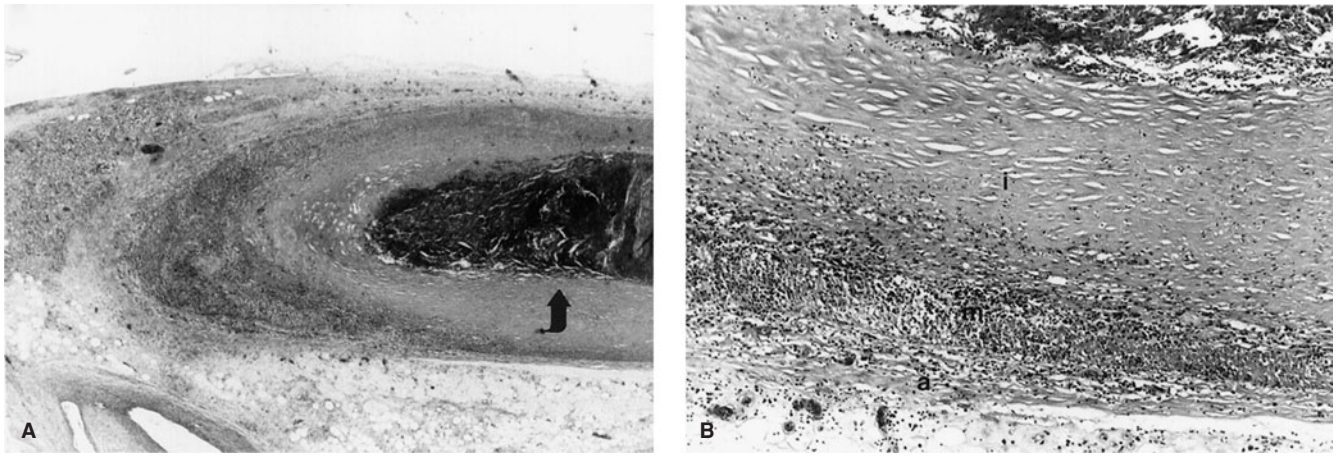

Figure 64-9. *A.* Predisposition to thrombosis is a complication of chronic allograft vasculopathy (CAV). In this photomicrograph, an artery already narrowed by CAV shows a complicating thrombus (*arrow*). *B.* A higher magnification of the artery shown in part *A* illustrates the adventitial (a), medial (m), and intimal (i) mononuclear inflammation, which is more prevalent and severe in CAV than in atherosclerosis seen in the general population.

of death after the first year following cardiac transplantation. Contrary to classic atherosclerotic lesions, the histologic findings of AV are characterized by diffuse, concentric involvement of both epicardial and small-caliber coronary vessels. There is a uniform pattern of near-luminal occlusion by neointimal proliferation and fewer early accumulations of extracellular lipid than with classic atherosclerosis. Infiltrates of T cells that encircle the entire vessel are characteristic.[40] The concentric nature of the lesion has led to emergence of intravascular ultrasound (IVUS) as the optimal method for clinical detection of AV given the failure of routine angiography to detect such concentric lesions reliably.[41] Endothelial cells generally remain intact but are known to be dysfunctional based on a paradoxical constrictive response to acetylcholine.[42]

AV has been linked to multiple potential etiologies with no clear single cause. Earlier belief that AV might be solely due to an arterial injury secondary to the ischemia-reperfusion associated with graft harvest and implantation is not tenable because animal models of syngeneic transplants do not develop the lesion. However, events around the procurement process that result in early endothelial activation and dysfunction have demonstrated a convincing correlation with the development of experimental[43] and clinical AV.[44] It has been difficult to correlate any of the usual risk factors for natural atherosclerosis, including hypertension, pretransplant hyperlipidemia, history of smoking, or prior atherosclerosis, with an increased risk of AV. However, aggressive treatment of posttransplantation hyperlipidemia with pravastatin was shown to reduce the incidence of AV in a randomized, placebo-controlled clinical trial using both IVUS and angiography.[45] Some studies have revealed the association of this condition with older donor age, whereas others have suggested that CMV infection might prompt the atherosclerotic process. Although there appears to be some association, it has been clearly demonstrated that CMV infection is not required for the process to occur, and the association may be more an association than cause and effect.[46,47] Antidonor cellular[48,49] and humoral[50–52] immune responses are associated with clinical AV lesions, but these processes might equally well be a marker for high risk as opposed to a direct cause of chronic rejection. Despite a significant improvement in the 1-year half-life of allografts in the modern cyclosporine era of improved immunosuppression, AV has remained refractory.[53] Increased expression of ICAM-1 and other adhesion molecules in AV lesions[54–56] points to the role of a smoldering, nonspecific immune response in the chronic rejection process, as documented in development and activation of nontransplant atherosclerosis.[57] Furthermore, there also might be an association between humoral rejection causing endothelial dysfunction and the development of future chronic vascular disease. Strategies aimed at treating humoral rejection therefore may lead to a reduction in the prevalence of AV.

Our current limited pathophysiologic understanding of this relentless process is based largely on small-animal models and retrospective patient series. By systematically isolating possible etiologic factors, animal models have provided significant insight into the basic science of the vasculopathic process in cardiac allografts. However, out of logistical necessity, the surrogate pathologic lesion occurs much earlier than the typical changes of chronic rejection in clinical patients. Thus the pathogenesis of the process being studied experimentally is almost certainly not the same as that occurring clinically. Indeed, many of the commonly used rodent models demonstrate suppression of AV lesion formation with standard immunosuppression such as cyclosporine,[58] a finding that significantly limits clinical relevance (Fig. 64-10).

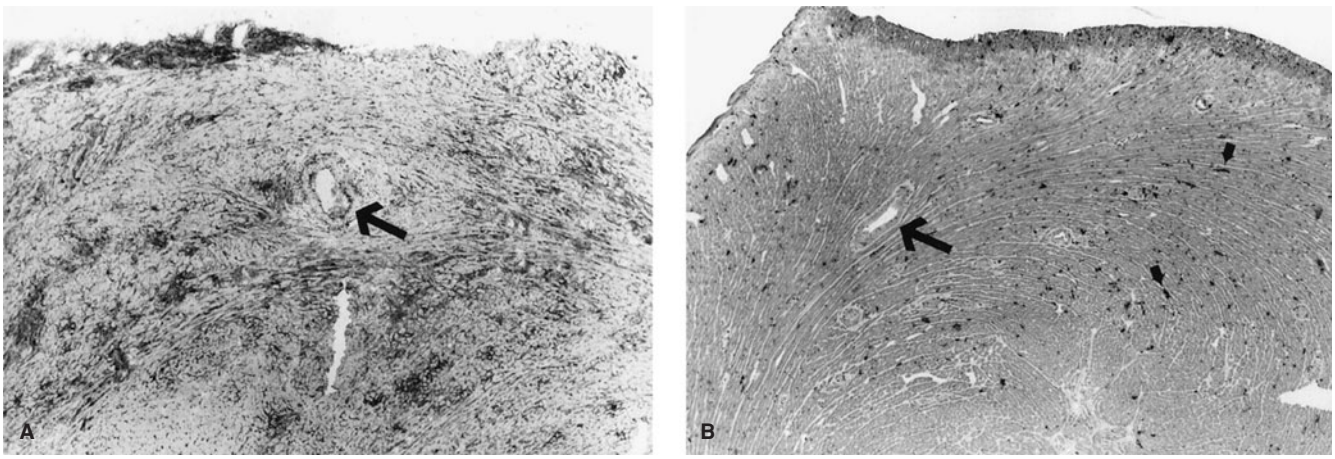

Figure 64-10. *A.* Experimental animal models of chronic allograft vasculopathy suggest that tolerance induction via the introduction of hematolymphoid chimerism can prevent chronic class II antigens on the microvasculature and large intramyocardial coronary arteries, which show early changes of chronic allograft vasculopathy (*arrow*). *B.* In contrast, donor MHC class II antigens in a cardiac allograft that is resistant to chronic rejection show staining only in the interstitial hematolymphoid cells (*small arrows*), whereas the arteries are normal appearing (*large arrows*).

Murase and colleagues have investigated pathogenic mechanisms of AV using MHC class I–mismatched miniature swine.[59] This more clinically relevant large-animal model supports the findings of most rodent models and suggests that there is an immune-mediated injury that initiates changes in the arterial wall. The artery then follows a "response to injury" pathway common to other forms of arteriosclerosis, prompting physical changes and relocation of smooth muscle cells from the media to a neointima. In addition, there is evidence that host stem cells deposit in the vessel wall and contribute to this neointimal hperplasia.[60] Irrespective of the cells of origin, neointimal formation is accelerated with growth factors, TNF, and IFN elaborated from the endothelium, as well as CD4 T cells. Macrophages are recruited and contribute cytokines and growth factors that promote the proliferation and synthesis of matrix by vascular smooth muscle cells.

Treatment strategies will remain elusive unless more complete control of the alloresponse can be maintained by the newer xenobiotics and monoclonal antibodies or induction of tolerance. Clinicians are anxious to explore the potential for new xenobiotics that have demonstrated a striking reduction in experimental AV based on their suppression of the smooth muscle response to the growth factors.[58]

Chronic Rejection of Lung Allografts

The lung allograft, too, appears to be affected by a chronic process that limits the long-term usefulness of the organ. This chronic attrition can affect 30 to 50% of recipients within 3 years of pulmonary transplantation and 60 to 70% of patients who survive for 5 years.[61] In the majority of patients, the problem is difficult to resolve once it develops, and the mortality rate at 3 years after diagnosis is 40% or higher. The term used to describe this chronic loss of function, *obliterative bronchiolitis* (OB), comes from the histologic findings of obliteration and fibrotic scarring of the terminal bronchioles[62] (Fig. 64-11). However, the clinical diagnosis is rarely based on histology given the low sensitivity of transbronchial biopsy.[63] The lesions of OB involve the lung in a nonuniform manner, and biopsy is performed mostly to rule out other causes of graft dysfunction, such as acute rejection, infection, and airway complications. Because symptoms are nonspecific, the most sensitive test for early detection of OB is a fall in forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75}$).[64] The term *bronchiolitis obliterans syndrome* (BOS) was formulated to describe chronic allograft dysfunction in the absence of confirming histology by a progressive decline

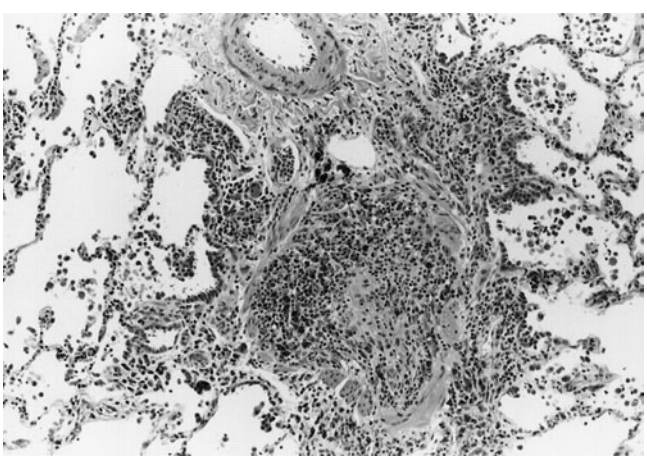

Figure 64-11. Bronchiolitis obliterans. A small bronchiole has its lumen completely obliterated by dense scar tissue and mononuclear inflammatory cells.

in FEV_1, deemed a more reliable and reproducible pulmonary function test.[65] BOS grades 0 to 3 are assigned according to the percentage of FEV_1 to best postoperative baseline value obtained. Bronchial wall thickening, distension of distal airways with air trapping, and frequent association of secondary acute infection have been detected on high-resolution chest computed tomographic (CT) scanning and are proposed as helpful in making the diagnosis.[66]

The histologic changes provide insight into the etiology of the process, including potential therapy. As in cardiac AV, OB appears to be the end result of an exaggerated injury response to the interplay among allogenic, ischemic, and viral etiologies. The lungs and airways appear to be quite susceptible to ischemia-reperfusion injury. Possible reasons include a propensity for ischemic damage of the delicate alveolar-capillary unit, difficulty in lung preservation given a static column of air in the graft, postoperative pulmonary hypertension owing to a hypertrophic right ventricle, and the lack of a direct arterial supply to the bronchus after transplant. It has been proposed that ischemia to the bronchial epithelium causes an exaggerated and chronic inflammatory response resulting in airway scarring. Although animal models have demonstrated a connection, ischemic time has not been shown convincingly to be an independent clinical risk factor for long-term graft failure.[67] However, clinical success has been achieved against chronic rejection in renal transplantation with the perioperative use of the free-radical scavenger superoxide dismutase[23]; the availability of a proven strategy for inhibiting RI in lung transplants with inhaled nitric oxide and pentoxifylline[68] warrants further follow-up to investigate a long-term effect on OB.

The transplanted lung is unique among solid-organ transplants in that it is exposed to the outside world. As a result, these lungs are particularly susceptible to the immunomodulary effects of respiratory viruses. By serving as an adjuvant for the cellular immune response or by a direct cytopathic effect on the airway, respiratory viruses such as CMV, respiratory syncytial virus, adenovirus, influenza, and parainfluenza infection all have been implicated as risk factors for BOS.[69] CMV infection, in particular, has a potent effect on donor-specific and nonspecific immune responses. An increase in INF and MHC class II antigen expression has been noted in bronchoalveolar lavage (BAL) cells during infections with CMV.[70] Most transplant centers believe in an association between CMV infection and BOS, although a precise relationship is far from uniformly accepted.

Although other facilitating factors certainly exist, several lines of clinical evidence support the alloresponse as a more important force behind the development of OB than cardiac AV (Figs. 64-12 and 64-13). First, acute rejection has been found consistently to be the leading risk factor for the eventual development of OB.[71] In particular, OB develops in the setting of indirect alloimmune[72] and alloantibody[73] responses to HLA-A mismatches and is stabilized occasionally by augmented immunosuppression[74,75] (see Fig. 64-13). Second, an identical form of OB can occur in bone marrow transplant recipients with graft-versus-host disease following recognition of the host lungs by the grafted alloreactive T cells.[76] Third, cells from bronchial lavages of OB patients have demonstrated TH1 cytokine mRNA profiles (i.e., IL-1, IL-2, IL-6, and IFN).[77] Finally, in the Pittsburgh study of microchimerism, it appeared that patients with OB had less evidence of microchimerism in blood, lymph nodes, and skin, which follows the general concept of less immune reactivity for those patients with a generalized chimeric state.[78]

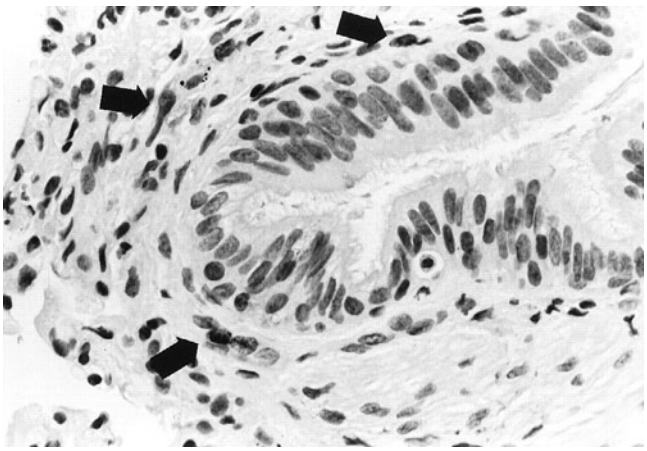

Figure 64-12. Bronchiolitis obliterans. Stains for S-100 protein decorate antigen-processing dendritic cells (*arrows*) present in increased numbers in the airways of lung allografts experiencing rejection.

The currently available experimental models of OB have provided insight into the human condition and new avenues for investigation. However, the lack of a large-animal model significantly limits their relevance. Attempts to model OB in nonhuman primate lung allografts have resulted in either acute rejection or normal lung tissue

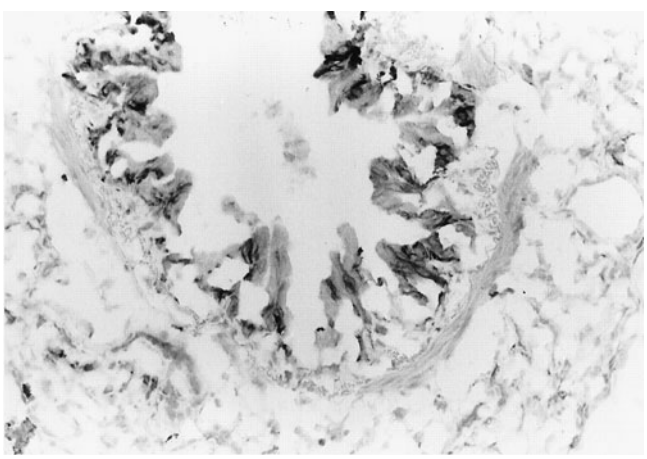

Figure 64-13. Bronchiolitis obliterans. Chronic airway rejection is characterized by increased expression of HLA class II antigens, especially HLA-DR (shown here) on respiratory epithelial cells.

depending on the level of immunosuppression used. Subcutaneous and intra-abdominal tracheal implants in rodents, but not nonhuman primates, develop close approximations of the pathologic lesions of OB at 1 and 2 months.[79,80] As in cardiac AV, the dissimilarity of the pathophysiology of these lesions prevents conclusions that have direct clinical relevance, especially regarding treatment. At present, the focus is on the newer immune drugs that might reduce not only the initial allogeneic response but also the secondary effects that result in mesenchymal cell recruitment for luminal scarring.

PRETRANSPLANT IMMUNOLOGIC EVALUATION AND MANAGEMENT OF SENSITIZED TRANSPLANT CANDIDATES

The prevention of donor organ rejection by the host continues to be of paramount importance in the field of thoracic transplantation given the detrimental sequelae of such episodes on short- and long-term graft function and survival. This remains to be the case despite the presence of multiple treatment modalities for such rejection episodes.

Various limbs of the immune system, both the specific and nonspecific arms, are responsible for hyperacute, acute, and chronic rejection episodes.

Preoperative Immune Screening and Prevention of Hyperacute Rejection

As mentioned in the preceding section, this type of rejection is believed to be the consequence of preformed host antibodies that cross-react with and attack the endothelium of blood vessels in donor organs. Hence the prevention of such a devastating event is based on the preoperative screening of transplant candidates for the existence of preformed antibodies that potentially could attack the donor graft. These include serologic studies to determine the ABO and HLA types (class I and II) of both hosts and donors in addition to the detection of preformed antibodies (PRAs) in transplant candidates against the major histocompatibility complexes.

Abo and RH compatibility

Transplantation should be performed between identical blood groups (such as A to A and B to B) or compatible blood groups (such as O to A, O to B, or A to AB) in order to avoid severe hyperacute rejection. Certain cases of successful organ transplantation, especially in the pediatric population, have been reported.[81] This, however, continues to be the exception rather than the rule, especially in the adult patient population.

HLA tissue typing of host and donor

The major histocompatibility complexes also play a central role in the immune response of hosts against donor grafts. Hence determination of the exact types of HLA antigens of both hosts and donors plays a very important role in solid-organ transplantation. HLA tissue typing generally is performed using the cytotoxicity method. More complex DNA typing methods are used when tissue typing cannot be identified using the cytotoxicity methods. Owing to donor shortages and logistics, transplantation between HLA-identical people is very difficult and not practical, especially in light of the fact that long-term outcomes are not strongly affected by HLA mismatches particularly if such mismatch is less than three of the important six HLA alleles of HLA-A, HLA-B, and HLA-DR, as discussed earlier in this chapter. This is in contrast to the case in other transplants, such as bone marrow transplantation, for instance. Recipients who possess antibodies against HLA types that are present in the donor, however, are at a higher risk of developing hyperacute rejection, and such organs generally are avoided.

Panel reactive antibodies

This is also considered to be an essential part of the pretransplant immune evaluation process. The host's serum is screened for the presence of anti-HLA antibodies (both HLA class I and class II). A high antibody titer (>10%) increases the risk of rejection (hyperacute if anti–class I antibodies are present and vascular or future chronic allograft rejection if anti–class II antibodies are present). Various reports have demonstrated inferior graft survival results with higher PRA titers in both heart and lung transplantation.[82,83] PRA levels generally are measured using the cytotoxicity method or the more sensitive flow beads method. Various interventions are used to decrease the PRA load if elevated, including plasmapheresis, Cytoxan, intravenous immunoglobulins, rituximab, and a combination of all, as will discussed below.[82,83]

Crossmatching

Prospective crossmatching usually is used at the time of transplantation prior to donor-organ procurement when PRA levels in the recipient are elevated (>10%). This is the last and most definitive test of donor versus recipient immunologic compatibility. The crossmatch tests the sera of recipients, which might contain anti-HLA antibodies, against donor lymphocytes (B and T cells) obtained from peripheral donor blood samples. Hyperacute rejection episodes posttransplantation have been reduced dramatically in sensitized patients owing to the use of prospective crossmatching techniques. The requirement of prospective crossmatching is time-consuming, however, and limits the eligibility of potential organs to closer geographic areas. Consequently, this is only used in patients with high PRA levels and therefore at a higher risk of developing hyperacute or accelerated acute rejection episodes (5 to 7 days). Retrospective crossmatching is also carried out routinely in many institutions in order to determine the presence of antidonor antibodies in transplant recipients that might account for any unexpected graft dysfunction posttransplantation.

Management of Pretransplant High PRA Levels and Treatment of Hyperacute Rejection

Various modalities have been used with different degrees of success to reduce the PRA load in sensitized transplant candidates or in the treatment of hyperacute rejection episodes[84,85]:

1. *Plasmapheresis.* This treatment modality has been used to treat a variety of autoimmune conditions such as multiple sclerosis and idiopathic thrombocytopenia. It works by replacing patients' own antibodies rich plasma with clean, fresh plasma or albumin solution. Multiple pheresis runs usually are required to achieve a meaningful reduction in PRA levels. This treatment has been shown to be effective in desensitizing transplant candidates, especially when combined with other agents such as Cytoxan or immunoglobulins.[86–93]
2. *Cytoxan (cyclophosphamide).* Cytoxan is an alkylating agent with cytotoxic and immunosuppressive activities. Its exact mechanism of action is not very well understood, but it works via an active intermediate metabolite that is purported to reduce B-cell production of antibodies. Cytoxan is used to treat certain cancers and some nonmalignant autoimmune diseases such as Wegener granulomatosis. This agent also has been used to reduce PRA levels in highly sensitized transplant candidates with variable degrees of success.[86,94–96] The combination of Cytoxan and immunoglobulins has been shown in certain studies to reduce PRA levels to levels safe enough to allow for successful heart transplantation.[95] Various side effects, however, are associated with this agent, such as bone marrow suppression and hemorrhagic cystitis.
3. *Intravenous immunoglobulins (IVIGs).* Many studies have demonstrated the efficacy of IVIGs in the treatment of sensitized transplant candidates. This treatment also has been combined with plasmapheresis or Cytoxan to treat high PRA levels.[88,94] Pretreatment with antihistamines and steroids is recommended to reduce the possible side effects of serum sickness–like symptoms such as fever and nausea.
4. *Rituximab.* This murine/human chimeric monoclonal antibody is specific for CD20 receptors that are expressed primarily by B cells. This agent dramatically reduces the number of circulating B cells in the blood. B-cell counts remain low for 6 to 9 months after treatment. This agent has been shown to be effective in the treatment of posttransplant lymphoproliferative disorders (PTLDs) in kidney, liver, heart, and lung transplant recipients.[97] Recent reports also have demonstrated the effectiveness of this compound in the treatment of hyperacute rejection in addition to the reduction in PRA levels pretransplantation. Some studies have reported a small risk of hypogammaglobulinemia and multiple fungal or viral infections in organ transplant recipients treated with rituximab.[98–101]
5. *Photopheresis.* Extracorporeal photopheresis (ECP) has been under investigation for a few years. It is based on the separation of a leukocyte/lymphocyte-enriched cell fraction from the peripheral blood, extracorporeal treatment of these cells with 8-methoxypsoralen (8-MOP), followed by exposure to ultraviolet A (UVA) light with subsequent reinfusion of the cells into the patient. This seems to lead to changes in the immunologic behavior of the photoinactivated/modulated cells. The treatment is well tolerated and causes few side effects. Some studies have demonstrated the efficacy of this modality in the treatment of heart and lung rejection, in addition to other conditions such as graft-versus-host rejection in bone marrow transplant patients.[102–105]
6. *Total bone marrow irradiation.* This therapy also has been used with variable degrees of success to treat high PRA levels or rejection episodes that are resistant to conventional treatment modalities.[106]

NEW IMMUNOSUPPRESSIVE DRUGS

The improved outlook for transplant recipients has followed the introduction of xenobiotic immunosuppressants, i.e., drugs produced by organic synthesis or microorganisms that suppress the immune system. Between 1960 and 1985, only steroids, azathioprine (AZA), and cyclosporine (CsA) had been adopted for use in clinical transplantation. These agents have been joined more recently by polyclonal and monoclonal anti-T-cell antibodies. In the last few years, progress in the molecular understanding of the alloresponse has made new discoveries possible and has allowed agents to be classified by mechanism of molecular action (Fig. 64-14 and Table 64-2).

Corticosteroids

Transplant physicians have recognized the benefits of corticosteroids from the very early days of clinical transplantation. These molecules have protean effects that, like any steroid, are mediated through intracellular receptors that alter gene transcription. The predominant anti-inflammatory effects of glucocorticoids, such as blockade of NF-κB-induced transcription of inflammatory cytokines and adhesion molecules, derive from the inhibition of gene transcription. On the other hand, the metabolic side effects, such as muscle wasting and diabetes, derive from positive transcriptional effects.[107] This concept of differing mechanisms of action has prompted investigations to develop corticosteriod analogues that bind to intracellular receptors to promote the inflammatory effects without the metabolic effects.

Glucocorticoids have been found to induce apoptosis in malignant T cells[108] and are therefore an especially appropriate choice of sole immunosuppression in the setting of

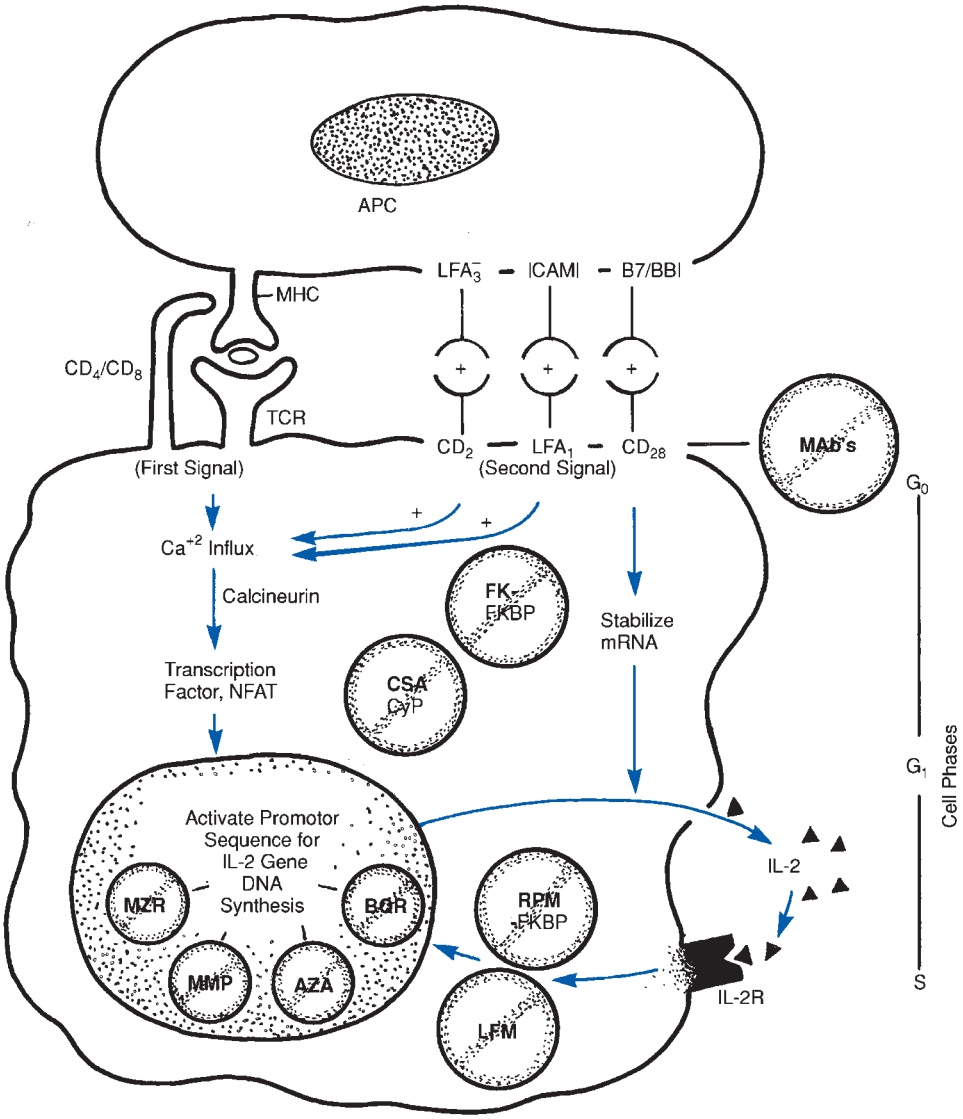

Figure 64-14. Immunosuppressants available to clinicians are directed toward inhibiting T-cell activation at various steps and by varied mechanisms, including interference with TCR complex (OKT3 Mab) and other surface ligands (anti-ICAM-1, anti-CD2, and others); Ca^{2+}-dependent (CsA and FK) signal transduction; inhibition of cytokine IL-2 action in promoting cellular proliferation (RPM and LFM); and inhibition of purine (AZA, MZR, and MMP) or pyrimidine synthesis BQR.

posttransplant lymphoproliferative disorder. Outside this subgroup, however, recent advances in the development of tolerance protocols have suggested that steroid use blocks certain immune signaling pathways necessary to induce donor-specific anergy or suppressor cells.[30] In addition, steroid weaning reduces the tendency toward diabetes and dyslipidemia, which may decrease the incidence of AV.[109]

Cytokine Synthesis Inhibitors

Cyclosporine (CsA) inhibits the gene activation necessary for IL-2 production. To accomplish this, CsA inhibits the function of a Ca^{2+}-activated calcineurin phosphatase when bound to its cytoplasmic receptor.[110] This prevents activation and nuclear translocation of the nuclear factor for activation of T cells (NFAT), precluding its engagement with the promoter sequence of the IL-2 gene. Blockade of the Ca^{2+} calcineurin phosphatase complex also inhibits the production of nitric oxide synthetase, a potential mechanism by which CsA seems to promote AV in animal models.[111]

Originally oil-based, CsA has been replaced by a novel microemulsion formula, Neoral, which has improved its bioavailability significantly and reduced pharmacokinetic variability among patients. Approximately 30% of heart transplant recipients develop nephrotoxicity, the primary toxicity of CsA, which appears to be mediated by the inhibition of prostaglandin metabolites. However, the prostaglandin analogue misoprostol has afforded little clinical benefit.[112] In

Table 64–2.

Compendium of Immunosuppressants

Drug	Proposed mechanism	Status
Cytokine synthesis		
Cyclosporine A	Inhibits SER/THR phosphatase	FDA approved
Tacrolimus (FK506)	Inhibits SER/THR phosphatase	FDA approved
Growth factor inhibitor		
Rapamycin	Unclear	FDA approved
Leflunomide (LFM)	Inhibits tyrosine kinase	In clinical trials
DNA synthesis inhibitor		
Azathioprine (AZA)	Inhibits PRPP amidotransferase (purine)	FDA approved
Methotrexate	Inhibits dihydrofolate reductase	FDA approved
Mycophenolate (MFF)	Inhibits IMP dehydrogenase (purine)	FDA approved
Mizoribine (MZR)	Inhibits IMP dehydrogenase (purine)	In clinical trials
Brequinar (BQR)	Inhibits DHO dehydrogenase (pyrimidine)	On hold
Receptor antagonists		
Antithymocyte globulin (equine or rabbit)	Kills T cells or alters traffic	FDA approved
Anti-CD3 (OKT3)	Kills CD3+ cells or alters traffic	FDA approved
Anti-IL-2 receptor	Kills IL-2R+ or alters traffic	In phase III clinical trials
DAB486-IL-2	Kills CD25+ cells or alters traffic	In clinical trials
Anti-LFA-1	Inhibits intercellular adhesion	In clinical trials
Anti-ICAM-1	Inhibits intercellular adhesion	In clinical trials
OKT4A	Induces CD4+ cell anergy	In clinical trials
IL-1 receptor antagonist	Inhibits IL-1 receptor	In clinical trials
Soluble HLA	Inhibits antigen presentation	Preclinical
Deoxyspergualin	Inhibits antigen presentation	In clinical trials
Cytokine inhibitors		
Anti-IL-6	Neutralizes IL-6	In clinical trials
Anti-TNF	Neutralizes TNF	In clinical trials
Soluble IL-1 receptor	Neutralizes IL-1	In clinical trials
IL-10	Inhibits cytokine synthesis	Preclinical

Source: Adapted with permission from Przepiorka D: Rational use of new immunosuppressive agents, in Recent Developments in Transplantation Medicine. Glenview, IL, Physicians & Scientists, 1994.

two recent series of heart transplant patients, calcineurin inhibition was the sole indication for metachronous kidney transplantation.[113,114] CsA-induced alterations in cell phenotype explain other side effects, such as hypertension and dyslipidemia.[115,116]

CsA was widely embraced as the central component for effective multidrug immunosuppression until FK506 (tacrolimus) was introduced to patients in Pittsburgh in 1988. Tacrolimus combines with a different cytosolic protein than CsA (FK-binding protein) but complexes with the same Ca^{2+}-activated calcineurin to prevent the activation of NFAT.[76] Tacrolimus has proven to be at least as effective in heart transplant patients[117] and possibly better in lung transplant patients.[118] It has found particular success following a switch from CsA-based immunosuppression when faced with a refractory acute rejection of the heart or lung[119] or bronchiolitis obliterans.[74] Given a mechanism of action similar to that of CsA, the reason for the improved effectiveness of tacrolimus in refractory rejection likely relates to more predictable pharmacokinetics.[120] Therefore, ongoing clinical trials comparing tacrolimus with Neoral are of great interest with regard to efficacy but are not likely to change the improved side-effect profile already demonstrated with tacrolimus in multicenter trials.[117] Compared with recipients receiving CsA, tacrolimus was found to be associated with less facial disfigurement, hirsutism, hypertension, and hyperlipidemia but equal nephrotoxicity and was perhaps associated with greater neurotoxic and diabetogenic effects.

Inhibitors of DNA Synthesis

Antimetabolites are immunosuppressive because they inhibit the synthesis of nucleotides necessary for DNA's rapidly dividing cells. The classic antimetabolite has been azathioprine (AZA), which inhibits purine synthesis and therefore DNA and RNA synthesis throughout all dividing cells. Mycophenolate mofetil (MMF) appears to be more selective for T and B cells than AZA[121] based on its ability to block the activity of the enzyme inosine monophosphate dehydrogenase and therefore the synthesis of purines in the de novo pathway. Unlike other parenchymal and peripheral blood cells, T and B cells cannot use the salvage pathway and depend solely on the de novo pathway for purine synthesis. Compared with AZA, randomized clinical trials have shown a reduction in acute rejection events and antibody production with MMF in both heart[122] and lung[123] transplant patients. The reduction in chronic graft loss that has been demonstrated with the use of MMF versus AZA in renal transplantation has not yet been confirmed in cardiothoracic transplants. Neutropenia has not been a limiting factor, as it has been with AZA.

Brequinar sodium (BQR) is a new addition to the antimetabolite group.[124] Unlike MMF, its action appears to be directed against dihydro-orotate dehydrogenase (DHODH), an enzyme in the pathway leading to synthesis of pyrimidines. The rationale for use of BQR is similar to that for MMF, given that activated immune cells are relatively more dependent on de novo synthesis of pyrimidine's effects than nonimmune cells, although unlike for purines, a salvage pathway does exist. As a result, BQR appears to be less selective for immune cells. Another DHODH inhibitor, leflunomide, has demonstrated a much more favorable therapeutic window, although profound weight loss has been seen in animal and human trials.[125] Leflunomide depletes ATP-dependent enzymes, which inhibits the glycosylation of adhesion molecules, providing another possible mechanism of immunosuppression.[126] Clinical utility of both BQR and leflunomide has been limited by myelotoxicity and gastrointestinal effects; planned clinical trials have been stopped.

IL-2 Signal Transduction Inhibitor

Rapamycin (RPM, sirolimus) is structurally similar to tacrolimus and binds with FK-binding protein (FKBP) but surprisingly does not inhibit the calcium-activated calcineurin.[120] Instead, RPM acts at a point downstream from the cytokine inhibitors and upstream from the antiproliferative agents. In alloreactive T cells, stimulation of the IL-2 receptor leads to clonal proliferation following initiation of the cell cycle and conversion from the resting (G_0) to proliferative (G_1/S) state. The RPM-FKBP complex binds the so-called target of rapamycin, a lipid kinase,[127] and prevents the signaling between IL-2 receptor activation and cell cycle initiation. Because of theoretical concerns of competition for FK-binding protein, sirolimus was combined initially with CsA,[128] but recent clinical trials in renal transplantation actually have demonstrated greater success when it is combined with FK506.[129] In vitro studies have demonstrated that RPM also induces cell cycle arrest in B cells and smooth muscle cells.[130] This smooth muscle cell antiproliferative effect is thought to be responsible for the arrest of AV in both small-animal[60] and large-animal[131] experimental models and for the clinical prevention of restenosis after using RPM-coated intracoronary stents.[132] In preliminary randomized studies, the use of RPM instead of AZA following heart transplantation has resulted in reduced AV by IVUS evaluation at 6 months[133] and 1 year.[134] Sirolimus is not nephroxic, but it may enhance the renal toxic effects of calcineurin inhibitors[103]; its main toxicity is hyperlipidemia.

Combinations of these drugs that act at the level of cytokine production, the proliferative response to cytokines, and/or the signaling between the two have demonstrated additive immunosuppressive effects.[135] This not only will effectively reduce the alloresponse but also potentially will do so with lower doses of each.

Inhibition of T- and B-Cell Maturation

Deoxyspergualin (DSG) does not inhibit the synthesis or actions of cytokine but has been shown to inhibit the maturation of T and B cells and APCs.[136] Clinical trials that were conducted in high-risk renal allograft recipients were stopped owing to a high incidence of leukopenia.

Receptor Antagonists and Monoclonal Antibodies

Polyclonal anti-T-cell preparations (ATGs) have been developed that recognize T-cell surface structures and kill these targets by inducing Fc-receptor-mediated cell lysis or by complement-dependent cell lysis. In the mid-1980s, the murine anti–human CD3 monoclonal antibody (OKT3) was developed that recognizes the epsilon protein of the CD3 complex on all T cells. When used as induction agents in thoracic transplantation, ATG and OKT3 have been found only to delay the onset of acute rejection at the expense of a profound, uncontrolled immunosuppression that increases the risk for opportunistic infections and malignancy.[137] Furthermore, their main toxicity, the cytokine release syndrome, is tolerated particularly poorly in heart and lung transplant recipients. As a result, their current use is limited in most centers for the treatment of refractory acute rejection and as a calcineurin inhibitor–sparing agent in those with prolonged postoperative renal dysfunction.

The development of a humanized monoclonal antibody (mAb) against the IL-2 receptor provided the opportunity for a more selective targeting of activated T cells, the only cells that express this receptor. In a small (55 heart transplant recipients) randomized clinical trial, induction therapy using this mAb, dacluzimab, reduced the frequency and severity of acute rejection events over the study period. In addition, there were essentially no side effects and no increased risk of infection or malignancy.[138] Pilot studies using mAb against the cell adhesion molecules LFA-1[139] and

ICAM-1[140] showed promise in preventing reperfusion injury but variable success against acute rejection. The combination of the two, which was synergistic against acute rejection in rodent models, has not been tried clinically. Also awaiting clinical trial is a strategy that inhibits T-cell costimulation such as the anti-CD154 mAb or CTLA-4 Ig that have produced tolerance in the nonhuman primate model.[30] Other monoclonal antibodies that are in various stages of clinical development may have a specific role in therapy, but hopes for a magic bullet likely will not be realized because the immune response is far from simple and is based on redundancy by way of alternative pathways. A combination of various mAbs likely would be the best protocol to address this redundancy. Unfortunately, no preclinical or clinical trials using a combination strategy have been performed in large part owing to financial conflicts between the different pharmaceutical companies that own the rights to these agents.

TOLERANCE

While immunosuppressive agents have permitted the replacement of heart and lungs to become realities, their toxic side effects and inability to prevent more chronic forms of rejection have driven the search for alternative strategies. Experimental models have suggested that the induction of tolerance is the most effective way to prevent chronic rejection.[141] Indeed, the absence of AV or OB has been considered to be the best clinical endpoint for the evaluation of successful tolerance induction in future trials by the National Heart, Lung and Blood Institute Heart and Lung Tolerance Working Group.[142] While a myriad of protocols have induced tolerance in small animals, only a few have been reproduced in swine or nonhuman primate transplant models. The list of studies relevant to thoracic surgery shrinks further when considering the elusiveness of translating tolerance protocols from one organ to the other. In addition, there is a general belief that induction of tolerance in thoracic organs is more difficult than for other organs, such as the liver or kidney.[143] To date, only three protocols have induced prolonged survival of cardiac allografts in large animals without immunosuppression (none in lung allografts): (1) the induction of mixed chimerism, which is thought to work through central tolerance, (2) the use of costimulatory blockade to induce peripheral tolerance, and (3) the cotransplantation of heart and kidney allografts, which works by unknown mechanisms.[143]

By introducing allogenic bone marrow cells into newborn mice, Billingham and colleagues induced a mixed chimeric state that was the first demonstration of allograft tolerance in 1953.[144] A recent analysis of renal transplant recipients from sibling donors has shown this type of tolerance to occur toward noninherited maternal HLA owing to prior in utero exposure to this foreign antigen.[145] In these mixed chimeras, bone marrow–derived elements of both host and donor appear in the thymus and present ligands for negative selection of newly developing T cells that are either donor or host reactive.[146] This induces clonal deletion, one of the most reliable approaches to achieving long-term donor-specific tolerance. In an adult organism, creation of a mixed chimera requires the infusion of donor hematopoietic cells along with a conditioning regimen to enhance engraftment. Conditioning using antilymphocyte serum has been attempted but has produced little[147] to no[148] evidence of durable hematopoietic cell engraftment and minimal impact on allograft survival. The most common method employed in preclinical and clinical trials has been the use of a toxic dose of total lymphoid irradiation (TLI), similar to that used to treat Hodgkin disease.[149] The use of a nonmyeloablative conditioning regimen of CD3 monoclonal Abs bound to the diphtheria immunotoxic instead of TLI has enabled the induction of stable mixed chimerism using donor stem cells with significantly less toxicity. Subsequent transplantation resulted in long-term tolerance in the swine model despite a minor-antigen mismatched histocompatibility barrier. Recently, the use of pleuripotent embryonic stem cells has allowed the development of mixed chimerism and tolerance without conditioning in rodents.[150] These preliminary results have not yet been reproduced in large animal models.

It has been observed that in heart[151] and lung[152] transplant recipients enjoying long-term survival, donor-type lymphoid and dendritic cells migrate from the graft and establish themselves in the unconditioned recipient's periphery.[153] In this case, donor cells exist at levels below cytometric detection in the periphery of solid-organ transplant recipients (1 in 10^5 cells, as detected by PCR techniques) with a kinetics and patchy distribution that resemble a spreading infection. In lung transplant recipients, this microchimerism has been associated with donor-specific hyporeactivity and a lower incidence of OB.[154]

The observations that microchimerism is a common event after heart and lung transplantation and that it is associated with long-term graft acceptance have stimulated attempts to augment microchimerism with perioperative bone marrow transfusion. Pham and colleagues have provided proof of the principle that induced microchimerism influences acute and chronic rejection in clinical heart[155] and lung[156] transplantation without producing graft-versus-host disease. However, a causal relationship between microchimerism and a decrease in target events such as rejection or graft survival was not established. The association between microchimerism and graft survival is inconsistent with the identification of both long-term survivors who do not have it and patients with multiple episodes of rejection who do.[157] Furthermore, only mixed chimerism, and not microchimerism, has been shown in animal models to induce systemic, stable allograft-specific tolerance.[158]

The second mechanism for the induction and maintenance of tolerance that occurs following costimulatory blockade is anergy, also known as *peripheral tolerance.*[159] The two-signal model of T-cell activation holds that an alloresponse to the interaction of the T-cell receptor with its antigen requires a second signal prompted by the other molecular participants of the immunologic synapse. Engagement of the T-cell receptor without these signals induces

anergy or a lack of T-cell proliferation on antigen stimulation. The advantage of this mechanism is achieved by exposing T cells to alloantigen under the umbrella of mAbs blocking costimulatory molecules such as CD28,[31] LFA-1, and CD2 ligand.The period of immunosuppression lasts only as long as the mAbs are at therapeutic levels in the host. As the mAbs clear, the immune competence returns to all antigens other than those to which tolerance had been induced.

It has long been recognized that passenger leukocytes, i.e., cells derived from the organ transplant, most commonly dendritic in nature, can escape the organ and accumulate in peripheral host lymphoid tissues. It is possible that donor-derived immature passenger dendritic cells mediate a form of anergy by indirect and direct presentation of alloantigen, with limited secondary signals necessary for T-cell proliferation. Kidney transplants are thought to have enhanced numbers of these cells as the proposed mechanism of their immunosuppressive effect on cardiac allograft rejection.

XENOTRANSPLANTATION

Animal-to-human transplantation, known as *xenotransplantation,* has been proposed to alleviate the critical shortage of human donor organs. Approximately 30% of the patients waiting for hearts and lungs will die without receiving a transplant. In 1964, four years before the first human allotransplant, Hardy attempted to replace a 68-year-old man's failing heart with one obtained from a chimpanzee.[160] Since then, there have been only six additional attempts at xenotransplantation reported using pig, sheep, baboon, or chimpanzee donors.[161,162] These cases, although unsuccessful, have provided insight and promise to the field. In 1984, Bailey and colleagues placed an ABO-incompatible baboon heart into a child with a hypoplastic left heart syndrome. Baby Faye, as the child was known, made remarkable progress for 20 days, when rather suddenly the xenograft stopped functioning. Examination of the heart gave evidence consistent with a humoral rejection, perhaps related to the blood group incompatibility.

Although nonhuman primates provide concordant organs for cross-species transplantation, phylogenetically disparate or discordant donor organs from pigs are favored for several reasons. First, broad use of the relatively rare and sentient primates is unlikely to gain societal acceptance. Second, retroviruses from pigs are much less likely than those from nonhuman primates to transmit disease to humans.[163] Finally, the short gestation, time to maturation, and large litters of pigs relative to primates simplify their breeding and improve their candidacy for germ-line gene therapy. Accordingly, the porcine heart has been the focus of most of the experimental work in heart and lung xenotransplantation and was the most recent clinical xenograft reported for use in cardiac transplantation in 1992.[164]

Xenograft Hyperacute Rejection

The first major obstacle to discordant cross-species transplantation generally is believed to be the process described as hyperacute rejection (HAR). Hyperacute rejection is mediated largely by preformed xenoreactive antibodies and the relative incompatibility of discordant xenograft complement regulatory proteins (e.g., decay-accelerating factor) with the human complement system. The primary human xenoreactive antibodies that initiate HAR against discordant pig hearts are specific for the blood group carbohydrate Gal (1–3 Gal), an antigen not present in concordant nonhuman primates.[165,166] Using the classical pathway, the binding of xenoreactive antibodies to the pig endothelium leads to the unregulated activation of complement owing to inadequate function of swine counterregulatory proteins for human complement. The resulting uncontrolled deposition of the terminal complement complexes (C5b67) on the swine endothelial cells disrupts the endothelial cell barrier function because they retract and generate intracellular gaps (type 1 activation). Platelets then are attracted to exposed extracellular matrix and release vasoactive substances, including thromboxane A2, that stimulate vasoconstriction. The procoagulant state is intensified because of the loss of heparin sulfate proteoglycans from their surfaces.

These findings have led White, Pedor, and Platt to develop swine that are transgenic for human DAF and CD-59. By overexpressing human DAF and CD-59, these transgenic organs successfully avert hyperacute rejection following pig-to-primate renal, heart, and lung transplantation.[167–169] The temporary, pretransplant depletion of complement using cobra venom[34] and anti-Gal antibodies using any of several different methods has provided further success against HAR.[170] Evidence exists that if HAR and acute vascular rejection (AVR) can be prevented initially, then the xenograft may "accommodate" in a manner in which it becomes resistant to future exposure to human antibody and complement.[36,171] This is thought to be mediated by increased expression of antiapoptotic genes and inhibition of NF-κB transcriptional activation in the xenograft endothelium. The enhancement of this pathway would serve obvious benefits in xenotransplantation. However, the greatest potential for a significant advance has been achieved by the recent creation of Gal-1,3 galactosyl transferase knockout pigs.

Acute Vascular Xenograft Reaction

Despite prevention of HAR by either disrupting antibody binding or by depleting or inhibiting complement, xenografts are subjected to a process named *acute vascular rejection* (AVR).[171] Although the histologic picture of AVR with its hemorrhage and thrombosis is very characteristic of HAR, it appears to be a distinct process not dependent on complement or appearing in concordant transplant combinations. The pathophysiology begins with naturally occurring antipig antibodies binding to the endothelial surface. This leads to levels of complement activation through the

membrane attack complex (MAC) that are below lytic levels but that lead to the induction of IL-1, which mediates other changes on the surface of the endothelial cell that, by and large, create a strongly procoagulant state (type 2 activation). These changes include the induction of procoagulant tissue factor, release of plasminogen activator inhibitor, a decrease in tissue plasminogen activator, and a loss in thrombomodulin activity. Thrombomodulin is expressed on the surface of vascular endothelial cells and reduces thrombotic process by thrombin-dependent activation of protein C, which, in turn, degrades the procoagulant cofactors factors Va and VIIIa. It has been noted also that E-selectin, responsible for leukocyte rolling on the endothelium, is also upregulated during AVR.

Cell-Mediated Xenograft Rejection

Although cell-mediated rejection has not been studied extensively in the xenograft model because of difficulties in overcoming HAR and AVR, recent investigations have suggested that xenografts have increased susceptibility to cell-mediated injury and as well as to attack by natural killer (NK) cells.[172] NK cells normally are inhibited by class I MHC receptors, yet when added to xenograft tissue culture, NK cells have been demonstrated to cause cytotoxicity and phenotypic changes in a disruptive endothelial cell monolayer consistent with retraction and gap formation typical of the activated endothelium described in HAR.[173,174] It was hoped that thymic selection, which permits T lymphocytes to recognize allogeneic cells directly, might be less effective in producing T lymphocytes that might recognize the porcine xenogenic cells. However, it has been determined that human T cells can recognize porcine cells directly through MHC class II antigen.[175]

Significant progress has been made with the discordant porcine-to-primate model. However, an impact on human transplantation awaits additional studies that promote a further understanding of the effects of the inhibition of early HAR, methods to persistently reduce AVR, and finally, a way of dealing with an enhanced cell-mediated rejection. It is likely that a combination of immunosuppressants, transgenic animals, and even tolerance-induction protocols may provide a suitable therapeutic cocktail. Chief clinical investigators in the field of xenotransplantation have stressed the need to look for intermediate endpoints as means of understanding processes because the long-term goal of routinely successful discordant xenografting will require solving multiple complex processes. It is likely, then, that well-prepared surgical groups will soon initiate bridge trials in which short-term survival of the xenograft might be predicted, and information gained will be invaluable to the science.

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CHAPTER 65

Heart Transplantation

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The number of patients with heart failure is growing. End-stage heart failure is associated with significant morbidity, need for recurrent hospitalizations, decrease in quality of life, and increased mortality. Cardiac transplantation has evolved as an effective therapy for many of these patients. Tremendous advancements in the fields of immunosuppression, rejection, and infection have transformed what was once considered an experimental intervention into a routine treatment available worldwide.

HISTORY OF HEART TRANSPLANTATION

The innovative French surgeon Alexis Carrel performed the first heterotopic canine heart transplant with Charles Guthrie in 1905.[1,2] Frank Mann at the Mayo Clinic further explored the idea of heterotopic heart transplantation in the 1930s. The neck became the preferred site of implantation in early experimental animal models because of the ease of monitoring the organ and the simplicity of gaining access to major vessels and because the recipient's heart acted as a built-in cardiac assist device for the transplanted organ.[3] Mann also proposed the concept of cardiac allograft rejection, which involved biologic incompatibility between donor and recipient manifested by an impressive leukocytic infiltration of the rejecting myocardium. In 1946, after unsuccessful attempts in the inguinal region, Vladimir Demikhov of the Soviet Union successfully implanted the first intrathoracic heterotopic heart allograft.[4] He later demonstrated that heart-lung and isolated lung transplantation also were technically feasible.

The use of moderate hypothermia, cardiopulmonary bypass, and an atrial cuff anastomotic technique permitted Norman Shumway (Fig. 65-1) and Richard Lower at Stanford University to further explore orthotopic heart transplantation using a canine model in 1960.[5] The first human cardiac transplant was a chimpanzee xenograft performed at the University of Mississippi by James Hardy in 1964.[6] Although the procedure using Shumway's technique was technically satisfactory, the primate heart was unable to maintain the recipient's circulatory load, and the patient succumbed several hours postoperatively. Despite great skepticism that cardiac transplantation ever would be performed successfully in humans, South African Christiaan Barnard surprised the world when he performed the first human-to-human heart transplant on December 3, 1967.[7] Over the next several years, poor early clinical results led to a moratorium on heart transplantation, with only the most dedicated centers continuing experimental and clinical work in the field. The pioneering efforts of Shumway and colleagues at Stanford eventually paved the way for the reemergence of cardiac transplantation in the late 1970s. The introduction of transvenous endomyocardial biopsy by Philip Caves in 1973 finally provided a reliable means for monitoring allograft rejection.[8] Ultimately, however, it was the advent of the immunosuppressive agent cyclosporine that dramatically increased patient survival and marked the beginning of the modern era of successful cardiac transplantation in 1981.[9,10] Heart transplantation is now a widely accepted therapeutic option for end-stage cardiac failure; however, the annual number of transplants in the United States (approximately 2200 per year) has remained relatively constant because of limited donor-organ availability.[11]

THE CARDIAC TRANSPLANT RECIPIENT

Recipient Selection

The evaluation of patients with end-stage heart disease and the selection of potential candidates for cardiac transplantation are undertaken by a multidisciplinary committee to ensure an equitable, objective, and medically justified allocation of the limited donor organs to patients with the greatest

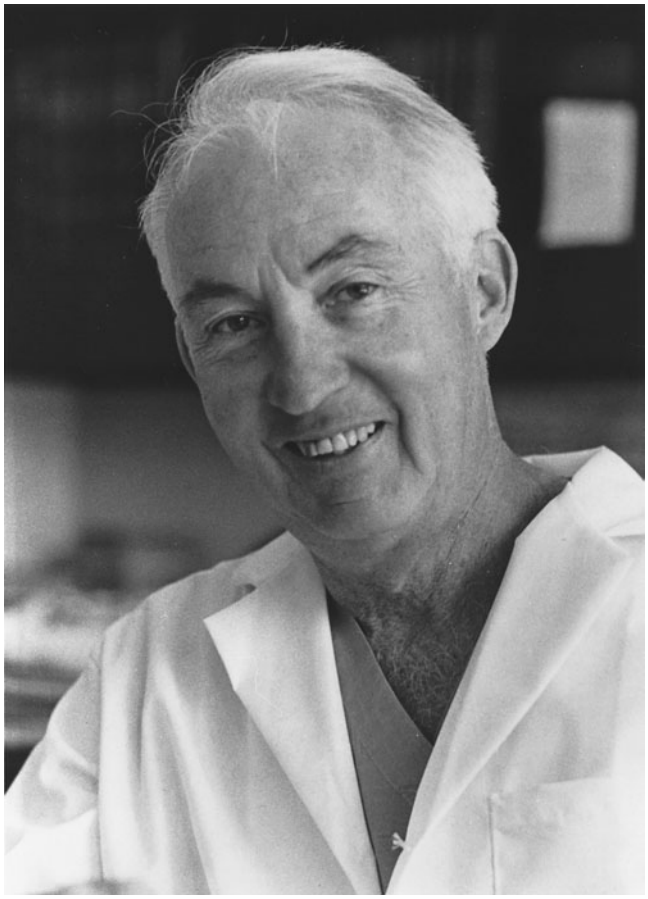

Figure 65-1. Norman Shumway.

chance of postoperative survival and rehabilitation. It is very important to establish a mutual long-term working relationship between patient, social support system, and the entire team at the beginning.

Indications and potential contraindications for cardiac transplantation are outlined in Table 65-1.[12] These inclusion and exclusion criteria vary somewhat among transplantation centers.[12–16] The basic objective is to identify those relatively healthy patients with end-stage cardiac disease refractory to other appropriate medical and surgical therapies who possess the potential to resume a normal active life and maintain compliance with a rigorous medical regimen after cardiac transplantation.

Etiology of end-stage cardiac failure

Determination of the etiology and potential reversibility of end-stage heart failure is critical for the selection of transplant candidates. Overall, from 1982 to 2004, the diagnosis for adult heart transplant recipients has been equally balanced between ischemic heart failure and nonischemic cardiomyopathy (45% each). Valvular (3 to 4%), adult congenital (2%), retransplantation (2%), and miscellaneous causes make up the remainder.[17]

The perception of the irreversibility of advanced cardiac failure is changing with the growing efficacy of tailored medical therapy, high-risk revascularization procedures, and newer antiarrhythmic pharmacologic agents, as well as implantable defibrillators and biventricular pacing. Additionally, other surgical modalities, such as ventricular assist devices (VADs) and surgical ventricular restoration (SVR), are gaining increasing application.[18,19] Furthermore, it is important to consider that prognosis may differ in patients with cardiomyopathy who have neither ischemic nor valvular heart disease. Caution should be exercised when judging prognosis in these patient subgroups, and a period of observation, intense pharmacologic therapy, and/or mechanical support should be undertaken before heart transplantation is considered.[16]

Evaluation of the potential cardiac transplant recipient

The complexity of the recipient evaluation mandates a team approach. The initial evaluation involves a comprehensive history and physical examination because this will help to determine etiology and contraindications. Table 65-2[15] summarizes the cardiac transplant evaluation tests. Routine hematologic and biochemical analyses and pertinent tests as illustrated by organ system are performed.

For the assessment of the heart itself, in addition to routine 12-lead electrocardiogram, Holter monitor, and echocardiography, all patients should undergo cardiopulmonary exercise testing to evaluate functional capacity if disease severity allows. Peak exercise oxygen consumption measured during maximal exercise testing ($\dot{V}O_{2,max}$) provides a measure of functional capacity and cardiovascular reserve, and an inverse relationship between $\dot{V}O_{2,max}$ and mortality in heart failure patients has been demonstrated.[20,21] Documentation of adequate effort during exercise, as evidenced by attaining a respiratory exchange ratio greater than 1.0 or achievement of an anaerobic threshold at 50 to 60% of $\dot{V}O_{2,max}$, is necessary to avoid underestimation of functional capacity.[13] Right-sided heart catheterization should be performed at the transplanting center to evaluate the severity of heart failure and thus the status level for transplant and to evaluate for the presence of pulmonary hypertension. It also helps to guide therapy while awaiting transplantation. Coronary cineangiography should be reviewed to confirm the inoperability of coronary artery lesions in ischemic cardiomyopathy. Either a positron-emission tomographic (PET) scan, a thallium-201 redistribution study, or a cardiac magnetic resonance imaging (MRI) study for viability is appropriate in selected patients who would be candidates for revascularization if sufficient viability is found.[13,15] Endomyocardial biopsy should be performed on all patients in whom the etiology of heart failure is in question, especially those with nonischemic cardiomyopathies symptomatic for fewer than 6 months.[15] This will assist in therapeutic decision making and exclude diseases such as amyloidosis, which is considered a relative contraindication to transplantation.

The neuropsychiatric evaluation should be performed by persons experienced in evaluating cardiac patients to determine if organic brain dysfunction or psychiatric illness is present. An experienced social worker should assess for the

Table 65–1.

Recipient Selection for Heart Transplantation

Indications

I. Systolic heart failure (as defined by ejection fraction <35%)
  A. Inclusive etiology
    1. Ischemic
    2. Dilated
    3. Valvular
    4. Hypertensive
    5. Other
  B. Excluded etiology
    1. Amyloid (controversial)
    2. HIV infection
    3. Cardiac sarcoma

II. Ischemic heart disease with intractable angina
  A. Ineffective maximal tolerated medical therapy
  B. Not a candidate for direct myocardial revascularization, percutaneous revascularization, or transmyocardial revascularization procedure
  C. Unsuccessful myocardial revascularization

III. Intractable arrhythmia
  A. Uncontrolled with pacing cardioverter defibrillator
    1. Not amenable to electrophysiology-guided single or combination medical therapy
    2. Not a candidate for ablative therapy

IV. Hypertrophic cardiomyopathy
  A. Class IV symptoms persist despite interventional therapies
    1. Alcohol injection of septal artery
    2. Myotomy and myomectomy
    3. Mitral valve replacement
    4. Maximal medical therapy
    5. Pacemaker therapy

V. Congenital heart disease in which severe fixed pulmonary hypertension is not a complication

VI. Cardiac tumor
  A. Confined to the myocardium
  B. No evidence of distant disease revealed by extensive metastatic work-up

Absolute Contraindications

I. Age > 70 years (may vary at different centers)

II. Fixed pulmonary hypertension (unresponsive to pharmacologic intervention)
  A. Pulmonary vascular resistance >5 Wood units
  B. Transpulmonary gradient >15 mm Hg

III. Systemic illness that will limit survival despite transplant
  A. Neoplasm other than skin cancer (less than 5 years disease free survival)
  B. HIV/AIDS (CDC definition of CD4 count of <200 cells/mm^3)
  C. Systemic lupus erythematosus (SLE) or sarcoid that has multisystem involvement and is currently active
  D. Any systemic process with a high probability of recurrence in the transplanted heart
  E. Irreversible renal or hepatic dysfunction

(continued)

Table 65–1.

Recipient Selection for Heart Transplantation (*continued*)

Potential Relative Contraindications
I. Recent malignancy
II. Chronic obstructive pulmonary disease
III. Recent and unresolved pulmonary infarction and pulmonary embolism
IV. Diabetes mellitus with end-organ damage (neuropathy, nephropathy, and retinopathy)
V. Peripheral vascular or cerebrovascular disease
VI. Active peptic ulcer disease
VI. Current or recent diverticulitis
VIII. Other systemic illness likely to limit survival or rehabilitation
IX. Severe obesity or cachexia
X. Severe osteoporosis
XI. Active alcohol or drug abuse
XII. History of noncompliance or psychiatric illness likely to interfere with long-term compliance
XIII. Absence of psychosocial support

presence of adequate social and financial support. At the time of listing, the transplant coordinator should ensure that the patient and family are informed of and understand the peculiarities of the waiting time, the preoperative period, the long-term maintenance medication, and the rules of living with the new heart. It is also important to discuss such issues as the patient's preferences for duration and type of life support if irreversible organ dysfunction ensues owing to deterioration of heart failure while awaiting transplant.

Indications for cardiac transplantation

Cardiac transplantation is reserved for a select group of patients with end-stage heart disease not amenable to optimal medical or surgical therapies. Prognosis for 1-year survival without transplantation should be less than 50%. Prediction of patient survival involves considerable subjective clinical judgment by the transplant committee because no reliable objective prognostic criteria are available currently. Low ejection fraction (<20%), reduced $\dot{V}O_{2,max}$ (<14 mL/kg per minute), arrhythmias, high pulmonary capillary wedge pressure (>25 mm Hg), elevated plasma norepinephrine concentration (>600 pg/mL), reduced serum sodium concentration (<130 mEq/dL), and more recently, N-terminal probrain natriuretic peptide (>5000 pg/mL) all have been proposed as predictors of poor prognosis and potential indications for transplantation in patients receiving optimal medical therapy.[20–26] Reduced left ventricular ejection fraction and low $\dot{V}O_{2,max}$ are widely identified as the strongest independent predictors of survival.

The indications for cardiac transplantation listing are continuously reviewed as new breakthroughs in the medical and surgical treatment of heart disease emerge.

Contraindications for cardiac transplantation

Table 65-1 lists the traditional absolute and relative contraindications. It should be acknowledged that strict guidelines can be problematic; therefore, each transplant program will vary regarding absolute criteria based on clinical circumstances. Furthermore, traditional contraindications for transplant listing are being questioned. Age is one of the most controversial exclusionary criteria for transplantation. The upper age limit for recipients is center-specific, but emphasis should be placed on the patient's physiologic rather than chronologic age. The Official Adult Heart Transplant Report 2005 from the registry of the International Society for Heart and Lung Transplantation (ISHLT) noted that over the last 20 years, the percentage of recipients older than 60 years of age has increased steadily, approaching 25% of all heart transplants between 1999 and 2003 compared with just above 5% between 1982 and 1988.[17,27] Although the elderly have a greater potential for occult systemic disease that may compli-

Table 65–2.

Cardiac Transplant Evaluation Tests

Laboratory	Complete blood count with differential and platelet count, creatinine, blood urea nitrogen, electrolytes, liver panel, lipid panel, calcium, phosphorus, total protein, albumin, uric acid, thyroid panel, antinuclear antibodies, erythrocyte sedimentation rate (ESR), rapid plasma reagin (RPR), iron binding tests, partial thromboplastin time, prothrombin time Blood type, IgG and IgM antibodies against cytomegalovirus, herpes simplex virus, HIV, varicella-zoster virus, hepatitis B surface antigen, hepatitis C antigen, toxoplasmosis, other titers when indicated Tuberculin skin test Prostate-specific antigen (male >50 years) Mammogram and Pap smear (female >40 years) Screening against a panel of donor antigens (panel reactive antibodies) and human leucocyte antigen phenotype 24-hour urine for creatinine clearance and total protein, urinalysis, urine culture Baseline bacterial and fungal cultures, stool for ova and parasites if indicated
Cardiac	12-lead ECG, 24-hour Holter monitor Echocardiogram Thallium-201 imaging, positron-emission tomographic (PET) scan, or cardiac magnetic resonance imaging (MRI) to assess viability if indicated Exercise stress test and respiratory gas analysis with oxygen uptake measurements: peak exercise oxygen consumption ($\dot{V}O_{2,max}$). Right- and left-sided heart catheterization at the transplant center Myocardial biopsy on selected patients in whom etiology of heart failure is in question
Vascular	Peripheral vascular studies Carotid Doppler and duplex ultrasound >55 years
Renal	Renal ultrasound and or intravenous pyelogram if indicated
Pulmonary	Chest x-ray Pulmonary function tests Chest CT scan to evaluate abnormal chest x-ray or thoracic aorta in older patients (usually >65 years)
Gastrointestinal	Upper endoscopy/colonoscopy if indicated Upper gastrointestinal series and/or barium enema if indicated Percutaneous liver biopsy if indicated
Metabolic	Bone densitometry
Neurologic	Screening evaluation
Psychiatric	Screening evaluation
Dental	Complete dental evaluation
Physical therapy	Evaluation
Social work	Patient attitude and family support, medical insurance, and general financial resources
Transplant coordinator	Education

cate their postoperative course, some recent reports have suggested that morbidity and mortality in carefully selected older patients are comparable with those of younger recipients, and they have fewer rejection episodes than younger patients.[28–31]

Fixed pulmonary hypertension (PH), usually manifested as elevated pulmonary vascular resistance (PVR), is one of the few absolute contraindications to orthotopic cardiac transplantation. Fixed PH increases the risk of acute right ventricular failure when the right ventricle of the allograft is unable to adapt to significant PH in the immediate postoperative period.[32] Use of the transpulmonary gradient (TPG), which represents the pressure gradient across the pulmonary vascular bed independent of blood flow, may avoid erroneous estimations of PVR, such as those that may occur in patients with low cardiac output.[16] Some have advocated the use of PVR index unit (PVRI), which corrects for body size.[33]

PVR, PVRI, and TPG are calculated by means of following formulas:

$$\text{PVR (Wood units)} = \frac{\text{MPAP (mm Hg)} - \text{PCWP (mm Hg)}}{\text{CO (L/min)}}$$

$$\text{PVRI (units)} = \frac{\text{MPAP (mm Hg)} - \text{PCWP (mm Hg)}}{\text{CO (L/min)} \times \text{BSA}} = \frac{\text{PVR}}{\text{BSA}}$$

$$\text{TPG (mm Hg)} = \text{MPAP (mm Hg)} - \text{PCWP (mm Hg)}$$

where MPAP is mean pulmonary arterial pressure, PCWP is pulmonary capillary wedge pressure, CO is cardiac output, CI is cardiac index, and BSA is body surface area.

A fixed PVR greater than 5 to 6 Wood units and a TPG greater than 15 mm Hg generally are agreed as absolute criteria for rejection of a candidate.[12,13,15,16,26] Over the years, several studies have found PH to have a significant effect on posttransplant mortality using variable parameters, threshold values, and follow-up periods.[33–38] There are also a few studies that found no significant difference in mortality at different time periods after transplantation between patients with and without preoperative PH.[39,40] Perhaps more significantly, measurable parameters of pulmonary hypertension improved significantly after heart transplantation. A study of 172 patients followed for up to 15.1 years, published in 2005 from the Johns Hopkins Hospital, showed that mild to moderate pretransplantation PH (PVR = 2.5 to 5.0 Wood units) was not associated with higher mortality rate, although there was increased risk of posttransplantation PH within the first 6 months.[41] However, when the continuous variable PVR was examined, each 1 Wood unit increase in preoperative PVR demonstrated a 15% or more increase in mortality, especially within the first year, but these associations did not reach statistical significance. Severe preoperative PH (PVR $\geq$ 5 Wood units) was associated with death within the first year after adjusting for potential cofounders but not with overall mortality or mortality at other time points.

In the preoperative evaluation of the transplant recipient, if PH is discovered, an assessment of its reversibility should be performed in the cardiac catheterization laboratory.[36] Sodium nitroprusside traditionally has been used at a starting dose of 0.5 μg/kg per minute and titrated by 0.5 μg/kg per minute until there is an acceptable decline in PVR, ideally 2.5 Wood units or at least by 50%, with maintenance of adequate systemic systolic blood pressure. If sodium nitroprusside fails to produce an adequate response, other vasodilators such as adenosine, prostanglandin E_1, milrinone, or inhaled nitric oxide or prostacyclin (e.g., aerosolized Illoprost) may be used.[13,42–44] Some patients who do not respond acutely may respond to continuous intravenous inotropic therapy, and repeat catheterization can be performed after 48 to 72 hours. Intravenous B-type natriuretic peptide, e.g., nesiritide (Natrecor), has shown some efficacy in refractory pulmonary hypertension.[45] Recently, ventricular assist devices (VADs) are playing an important role in heart transplantation candidates with PH.[46] A period of left ventricular assist device (LVAD) support may allow for a decrease of pulmonary artery pressure secondary to unloading of the left ventricle. Patients with irreversible PH may be candidates for heterotopic heart or heart-lung transplantation.[47] Use of modestly larger donor hearts for recipients with severe pretransplantation PH can provide additional right ventricular reserve.

Systemic diseases with poor prognosis and potential to recur in the transplanted heart or the potential to undergo exacerbation with immunosuppressive therapy are considered absolute contraindications for heart transplantation. Heart transplantation for amyloid remains controversial because amyloid deposits recur in the transplanted heart. Although case reports of long-term survival can be found in the literature,[48] survival beyond 1 year tends to be reduced.[49] In some cases, patients now have combined heart and kidney or heart and liver transplant for amyloidosis.[50] Human immunodeficiency virus (HIV)–infected patients generally are excluded. Previously, any occurrence of neoplasm was a reason to exclude patients from transplantation. Currently available data do not appear to justify excluding these patients.[14,51] Most surgeons consider only patients who are free of disease for at least 5 years.

Irreversible renal dysfunction is a contraindication to heart transplantation. A creatinine clearance of less than 50 mL/min and a serum creatinine concentration of greater than 2 mg/dL are associated with increased risk of postoperative dialysis and decreased survival following heart transplantion.[16,52,53] However, patients may be considered for combined heart and kidney transplantation. Irreversible hepatic dysfunction has implications similar to renal dysfunction.[16] If transaminase levels are more than twice their normal value and associated with coagulation abnormalities, percutaneous liver biopsy should be performed to exclude primary liver disease. This should not be confused with chronic cardiac hepatopathy, which is characterized by elevated cholestatic parameters along with little or no changes in transaminases and is potentially reversible after heart transplantation.[54]

Severe chronic bronchitis or obstructive pulmonary disease may predispose patients to pulmonary infections and may result in prolonged ventilatory support after heart

transplantation. Patients who have a ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) of less than 40 to 50% of predicted or an FEV_1 of less than 50% of predicted despite optimal medical therapy are considered poor candidates for transplantation.[13,16] Transplantation in patients with diabetes mellitus is only contraindicated in the presence of significant end-organ damage (e.g., diabetic nephropathy, retinopathy, or neuropathy).[13,14,16] Some centers have expanded their criteria successfully to include patients with mild to moderate end-organ damage.[55] Active infection was a sound reason to delay transplantation before assist devices became more commonplace. Up to 48% of patients with implanted LVADs reportedly have evidence of infection. Interestingly, treatment for LVAD infection in these patients is to proceed with urgent transplantation.[56]

Other relative contraindications include severe noncardiac atherosclerotic disease, severe osteoporosis, and active peptic ulcer disease or diverticulitis, all of which may lead to increased morbidity.[13,14,16] Cachexia, defined as a body mass index (BMI) of less than 20 or less than 80% ideal body weight (IBW), and obesity, defined as BMI greater than 35 or greater than 140% of IBW, are associated with an increased mortality after transplantation.[57] Poor nutritional status also may limit early postoperative rehabilitation.

The ultimate success of transplantation depends on the psychosocial stability and compliance of the recipient.[58] The rigorous postoperative regimen of multidrug therapy, frequent clinic visits, and routine endomyocardial biopsies demands commitment on the part of the patient. A history of psychiatric illness, substance abuse, or previous noncompliance (particularly with medical therapy for end-stage heart failure) may be sufficient cause to reject the candidacy of a patient. Lack of a supportive social system is an additional relative contraindication.

Management of the Potential Cardiac Recipient

Medical therapy for end-stage cardiac failure

In addition to conventional management of congestive heart failure, specific comorbidities should be managed aggressively. Patients with elevated levels of preformed panel reactive antibodies (PRAs) to human leukocyte antigens (HLAs) have higher rates of organ rejection and decreased survival than do patients without such antibodies.[59] Consequently, before proceeding with transplantation, many medical centers do prospective cross-matching, i.e., mix lymphocytes from the organ donor with sera from the prospective organ recipient, to determine whether a higher rejection rate or an immediate episode of rejection will occur. The problem has been compounded by the increased frequency of preformed reactive antibodies in patients with VADs who are awaiting cardiac transplantation.[60] Performing a prospective crossmatch can be time-consuming and often is impossible because of the unstable condition of the organ donor or travel logistics, leading to increased costs for transplantation and longer waiting times for recipients. Plasmapheresis, intravenous immunoglobulins, cyclophosphamide, and mycophenolate mofetil all have been used to lower the PRA levels with variable results.[13,61]

Pharmacologic bridge to transplantation

Critically compromised patients require admission to the intensive-care unit for intravenous inotropic therapy. Dobutamine, a synthetic catecholamine, remains the prototype of this drug group. However, the phosphodiesterase III inhibitor milrinone is similarly effective.[62,63] The catecholamine dopamine is used often as a parenteral positive inotrope, but at moderate to high dose it evokes considerable systemic vasoconstriction. In candidates in whom an inotropic infusion has progressed to higher doses, combinations of dobutamine with milrinone are used. For transplant candidates dependent on inotropic infusions, eosinophilic myocarditis may develop as an allergic response to the dobutamine and may result in accelerated decline.[64] VADs are being considered earlier, particularly as indices of nutrition decline.

Mechanical bridge to transplantation

Placement of an intra-aortic balloon pump (IABP) may be necessary in patients with heart failure who are refractory to initial pharmacologic measures. Ambulatory IABP through the axillary artery has been reported in few patients as a bridge to cardiac transplantation.[65]

The landmark Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial provided evidence that LVAD support provided a statistically significant reduction in the risk of death from any cause when compared with optimal medical management. The survival rates for patients receiving LVADs ($n = 68$) versus patients receiving optimal medical management ($n = 61$) were 52% versus 28% at 1 year and 29% versus 13% at 2 years ($P = .008$, log-rank test).[18,66] The extended follow-up confirmed the initial observation that LVAD therapy renders significant survival and quality-of-life benefits compared with optimal medical management for patients with end-stage heart failure. A recent systematic review of the published literature supported these findings. In the studies reviewed, implantation of an LVAD provided support for up to 390 days, with as many as 70% of patients surviving to transplantation.[67]

The total artificial heart (TAH) positioned orthotopically replaces both native cardiac ventricles and all cardiac valves. Potential advantages of this device include eliminating problems commonly seen in the bridge to transplantation with left ventricular and biventricular assist devices, such as right-sided heart failure, valvular regurgitation, cardiac arrhythmias, ventricular clots, intraventricular communications, and low blood flows. Copeland and colleagues reported that the TAH allowed for bridge to transplantation in 79% of their patients with 1 year and 5-year survival rates after transplantation of 86% and 64%, respectively.[68]

Since these devices cannot be weaned, it is imperative that the patient's candidacy for transplantation be scruti-

Table 65–3.

Current Recipient Status Criteria of the United Network for Organ Sharing (UNOS)*

Status IA
A. Patients who require mechanical circulatory assistance with one or more of the following devices: 1. Total artificial heart 2. Left and/or right ventricular assist device implanted for 30 days or less 3. Intra-aortic balloon pump 4. Extracorporeal membrane oxygenator (ECMO)
B. Mechanical circulatory support for more than 30 days with significant device-related complications
C. Mechanical ventilation
D. Continuous infusion of high-dose inotrope(s) in addition to continuous hemodynamic monitoring of left ventricular filling pressures
E. Life expectancy without transplant less than 7 days
Status IB
A. A patient who has at least one of the following devices or therapies in place: 1. Left and/or right ventricular assist device implanted for more than 30 days 2. Continuous infusion of intravenous inotropes
Status II
All other waiting patients who do not meet status Ia or Ib criteria

**UNOS Executive Order, August 1999.*

nized prior to placement of the device. Trends toward better device durability and reduced complication rates likely will continue to improve through the development of newer, more innovative VADs, allowing destination therapy to be considered more frequently.[69]

Life-threatening ventricular arrhythmias

Symptomatic ventricular tachycardia or fibrillation and a history of sudden cardiac death are indications for placement of an automatic implantable cardioverter-defibrillator (AICD), long-term antiarrhythmic therapy with amiodarone, or occasionally, radiofrequency catheter ablation, which have shown improved survival.[70,71]

Recipient Prioritization for Transplantation

The prioritization of appropriate recipients for transplantation is based on survival and quality of life expected to be gained in comparison with maximal medical and surgical alternatives.[15] The United Network for Organ Sharing is a national organization that maintains organ transplantation waiting lists and allocates identified donor organs on the basis of recipients' priority status.[72] This priority status is based on a recipient's status level (e.g., IA, IB, or II), blood type, body size, and duration of time at a particular status level.[13] Geographic distance between donor and potential recipient is also taken into consideration. Highest priority is given to local status IA patients possessing the earliest listing dates. The recipient status criteria established by UNOS in 1999 are outlined in Table 65-3. In 1994, the percentage of patients awaiting transplantation for more than 2 years was 23%; this increased to 49% by 2003. From 1999 (with the institution of a new status system) through 2003, the distribution of patient status at transplant was 40% of transplanted recipients classified as status 1A, 35% as status 1B, and 25% as status 2.[73] Patients considered for transplantation should be examined at least every 3 months for reevaluation of recipient status. Yearly right-sided heart catheterization is indicated for all candidates on the waiting list and in selected cases for patients rejected because of pulmonary hypertension. Presently, there is no established method to delist patients who have stabilized on medical therapy without loss of their previously accrued waiting time.

THE CARDIAC DONOR

Donor Availability

The availability of donor organs remains the major limiting factor to heart transplantation. In the early years of heart

transplantation, the number of heart transplants performed in the United States increased steadily to a peak in 1995 of 2363 and then reached a plateau in 1998. Since 1998, there has been a gradual decline in heart transplants per year to a level of 2055 in 2003.[73] Interestingly, likely owing to improved preoperative care, the death rate for patients on the waiting list for a cardiac allograft has decreased steadily.[73]

The Uniform Anatomic Gift Act of 1968 states that all competent individuals over the age of 18 may donate all or part of their bodies and established the current voluntary basis of organ donation practiced in the United States.[74] To accommodate the increasing demand for organs, the original stringent criteria for donor eligibility have been relaxed, and educational campaigns have increased awareness of the need for a larger donor pool. In 1986, the Required Request Law, which required hospitals to request permission from next of kin to recover organs, was passed to encourage physician compliance in the donor request process.[75] Future reforms will be molded by the evolving public attitude to transplantation and likely will focus on continued public and physician education.

Allocation of Donor Organs

In an effort to increase organ donation and to coordinate an equitable allocation of allografts, Congress passed the National Organ Transplant Act in 1984.[76] This act resulted in the drafting of the aforementioned Required Request Law, as well as the awarding of a federal contract to the United Network of Organ Sharing (UNOS) for the development of a national organ procurement and allocation network.[77] To facilitate transplantation, the United States is divided into 11 geographic regions.

Organs are offered to sick patients within the region in which they were donated before being offered to other parts of the country. This helps to reduce organ preservation time, improve organ quality and survival outcomes, reduce the costs incurred by the transplant patient, and increase access to transplantation.

Donor Selection

Once a brain dead individual has been identified as a potential cardiac donor, the patient undergoes a rigorous three-phase screening regimen. The primary screening is undertaken by the organ procurement agency. Information regarding the patient's age, height and weight, gender, ABO blood type, hospital course, cause of death, and routine laboratory data including cytomegalovirus (CMV), HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) serologies are collected. Cardiac surgeons or cardiologists perform the secondary screening, which involves further investigation in search of potential contraindications (Table 65-4), determination of the hemodynamic support necessary to sustain the donor, and review of the electrocardiogram, chest roentgenogram, arterial blood gas determination, and echocardiogram. Even when adverse donor criteria are reported, a team often is dispatched to the hospital to evaluate the donor on-site.

Table 65–4.

Donor Selection for Heart Transplantation

I. Suggested criteria for cardiac donor
   A. Age < 55
   B. Absence of the following:
      1. Prolonged cardiac arrest
      2. Prolonged severe hypotension
      3. Preexisting cardiac disease
      4. Intracardiac drug injection
      5. Severe chest trauma with evidence of cardiac injury
      6. Septicemia
      7. Extracerebral malignancy
      8. Positive serologies for human immunodeficiency virus, hepatitis B (active), or hepatitis C
      9. Hemodynamic stability without high-dose inotropic support (<20 μg/kg per minute of dopamine)

II. Suggested cardiac donor evaluation
   A. Past medical history and physical examination
   B. Electrocardiogram
   C. Chest roentgenogram
   D. Arterial blood gases
   E. Laboratory tests (ABO, HIV, HBV, HCV)
   F. Echocardiogram, pulmonary artery catheter evaluation, and in selected cases, coronary angiogram

Although echocardiography is effective in screening for anatomic abnormalities of the heart, the use of a single echocardiogram to determine the physiologic suitability of a donor is not supported by evidence.[78] The Papworth Hospital transplant program in Great Britain increased its donor yield substantially by using a pulmonary artery catheter to guide the physiologic assessment and management of ventricular dysfunction.[79] Coronary angiography is indicated in the presence of advanced donor age (traditionally for male donors > 45 years of age and female donors > 50 years of age).[80] Angiography also should be performed if there is a history of cocaine use or if the donor has three risk factors for coronary artery disease (CAD), such as hypertension, diabetes, smoking history, dyslipidemia, or family history of premature CAD.[78]

The final and often most important screening of the donor occurs intraoperatively at the time of organ procurement by the cardiac surgical team. Direct visualization of the heart is performed for evidence of ventricular or valvular dysfunction, previous infarction, or myocardial contusion secondary to closed-chest compressions or blunt chest trauma. The coronary arterial tree is palpated for gross calcifications indicative of atheromatous disease. If direct examination of the heart is unremarkable, the recipient hospital is notified, and the procurement surgeons proceed with donor cardiectomy, usually in conjunction with multiorgan procurement.

Expanded Donor Criteria and Alternate Listing

As the donor shortage has worsened and the number of patients waiting for transplants has increased, one of the areas of increasing interest is the use of marginal donors for marginal recipients. For this purpose, an alternate recipient list is being used by some centers to match certain recipients who might be excluded from a standard list with marginal donor hearts that otherwise would go unused. Expanded donor criteria include the use of donors substantially smaller than the recipients, donors with coronary artery disease that may require coronary artery bypass grafting (CABG), left ventricular dysfunction, or donors from older age groups.[78] Acceptable operative mortality has been reported,[81] and the University of California, Los Angeles (UCLA) heart transplant group has shown that alternate listing did not independently predict early or late mortality.[82]

It also appears more beneficial in terms of patient survival to receive an allograft from a donor older than 40 years of age than to remain on the waiting list.[83] Other high-risk donors, such as HCV-positive or HBV (core IgM-negative)–positive donors, may be appropriate in selected higher-risk recipients.[78]

Also of special interest is the effect of donor alcohol and cocaine abuse on heart transplantation. A small single-center study showed unfavorable early outcome of patients receiving hearts from alcoholic donors (>2 oz of pure alcohol daily for 3 or more months), suggesting the presence of a subclinical preoperative alcoholic cardiomyopathy and poor tolerance of rejection episodes after transplantation.[84] Because of widespread cocaine abuse, donor guidelines have declared intravenous drug abuse a "relative" contraindication for donor selection.[80] However, the dilemma of selecting donor hearts from nonintravenous drug abusers remains an open issue. A favorable outcome for patients who received transplanted hearts obtained from nonintravenous cocaine users has been reported.[85] However, judicious use of donors with a history of cocaine use is strongly advised.[86] Specific recommendations were made in a recent consensus report to improve the yield of donor hearts.[78]

Management of the Cardiac Donor

Medical management of cardiac donors, an integral part of organ preservation, is complicated by the complex physiologic phenomenon of brain death and the need to coordinate procurement with other organ donor teams. Brain death is associated with an "autonomic and cytokine storm." The release of noradrenaline (norepinephrine) leads to subendocardial ischemia. Subsequent cytokine release results in further myocardial depression. This is accompanied by pronounced vasodilatation and loss of temperature control.[15] Rapid afterload reduction may be achieved with sodium nitroprusside, whereas volatile anesthetics assist in reducing the intensity of sympathetic bursts. The initial period of intense autonomic activity is followed by loss of sympathetic tone and a massive reduction in systemic vascular resistance. Overall, brain stem death results in severe hemodynamic instability, the degree of which appears to be directly related to the severity of the brain injury and may result from vasomotor autonomic dysfunction, hypovolemia, hypothermia, and dysrhythmias.[87]

Aggressive volume resuscitation sometimes is necessary, and the use of a Swan-Ganz catheter may be crucial to guide therapy.[88] Fluid overload should be avoided to prevent postoperative allograft dysfunction caused by chamber distension and myocardial edema. Inotropic support (e.g., dopamine or dobutamine, epinephrine, or norepinephrine) to maintain a mean arterial blood pressure (MAP) of 60 mm Hg or more in the presence of a central venous pressure (CVP) of 6 to 10 mm Hg is recommended.[78] ATP is depleted rapidly by exogenous catecholamine administration, and this has an adverse effect on posttransplantation cardiac function.[87] Low-dose vasopressin is being used increasingly as first-line support because, in addition to treating diabetes insipidus, it independently improves arterial blood pressure and reduces exogenous inotrope requirements in brain stem dead donors.[89,90] Maintenance of normal temperature, electrolyte levels, osmolarity, acid-base balance, and oxygenation is critical for optimal donor management. Central diabetes insipidus develops in more than 50% of donors because of pituitary dysfunction, and massive diuresis complicates fluid and electrolyte management.[91] The initial treatment of diabetes insipidus is aimed at correcting hypovolemia and returning the plasma sodium concentration to normal levels by fluid replacement with 5% dextrose or nasogastric water. In severe cases, intermittent treatment with the synthetic

analogue 1-D-amino-8-D-arginine vasopressin (DDAVP) also may be required in addition to vasopressin infusion.[87]

Several studies have demonstrated beneficial effects of thyroid hormones and steroids on cardiac performance in brain stem dead organ donors.[79,89,92] Recent guidelines advocate the addition of a standardized hormonal resuscitation package consisting of methylprednisolone (15 mg/kg bolus), triiodothyronine (4-μg bolus followed by infusion of 3 μg/h), and arginine vasopressin (1-unit bolus followed by 0.5 to 4 units/h) to the standard donor management protocol.[78] Donors also receive insulin, titrated to keep blood glucose at 120 to 180 mg/dL. Other pertinent strategies include standard ventilator management with diligent endotracheal suctioning and a thermoregulation goal of 34 to 36°C using warming blankets and lights, warm intravenous fluids, and warm inspired air. Broad-spectrum antibiotic therapy with a cephalosporin is initiated following collection of blood, urine, and tracheal aspirate for culture. The approach for management of the cardiac donor recommended at the conference entitled, "Maximizing Use of Organs Recovered from the Cadaver Donor: Cardiac Recommendations," is shown on Table 65-5 and summarized in Fig. 65-2.[78]

Table 65–5.

Management of the Cardiac Donor

I. Conventional management, before the initial echocardiogram
   - A. Adjust volume status (target central venous pressure 6 to 10 mm Hg).
   - B. Correct metabolic perturbations, including
     1. Acidosis (target pH 7.40 to 7.45).
     2. Hypoxemia (target P_{O_2} > 80 mm Hg, O_2 saturation >95%).
     3. Hypercarbia (target P_{CO_2} 30 to 35 mm Hg).
   - C. Correct anemia (target hematocrit 30%, hemoglobin 10 g/dL).
   - D. Adjust inotropes to maintain mean arterial pressure at 60 mm Hg. Norepinephrine and epinephrine should be tapered off rapidly in favor of dopamine or dobutamine.
   - E. Target = dopamine <10 μg/kg per minute or dobutamine <10 μg/kg per minute.

II. Obtain an initial echocardiogram
   - A. Rule out structural abnormalities (substantial left ventricular hypertrophy, valvular dysfunction, congenital lesions).
   - B. If left ventricular ejection fraction is 45%, proceed with recovery (consider aggressive management as shown below to optimize cardiac function before recovery) with final evaluation in the operating room.
   - C. If left ventricular ejection fraction is <45%, aggressive management with placement of a pulmonary arterial catheter and hormonal resuscitation is strongly recommended.

III. Hormonal resuscitation
   - A. Triiodothyronine (T_3): 4-μg bolus, then continuous infusion at 3 μg/h.
   - B. Arginine vasopressin: 1-unit bolus, then continuous infusion at 0.5 to 4 units/h, titrated to a systemic vascular resistance of 800 to 1200 dyne/s/cm^5.
   - C. Methylprednisolone: 15 mg/kg bolus
   - D. Insulin: 1 unit/h minimum; titrate to maintain blood sugar at 120 to 180 mg/dL.

IV. Aggressive hemodynamic management
   - A. Initiated simultaneously with hormonal resuscitation.
   - B. Placement of pulmonary artery catheter.
   - C. Duration of therapy 2 hours.
   - D. Adjustment of fluids, inotropes, and pressors every 15 minutes based on serial hemodynamic measurements to minimize use of beta-agonists and meet the following target (Papworth) criteria:
     1. Mean arterial pressure >60 mm Hg.
     2. Central venous pressure 4 to 12 mm Hg
     3. Pulmonary capillary wedge pressure 8 to 12 mm Hg
     4. Systemic vascular resistance 800 to 1200 dyne/s/cm^5.
     5. Cardiac index >2.4 L/min/m^2.
     6. Dopamine <10 μg/kg per minute or dobutamine <10 μg/kg per minute.

Source: Reprinted with permission from Zarroff JG et al.[78]

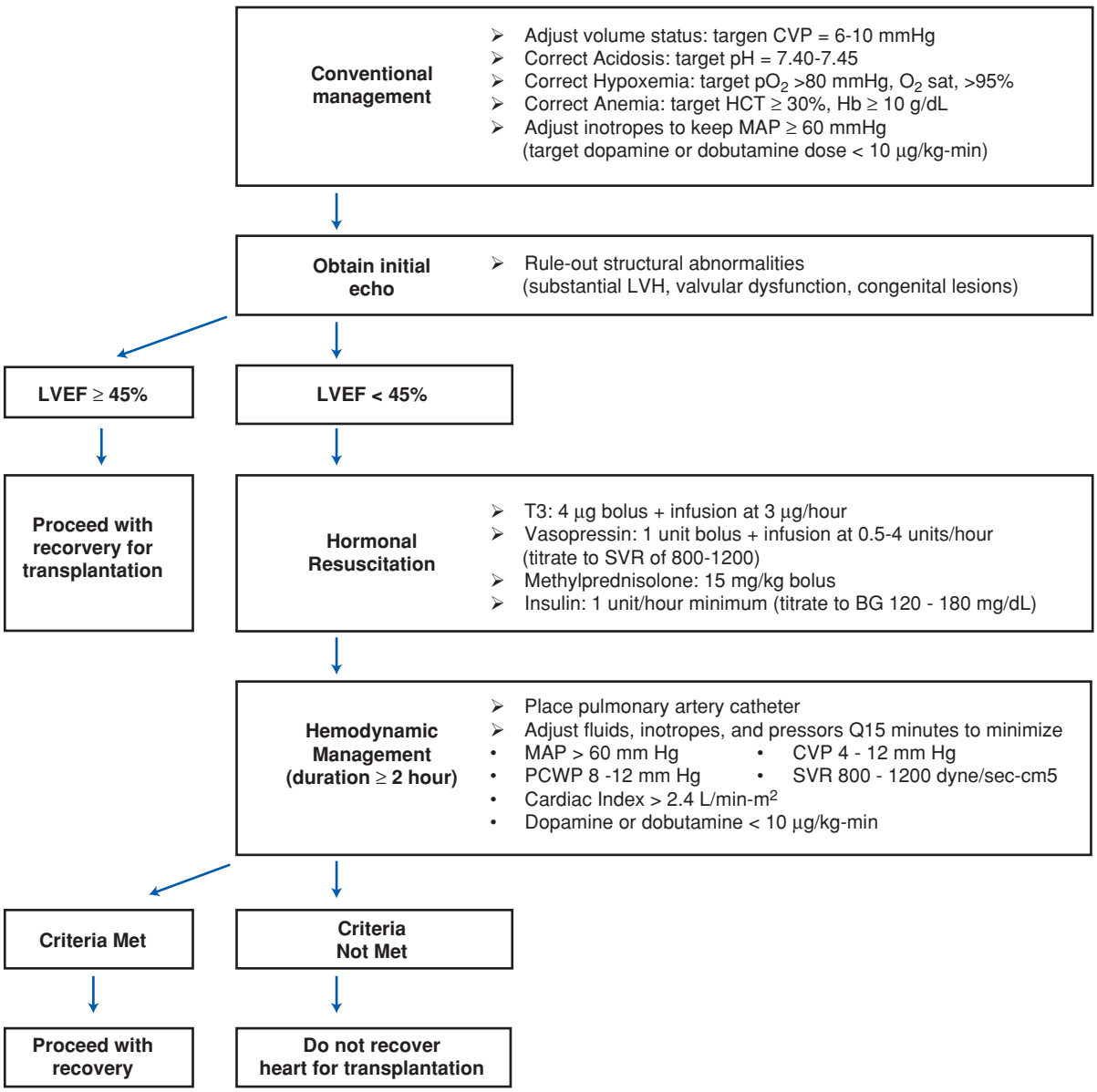

Figure 65-2. Recommended heart donor management algorithm. *(Source: Reprinted with permission from Zarroff et al.[78])*

Donor Heart Procurement

A median sternotomy is performed, and the pericardium is incised longitudinally. The heart is inspected and palpated for evidence of cardiac disease or injury. The superior and inferior venae cavae and the azygous vein are mobilized circumferentially and encircled with ties. The aorta is dissected from the pulmonary artery and isolated with umbilical tape. To facilitate access to the epigastrium by the liver procurement team, the cardiac team often then temporarily retires from the operating room table or assists with retraction. Once preparation for liver, pancreas, lung, and kidney explantation is completed, the patient is administered 30,000 units of heparin intravenously. The azygous vein and superior vena cava are doubly ligated (or stapled) and divided distal to the azygous vein, leaving a long segment of superior vena cava (Fig. 65-3). The inferior vena cava is clamped at the level of the diaphragm (if the abdominal inferior vena cava is vented) and then divided proximal to the clamp to permit efflux of the cardioplegia. Additional venting is achieved with transection of the right superior pulmonary vein. If the lungs are to be recovered, the left atrial appendage is incised. The aortic cross-clamp is applied at the takeoff of the innominate artery, and the heart is arrested with a single flush (1000 mL or 10 to 20 mL/kg) of cardioplegia solution infused through a 14-gauge needle inserted proximal to the cross-clamp. Rapid cooling of the heart is achieved with copious amounts of cold saline and cold saline slush poured into the pericardial well. Following the delivery of cardioplegia, cardiectomy proceeds as the apex of the heart is elevated cephalad and any remaining intact pulmonary veins are

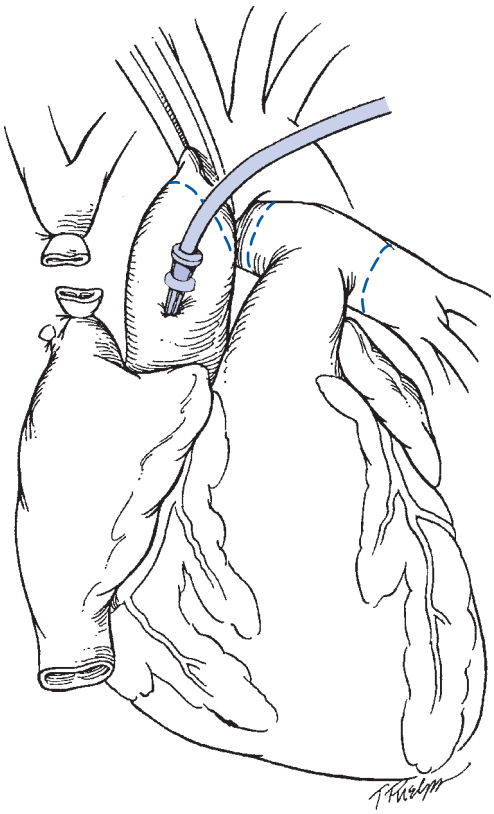

Figure 65-3. Donor cardiectomy.

divided. This maneuver is modified appropriately to retain adequate left atrial cuffs for both lungs and the heart if the lungs also are being procured. While applying caudal traction to the heart with the nondominant hand, the ascending aorta is transected proximal to the innominate artery, and the pulmonary arteries are divided distal to the bifurcation (again, modification is necessary if the lungs are being procured). More generous segments of the great vessels and superior vena cava may be required for recipients with congenital heart disease.

Once the explantation is complete, the allograft is examined for evidence of a patent foramen ovale, which should be closed at that time. Any valvular anomalies are identified. The allograft then is placed in a sterile container for transport to the recipient hospital.

Organ Preservation

Current clinical graft preservation techniques generally permit a safe ischemic period of 4 to 6 hours.[93] Factors contributing to the severity of postoperative myocardial dysfunction include insults associated with suboptimal donor management, hypothermia, ischemia-reperfusion injury, and depletion of energy stores. A single flush of a cardioplegic or preservative solution followed by static hypothermic storage at 4 to 10°C is the preferred preservation method by most transplant centers.[94] Crystalloid solutions of widely different compositions are available, and the debate over them speaks for the fact that no ideal solution currently exists. Depending on their ionic composition, solutions are classified as intracellular or extracellular.[93] Intracellular solutions, characterized by moderate to high concentrations of potassium and low concentrations of sodium, purportedly reduce hypothermia-induced cellular edema by mimicking the intracellular milieu. Commonly used examples of these solutions include University of Wisconsin, Euro-Collins, and in Europe, Bretschneider (HTK) and intracellular Stanford solutions. Extracellular solutions, characterized by low to moderate potassium and high sodium concentrations, avoid the theoretical potential for cellular damage and increased vascular resistance associated with hyperkalemic solutions. Hopkins, Celsior, Krebs, and St. Thomas Hospital solutions are representative extracellular cardioplegic solutions. Several comparisons of the different types of intracellular and extracellular solutions have shown variable results.[95–99] Although a plethora of pharmacologic additives have been included in cardioplegic-storage solutions, the greatest potential for future routine use may lie with impermeants, substrates, and antioxidants.[100] A number of pharmacologic and mechanical strategies for leukocyte inhibition and depletion also have been explored.[101] Potential benefits of continuous hypothermic perfusion (CHP) preservation such as uniform myocardial cooling, continuous substrate supplementation, and metabolic by-product washout are currently overshadowed by exacerbation of extracellular cardiac edema and logistical problems inherent to a complex perfusion apparatus. Newer portable apparatus are being developed, and recent studies showed reduction in oxidative stress and attenuation of DNA damage in canine heart transplant models preserved by 24-hour CHP compared with 4 hours of static preservation.[102–104]

Donor-Recipient Matching

Criteria for matching potential recipients with the appropriate donor are based primarily on ABO blood group compatibility and patient size. ABO barriers should not be crossed in heart transplantation because incompatibility may result in fatal hyperacute rejection. Donor weight should be within 30% of recipient weight except in pediatric patients, where closer size matching is required. In cases of elevated pulmonary vascular resistance in the recipient (5 to 6 Wood units), a larger donor is preferred to reduce the risk of right ventricular failure in the early postoperative period. Although practices vary by transplant program, generally, if the percent of panel reactive antibody (PRA) is greater than 10%, indicating recipient presensitization to alloantigen, a prospective negative T-cell cross-match between the recipient and donor sera is mandatory prior to transplantation.[59,105] A cross-match is always performed retrospectively, even if the PRA is absent or low. Retrospective studies also have demonstrated that better matching at the HLA-DR locus results in fewer episodes of rejection and infection with

an overall improved survival.[106] Because of current allocation criteria and limits on ischemic time of the cardiac allograft, routine prospective HLA matching is not possible logistically.

Hyperacute Rejection

Hyperacute rejection results from preformed donor-specific antibodies in the recipient.[107] ABO blood group and panel reactive antibody screening have made this condition a rare complication. The onset of hyperacute rejection occurs within minutes to several hours after transplantation, and the results are catastrophic. Gross inspection reveals a mottled or dark red, flaccid allograft, and histologic examination confirms the characteristic global interstitial hemorrhage and edema without lymphocytic infiltrate. Immunofluorescence techniques reveal deposits of immunoglobulins and complement on the vascular endothelium.[108] Immediate plasmapheresis, intravenous immunoglobulin (IVIG), and mechanical support are instituted, and retransplantation may be the only successful strategy.

OPERATIVE TECHNIQUES IN HEART TRANSPLANTATION

Orthotopic Heart Transplantation

Operative preparation of the recipient

The original technique of orthotopic cardiac transplantation described by Shumway and Lower is still used commonly today.[5] Following median sternotomy and vertical pericardiotomy, the patient is heparinized and prepared for cardiopulmonary bypass. Bicaval venous cannulation and distal ascending aortic cannulation just proximal to the origin of the innominate artery are optimal. Umbilical tape snares are passed around the superior and inferior venae cavae. Bypass is initiated, the patient is cooled to 28°C, caval snares are tightened, and the ascending aorta is cross-clamped. The great vessels are transected above the semilunar commissures, whereas the atria are incised along the atrioventricular grooves, leaving cuffs for allograft implantation. Removal of the atrial appendages reduces the risk of postoperative thrombus formation. Following cardiectomy, the proximal 1 to 2 cm of aorta and pulmonary artery are separated from one another with electrocautery, taking care to avoid injuring the right pulmonary artery. Continuous aspiration of pulmonary venous return from bronchial collaterals is achieved by insertion of a vent into the left atrial remnant either directly or via the right superior pulmonary vein.

Timing of donor and recipient cardiectomies is critical to minimize allograft ischemic time and recipient bypass time. Frequent communication between the procurement and transplant teams permits optimal coordination of the procedures. Ideally, the recipient cardiectomy is completed just prior to arrival of the cardiac allograft.

Implantation

The donor heart is removed from the transport cooler and placed in a basin of cold saline. If not previously performed, preparation of the donor heart is accomplished. Electrocautery and sharp dissection are used to separate the aorta and pulmonary artery. The left atrium is incised by connecting the pulmonary vein orifices, and excess atrial tissue is trimmed, forming a circular cuff tailored to the size of the recipient left atrial remnant (Fig. 65-4). Implantation begins with placement of a double-armed 3-0 Prolene suture through the recipient left atrial cuff at the level of the left superior pulmonary vein and then through the donor left atrial cuff near the base of the atrial appendage (Fig. 65-5). The allograft is lowered into the recipient mediastinum atop a cold sponge to insulate it from direct thermal transfer from adjacent thoracic structures. The suture is continued in a running fashion caudally and then medially to the inferior aspect of the interatrial septum (Fig. 65-6). On completion of the posterior left atrial suture line, continuous topical cold saline irrigation of the pericardial well is initiated, and the patient is oriented in a left-side down and head-up position to allow drainage of the saline away from the operative field and maximal cold saline exposure of the left and right ventricles. Alternatively, saline slush is applied generously to the surface of the heart. The second arm of the suture is run

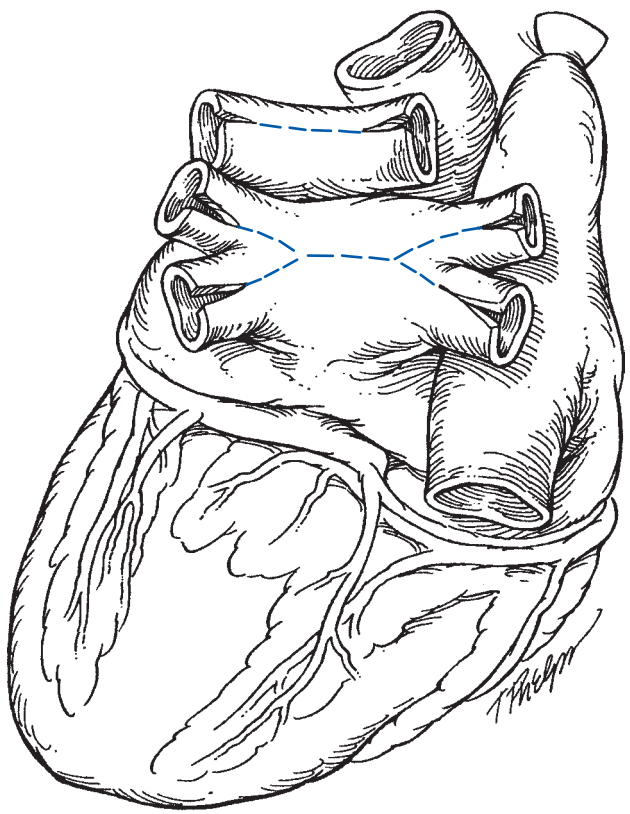

Figure 65-4. Donor allograft preparation for orthotopic heart transplantation. Pulmonary vein orifices joined to form left atrial cuff.

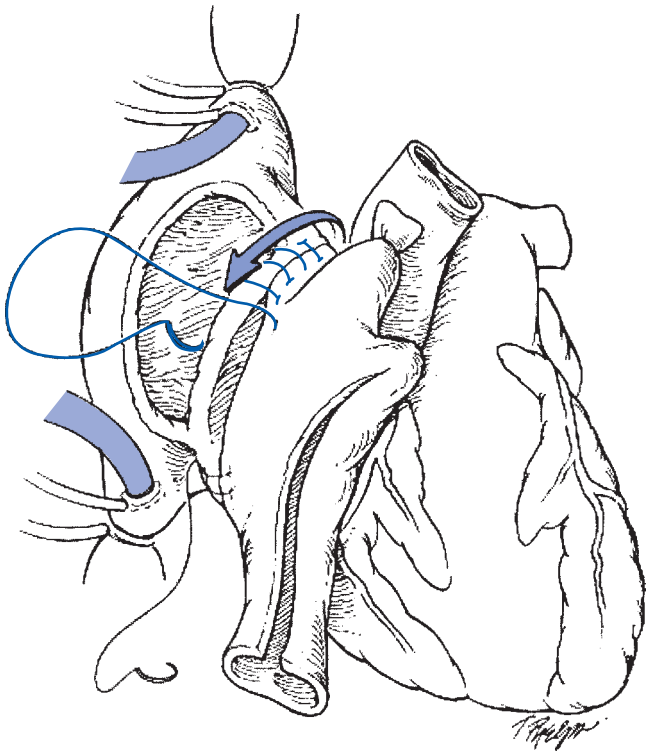

Figure 65-5. Implantation of allograft. First suture is placed at the level of the left superior pulmonary vein.

along the roof of the left atrium and down the interatrial septum. It is important to continually assess size discrepancy between donor and recipient atria so that appropriate plication of excess tissue may be performed. The left atrium is filled with saline, and the two arms of suture are tied together on the outside of the heart. Some centers introduce a line into the left atrial appendage for continuous endocardial cooling of the allograft (50 to 75 mL/min) and evacuation of intracardiac air. Other centers use constant insufflation of carbon diaoxide into the mediastinum.

Once the left atrial anastomosis is complete, a curvilinear incision is made from the inferior vena caval orifice toward the right atrial appendage of the allograft. This modification in the right atriotomy initially introduced by Barnard reduces the risk of injury to the sinoatrial node and accounts for the preservation of sinus rhythm observed in most recipients.[109] The tricuspid apparatus and interatrial septum are inspected. Recipients are predisposed to increased right-sided heart pressures in the early postoperative period owing to preexisting pulmonary hypertension and volume overload. Both conditions are poorly tolerated by the recovering right ventricle. To avoid refractory arterial desaturation associated with right-to-left shunting, patent foramen ovale are oversewn.[110] The right atrial anastomosis is performed in a running fashion similar to the left, with the initial anchor suture placed either at the most superior or inferior aspect of the interatrial septum so that the ends of the suture meet in the middle of the anterolateral wall (Fig. 65-7).

The end-to-end pulmonary artery anastomosis is next performed using a 4-0 Prolene suture beginning with the

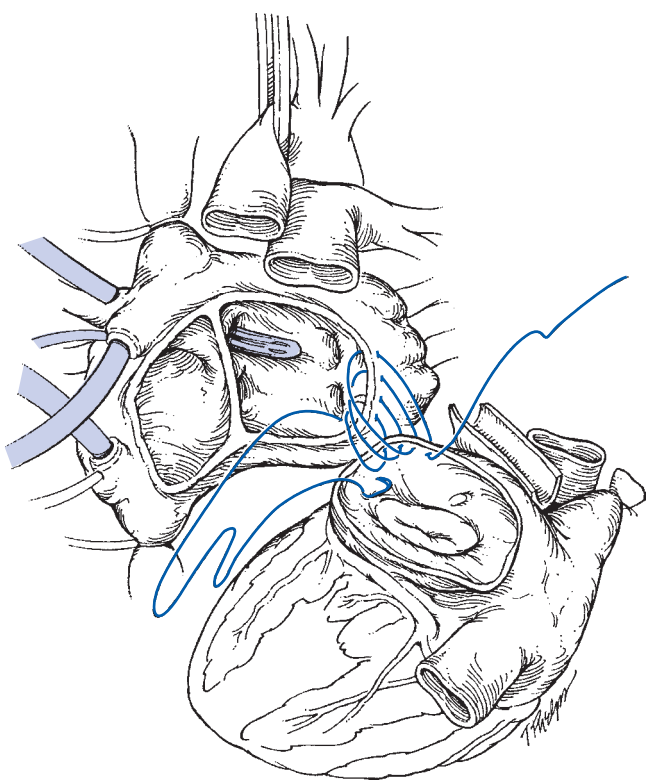

Figure 65-6. Implantation of allograft (continued). Left atrial anastomosis.

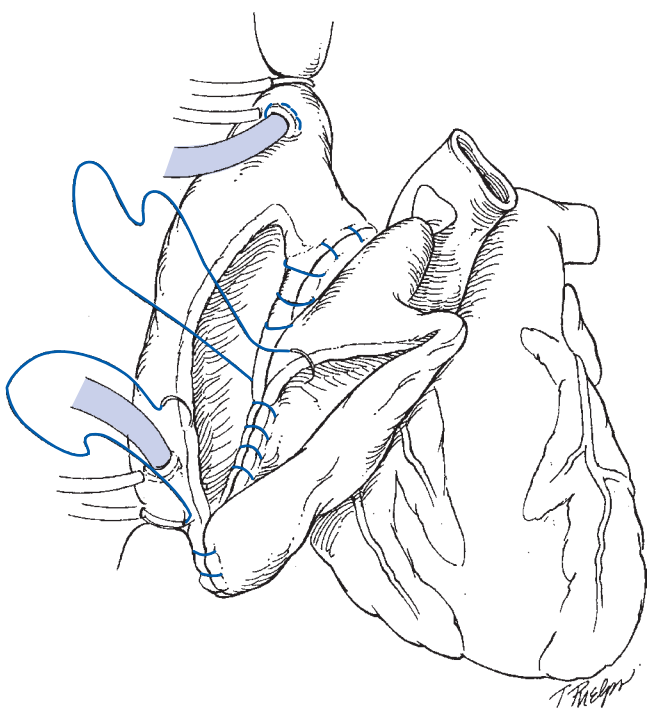

Figure 65-7. Implantation of allograft (continued). Right atrial anastomosis.

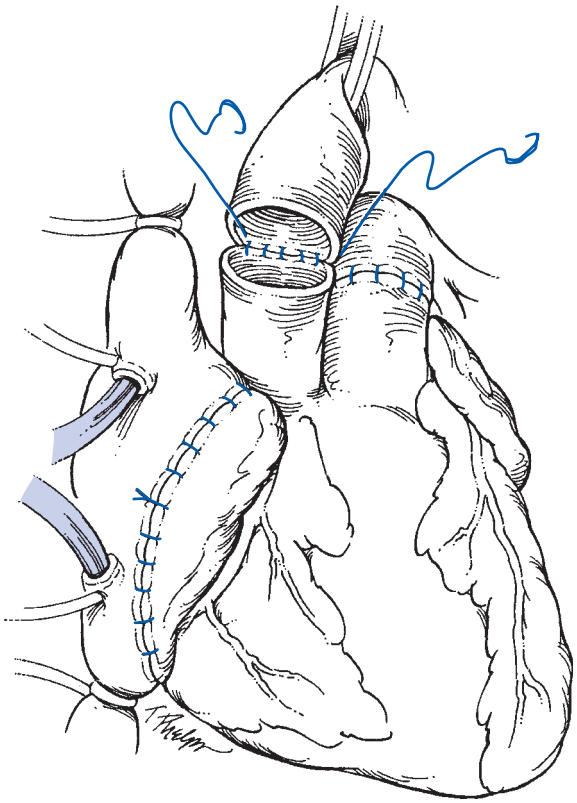

Figure 65-8. Implantation of allograft (continued). Aortic anastomosis.

posterior wall from inside of the vessel and then completing the anterior wall from the outside. It is crucial that the pulmonary artery ends be trimmed to eliminate any redundancy in the vessel that might cause kinking.[111] Finally, the aortic anastomosis is performed using a technique similar to that for the pulmonary artery, except that some redundancy is desirable in the aorta because it facilitates visualization of the posterior suture line (Fig. 65-8). Rewarming usually is begun prior to the aortic anastomosis, which is performed in a standard end-to-end fashion. Routine deairing techniques then are employed. Cold saline lavage is discontinued, lidocaine (100 to 200 mg intravenously) is administered, and the aortic cross-clamp is removed. Half of patients require electrical defibrillation. A needle vent is inserted in the ascending aorta for final deairing, with the patient in steep Trendelenburg position. Suture lines are inspected carefully for hemostasis. Inotrope infusion is initiated, and temporary pacing may be required. The patient is weaned from cardiopulmonary bypass, and the cannulae are removed. Temporary epicardial pacing wires are placed in the donor right atrium and ventricle. Following insertion of mediastinal and pleural tubes, the median sternotomy is closed in the standard fashion.

Cold blood cardioplegia is used in many centers. An initial dose often is given following removal from the cold storage solution prior to implantation. A second dose, or the single dose as given by some centers, is administered after the right atrial anastomosis or inferior vena cava (IVC) anastomosis when a bicaval technique is used.

Alternative techniques for orthotopic heart transplantation

The most commonly employed technique today is a bicaval anastomotic technique. With this technique, the recipient right atrium is excised completely, leaving a left atrial cuff and a generous cuff of the IVC and superior vena cava (SVC), respectively. The left atrial cuff of the donor is anastomosed to the left atrial cuff of the recipient as with the standard Shumway technique. Individual end-to-end anastomoses of the IVC and SVC are performed. The IVC anastomosis usually is performed following the left atrial anastomosis and the SVC anastomosis depending on the surgeon's preference. Total heart transplantation involves complete excision of the recipient heart with bicaval end-to-end anastomoses and bilateral pulmonary venous cuff anastomoses.[112] The Wythenshawe bicaval technique is performed in a similar fashion except that the recipient left atrium is prepared as a single cuff with all four pulmonary vein orifices[113] (Fig. 65-9). Although these procedures are more technically difficult than standard orthotopic transplantation, series using these techniques have reported shorter hospital stays, reduced postoperative dependence on diuretics, and lower incidences of atrial dysrhythmias, conduction disturbances, mitral and tricuspid valve incompetence, and right ventricular failure.[114–116] Furthermore, a study comparing biatrial versus bicaval transplant showed an improved 12-month survival in the bicaval group.[117] Long-term outcomes and prospective, randomized studies evaluating these alternative techniques are still needed.

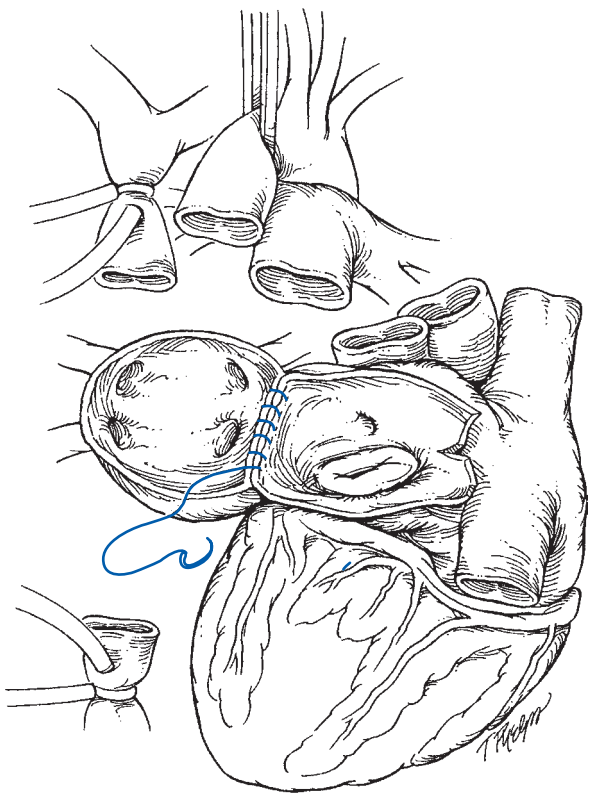

Figure 65-9. Bicaval heart transplantation.

Heterotopic Heart Transplantation

Pulmonary hypertension and right-sided heart failure have remained the leading causes of death in cardiac transplantation. This has led to an interest in heterotopic heart transplantation. Currently, heterotopic heart transplants are performed rarely but may be indicated in patients with irreversible pulmonary hypertension or significant donor-recipient size mismatch.[47,118]

POSTOPERATIVE MANAGEMENT

Hemodynamic Management

Heart allograft physiology

The intact heart is innervated by antagonistic sympathetic and parasympathetic fibers of the autonomic nervous system. Transplantation necessitates transection of these fibers, yielding a denervated heart with altered physiology. Devoid of autonomic input, the sinoatrial (SA) node of the transplanted heart fires at its increased intrinsic resting rate of 90 to 110 beats per minute. The allograft relies on distant noncardiac sites as its source for catecholamines; thus its response to stress (e.g., hypovolemia, hypoxia, and anemia) is somewhat delayed until circulating catecholamines can exert their positive chronotropic effect on the heart.[119] The absence of a normal reflex tachycardia in response to venous pooling accounts for the frequency of orthostatic hypotension in transplant patients.

Denervation alters the heart's response to therapeutic interventions that act directly through the cardiac autonomic nervous system.[120] Carotid sinus massage, Valsalva maneuver, and atropine have no effect on SA node firing or atrioventricular conduction. Because of depletion of myocardial catecholamine stores associated with prolonged inotropic support of the donor, the allograft often requires high doses of catecholamines.

Routine hemodynamic management

Donor myocardial performance is transiently depressed in the immediate postoperative period. Allograft injury associated with donor hemodynamic instability and the hypothermic, ischemic insult of preservation contribute to the reduced ventricular compliance and contractility characteristics of the newly transplanted heart.[121] Abnormal atrial dynamics owing to the midatrial anastomosis exacerbate the reduction in ventricular diastolic loading. An infusion of epinephrine or dobutamine is initiated routinely in the operating room to provide temporary inotropic support. Cardiac denervation brings in several consequences, which may include a chronotropic and an inotropic supersensitivity to exogenous catecholamines.[122] Restoration of normal myocardial function usually permits the cautious weaning of inotropic support within 2 to 4 days.

Early allograft failure

Early cardiac failure still accounts for up to 20% of perioperative deaths of heart transplant recipients.[123] The cause may be multifactorial, but the most important etiologies are myocardial dysfunction owing to donor instability, pulmonary hypertension, ischemic injury during preservation, and acute rejection. Mechanical support with an intra-aortic balloon pump or ventricular assist device can be attempted in patients refractory to pharmacologic interventions, although this measure, as well as retransplantation, is associated with very high mortality.[124,125]

Chronic left ventricular failure frequently is associated with elevated pulmonary vascular resistance, and the unprepared donor right ventricle may be unable to overcome this increased afterload. Although recipients are screened to ensure that those with irreversible pulmonary hypertension are not considered for transplantation, right-sided heart failure remains a leading cause of early mortality.[126] Initial management involves employing pulmonary vasodilators such as inhaled nitric oxide, nitroglycerin, or sodium nitroprusside. Pulmonary hypertension that is refractory to these vasodilators sometimes responds to prostaglandin E_1 (PGE_1) or prostacyclin.[32,127,128] Intra-aortic or pulmonary artery balloon counterpulsation and right ventricular assist devices also can be used in patients unresponsive to medical therapy.[129]

Arrhythmias

Denervation of the transplanted heart leads to loss of autonomic nervous system modulation of the heart's electrophysiologic properties. Parasympathetic denervation causes loss of basal suppression of SA node automaticity, leading to a persistent increase in resting heart rate and a loss of normal, rapid heart rate modulation. This parasympathetic loss also causes elimination of the chronotropic effects of digoxin and atropine after heart transplantation. At the same time, sympathetic denervation causes a decrease and delay in exercise- or stress-induced augmentation of SA node automaticity, resulting in a decreased maximum heart rate with exercise.[130]

Sinus or junctional bradycardia occurs in up to half of transplant recipients. Risk factors for sinus node dysfunction include prolonged organ ischemia, angiographic nodal artery abnormalities, biatrial as opposed to bicaval anastomosis, preoperative amiodarone use, and rejection.[131–133] Adequate heart rate is achieved with inotropic drug infusions and/or temporary epicardial pacing. Most bradyarrhythmias resolve over 1 to 2 weeks. Theophylline has been effective in patients with bradyarrhythmias and has decreased the need for permanent pacemakers in this patient population.[134]

Atrial fibrillation, atrial flutter, and other supraventricular arrhythmias have been reported in 5 to 30% of patients after heart transplantation.[130] Individual assessment of the risk:benefit ratio for anticoagulation therapy is necessary. Supraventricular tachycardia (SVT) in transplant patients should be treated in the same manner as in nontransplant

patients but with lower doses. Recurrent arrhythmias from reentry circuits or defined ectopic foci often can be cured by radiofrequency ablation.

Premature ventricular complexes (PVCs) generally are considered not ominous. Because of their rapidly terminal nature, sustained ventricular tachycardia (VT) and ventricular fibrillation presumably are responsible for a significant portion of the 10% of sudden and unexplained deaths in heart transplant patients.[135]

Unique aspects of common antiarrhythmic drugs reflecting the differences in their therapeutic effects in heart transplant recipients compared with nontransplant patients are shown in Table 65-6.[130] Persistence of any form of arrhythmia should warrant further investigative efforts and an aggressive search for the presence of indicators of cardiac ischemia, rejection, pulmonary pathology, or infection. If arrhythmic episodes are frequent or underlying cardiac pathology is severe, retransplantation may be considered.

Systemic hypertension

Systemic hypertension should be treated to prevent unnecessary afterload stress on the allograft. In the early postoperative period, intravenous sodium nitroprusside or nitroglycerin usually is administered. Nitroglycerin is associated with less pulmonary shunting because of a relative preservation of the pulmonary hypoxic vasoconstrictor reflex.[136] Nicardipine infusion has been reported to control postoperative hypertension more rapidly and was superior to sodium nitroprusside in maintaining left ventricular performance immediately after drug infusion.[137] If hypertension persists, an oral antihypertensive can be added, if possible, to permit weaning of the parenteral agents.

Respiratory Management

The respiratory management of the cardiac transplant recipient uses the same protocols employed following routine cardiac surgery.

Renal Function

Preoperative renal insufficiency owing to chronic heart failure and the nephrotoxic effects of calcineurine inhibitors cyclosporine place the recipient at increased risk of renal insufficiency. Acute calcineurine inhibitor cyclosporine-induced renal insufficiency usually will resolve with a reduction in dose. Continuous intravenous infusion to eliminate the wide fluctuations in levels associated with oral dosing can be attempted. Furthermore, concurrent administration of mannitol with calcineurine inhibitor cyclosporine may reduce its nephrotoxicity. Most centers administer a cytolytic agent in the immediate postoperative period and delay the initiation of calcineurine inhibitor cyclosporine therapy.

Outpatient Follow-up

Prior to discharge, patients should receive comprehensive education about their medications, diet, exercise, and infection recognition. Close follow-up by an experienced transplant team is the cornerstone for successful long-term survival after cardiac transplantation. This comprehensive team facilitates the early detection of rejection, opportunistic infections, patient noncompliance, and adverse sequelae of immunosuppression. Clinic visits routinely are scheduled concurrently with endomyocardial biopsies and include physical examination, a variety of laboratory studies, chest roentgenogram, and electrocardiogram.

IMMUNOSUPPRESSIVE THERAPY

An organism's ability to distinguish self from nonself is critical for its survival in a hostile environment. In transplantation, the recipient's host defense mechanisms recognize the human leukocyte antigens (HLAs) on allograft cells as being nonself and, if permitted, will respond to eradicate the foreign cells.[138] The ultimate goal of immunosuppressive therapy is selective modulation of the recipient's immune response to prevent rejection while concurrently sparing immune defenses against infections or neoplasia and minimizing the toxicity associated with immunosuppressive agents. The mechanisms of action and toxicity of currently used immunosuppressive agents are summarized in Table 65-7.

Pharmacologic Immunosuppressive Strategies

With the current 30-day mortality of less than 10%, the overwhelming majority of posttransplant deaths occur after 30 days.[139] Thus the "perfect" immunosuppressive regimen would save many more lives than the "perfect" surgical technique or donor organ. Changes in immunosuppressive therapy have had a major impact on improving survival after heart transplantation, as evidenced by the decreasing number of deaths owing to rejection in recent years.[140]

Immunosuppression following transplantation consists of an early induction phase followed by a long-term maintenance phase. This basic strategy essentially is universal, although the choice of immunosuppressive agents, dosages, and combination protocols vary between transplantation centers.

Currently, the "standard" maintenance immunosuppression protocols for heart transplantation (so-called triple therapy) include (1) a calcineurin inhibitor (CNI) such as cyclosporine or tacrolimus, (2) an antiproliferative agent such as azathioprine (AZA), mycophenolate mofetil (MMF), or rarely, cyclophosphamide, and (3) corticosteroids such as prednisone or prednisolone. Many centers also add an antilymphocyte antibody perioperatively such as antithymocyte globulin (ATG), OKT3, or an interleukin-2 (IL-2) receptor blocker (basiliximab or daclizumab) to create a quadruple-drug regimen. In recent years, sirolimus (Rapamycin) and everolimus (a derivative of Rapamycin), which act by blocking several events downstream of the IL-2 receptor, have been introduced into clinical heart transplantation. In the

Table 65–6.

Differences in Therapeutic Agent Effects in Heart Transplant Recipients Compared with Nontransplant Patients

Arrhythmia therapy	Differences in after transplantation
Drugs	
AV nodal agents	
Digoxin	No effect on heart rate
β-Adrenergic antagonists	Exacerbation of exercise intolerance
Calcium channel antagonists	Accentuated slowing of SA and AV nodes; may alter cyclosporine levels
Adenosine	Accentuated slowing of SA and AV nodes
Adrenergic agonists	
Norepinephrine	Unchanged peripheral effect, slightly more inotropic and chronotropic effect
Epinephrine	Unchanged peripheral effect, slightly more inotropic and chronotropic effect
Dopamine	Unchanged peripheral effect, less inotropic effect
Dobutamine	Unchanged
Ephedrine	Unchanged peripheral effect, less inotropic effect
Neosynephrine	Unchanged peripheral effect, no reflex bradycardia
Isoproteronol	Unchanged
Antiarrhythmic agents	
Class Ia (quinidine, disopyramide, procainamide)	No cardiac vagolytic effect
Class Ib (lidocaine, mexilitine)	None reported
Class Ic (flecainide, encainide, moricizine, propafenone)	None reported
Class III (amiodarone, sotalol, ibutilide, dofetilide)	Possible exaggerated or atypical response
Anticoagulants	
Heparin	None reported
Warfarin	None reported
Miscellaneous	
Atropine	No effect on heart rate
Methylxanthines (theophylline, aminophylline)	Possibly more chronotropic effect
Cardioversion	None reported
Radiofrequency catheter ablation	Possible differences in pathway or chamber anatomy
Electrical devices	
Pacemaker	None reported
Intracardiac defibrillator	None reported

SA - sinoatrial; AV - atrioventricular.
Source: Reprinted with permission from Stecker et al.[130]

Table 65–7.

Actions and Toxicities of Immunosuppressive Agents

Drug	Classification and action	Adverse effects
Corticosteroids	Lymphocyte depletion Affect elements involved in all stages of the T-cell activation process. Inhibits cytokine production of macrophages	Cushingoid appearance Weight gain with central obesity Hypertension Hyperglycemia/diabetes Hyperlipidemia Peptic and esophageal ulceration and gastrointestinal (GI) bleeding Cataract formation Aseptic bone necrosis Osteoporosis Myopathy Personality changes and psychosis Poor wound healing Easy bruising
Cyclosporine	Calcineurine Inhibitor; blocks T-cell IL-2 production. Inhibits T-cell proliferation and differentiation	Nephrotoxicity Hypertension Neurotoxicity (parasthesia, seizure, tremor, headache) Gingival hyperplasia Hypertrichosis (hirsutuism) Hyperuricemia, gout Hepatotoxicity Hyperlipidemia Hyperglycemia
Tacrolimus (FK506)	Calcineurine inhibitor; blocks T-cell IL-2 production. Inhibits T-cell proliferation and differentiation	Equivalent to cyclosporine: Nephrotoxicity Higher incidence than cyclosporine: Diabetes mellitus Neurotoxic reaction Lower incidence than cyclosporine: Hypertension Hyperlipidemia Hirsutism Gingival hyperplasia
Azathioprine	Antiproliferative. Inhibits early stages of purine metabolism. Blocks most T-cell functions; inhibits primary antibody synthesis; decreases number of circulating monocytes and granulocytes	Bone marrow suppression: Leukopenia Anemia Thrombocytopenia Pancytopenia Pancreatitis Hepatitis GI distress (nausea, vomiting, abdominal pain, diarrhea) Cholestatic jaundice
Mycophenolate	Antiproliferative	GI upsets
Mofetil (MMF)	Selective inhibitor of de novo pathway of purine biosynthesis, thereby providing more specific and potent inhibition of T-cell and B-cell proliferation	Diarrhea Increased risk of tissue-invasive cytomegalovirus infection Leukopenia Thrombocytopenia Pancytopenia

(continued)

Table 65–7.

Actions and Toxicities of Immunosuppressive Agents (*continued*)

Sirolimus (Rapamycin) Everolimus (Certican)	Antiproliferative Proliferation signal inhibtor; prevents T-cell progression from the G_1 to the S phase by blocking signaling downstream IL-2	Hyperlipidemia Thrombocytopenia Leukopenia Hypertension Peripheral edema Impaired wound healing
Polyclonal antibodies, thymoglobulin, Antithymocyte, sera/globulin (ATS, ATG-Frenius,) antilymphocyte globulin (ALG)	Deplete circulating T cells using several antibody-mediated mechanisms of destruction of immune cells	Fever and chills Serum sickness Polyarthralgias Anemia Leukopenia Thrombocytopenia GI distress Rash Alopecia
OKT3 (Muronomab-CD3)	Monoclonal antibody Blocks the function of both naive T cells and established cytotoxic T cells	Cytokine release syndrome: Fever, chills, weakness, bronchospasm, hypotension (peripheral vasodilatatio GI distress Pulmonary edema Increased opportunistic infections Increased lymphoproliferative disorders Antimurine antibody development Rebound rejection after drug discontinuation.
Daclizumab (Zenepax) Basiliximab (Simulect)	IL-2 receptor blockers Inhibit IL-2-dependent T-cell activation Monoclonal antibodies with greater human component	Generally well tolerated. Studies ongoing

setting of pretransplant renal insufficiency, a popular protocol involves delaying the initiation of the calcineurin inhibitors for 1 to 2 weeks postoperatively to allow for recovery of renal function and using antilymphocyte antibody therapy in the interim, so-called sequential therapy.[141] The use of a multidrug regimen permits adequate immunosuppression with reduced doses of individual agents to minimize their toxicity. The immunosuppressive regimen currently used at the Johns Hopkins Hospital is outlined in Table 65-8.

Individual Immunosuppressive Agents

Corticosteroids

Corticosteroids have played an integral role in immunosuppression since the beginning of cardiac transplantation. These nonselective agents influence essentially all limbs of the immune response.[142] Currently, methylprednisolone is used during induction, and prednisone usually is part of maintenance immunosuppressive regimens. Corticosteroids are also the first-line therapy for acute rejection in most centers. The numerous untoward sequelae associated with long-term corticosteroid therapy have driven clinicians to reduce doses significantly or even eliminate these drugs from maintenance regimens.[143]

The timing of steroid withdrawal varies; some clinicians discontinue prednisone within several weeks of transplantation,[144,145] whereas others delay the taper until several months after transplantation.[146,147] Successful early withdrawal of corticosteroid therapy has been associated with improved long-term survival.[148] The 2005 ISHLT report indicates that prednisone is still used by almost 75% of patients at 1-year after transplant.[17]

Cyclosporine

Cyclosporine (Sandimmune) is an 11-amino-acid cyclic peptide produced by the fungus *Tolypocladium inflatum*.[149] It inhibits the calcium-calcineurin pathway, one of the three sig-

Table 65–8.

Immunosuppressive Regimen for Heart Transplantation at the Johns Hopkins Hospital

I.	Preoperative preparation: None
II.	Intraoperative management: Methylprednisolone: 500 mg IV (after administration of protamine) Daclizumab (Zenapax) 1 mg/kg IV
III.	Immediate postoperative therapy: Methylprednisolone: 125 mg/kg IV for 3 doses followed by Prednisone: 1 mg/kg PO qd tapered to 20 mg over 2 to 3 weeks Mycophenolate mofetil 1 g PO/IV bid Cyclosporine (prefer Neoral): Initiate at 50 mg PO bid, and titrate dose to maintain serum level between 250 and 300 ng/mL during first 3 months *or* Tacrolimus: Initiate at 2 mg PO bid, and titrate to maintain serum level between 10 and 15 ng/mL during the first 3 months. Daclizumab (Zenapax) 1 mg/kg IV on postoperative day 7, then given every 2 weeks for a total of 5 doses
IV.	Postoperative maintenance therapy: Prednisone: 20 mg PO qd until 3 months, decrease to 10 mg qd to 6 months, 5 mg qd, and taper to off by the end of 1 year. Mycophenolate mofetil: 1 g PO/IV bid Cyclosporine (prefer Neoral): Initiate at 50 mg PO bid, and titrate dose to maintain serum level between 250 and 300 ng/mL during first 3 months *or* Tacrolimus: Initiate at 2 mg PO bid, and titrate to maintain serum level between 10 and 15 ng/mL during the first 3 months

[*] *CycloTrac SP ^{125}I RIA Kit, INCSTAR, Stillwater, MN.*

nal transduction pathways that activate transcription factors triggering the expression of molecules with key roles in the immune response, including IL-2, CD154, and CD25.[150] Consequently, cytotoxic T-lymphocyte proliferation is attenuated. By sparing macrophages, neutrophils, suppressor T lymphocytes, and some B lymphocytes, cyclosporine provides more selective immunosuppression than azathioprine and corticosteroids.[151] It also has permitted the reduction in corticosteroid doses in maintenance immunosuppression.[143] After cyclosporine was introduced in clinical heart transplant in the early 1980s, prognosis after heart transplant improved markedly, and in 2001, the ISHLT Registry showed that approximately 50% of patients who underwent heart transplantation after 1982 survived more than 10 years.[152] Indeed, the improved survival of cardiac recipients in the cyclosporine era is primarily a result of a reduction in infection-related mortality likely associated with a relative preservation of host defense against microbials.[153] Doses of cyclosporine are adjusted to achieve trough serum levels of between 150 and 300 ng/mL.[154] The low therapeutic index of cyclosporine and wide variation in individual pharmacokinetics mandates close monitoring of levels. For patients who develop renal insufficiency, cyclosporine temporarily may be administered as a continuous infusion to reduce wide fluctuations in serum levels. In 1995, the original oil-based formulation largely was replaced by a new microemulsion formulation (Neoral) with greater bioavailability and more predictable intestinal absorption and pharmacokinetics.[155,156]

Tacrolimus

Tacrolimus (FK506) is a macrolide antibiotic from *Streptomyces tsukubaensis* that binds to another immunophilin, FK506-binding protein 12 (FKBP12), thereby forming a complex that inhibits calcineurin with greater molar potency than does cyclosporine and decreases the formation of IL-2.[157] Two prospective, multicenter, randomized trials, one in Europe and the other in the United States, have compared the standard oil-based cyclosporine formulation with tacrolimus in association with azathioprine and steroids. The two calcineurin inhibitors showed similar efficacies in preventing rejection and death within the first year after transplant, but tacrolimus caused fewer cases of hypertension and hyperlipidemia than cyclosporine.[158,159] Similarly, the 18-month results of a large multicenter tacrolimus versus cyclosporine microemulsion study have shown the two drugs to be associated with similar incidences of rejection and death but that recurrent rejection was less severe and the incidences of hypertension and hyperlipidemia were lower if

tacrolimus was used.[160] Furthermore, FK506 has been found to be most effective in reversing recalcitrant rejection.[161] This has prompted some institutions that use cyclosporine to employ FK506 as a "rescue" agent. It also has been suggested that ethnic disparity in clinical outcome after heart transplantation is abrogated using tacrolimus-based immunosuppression.[162]

So far, neither cyclosporine nor tacrolimus has been shown to prevent cardiac allograft vasculopathy (CAV) or to reduce the progression of this complication during long-term follow-up, although with tacrolimus the risk of CAV associated with hypertension and hyperlipidemia may be lower, but the risk associated with impaired glucose metabolism may be higher. With both drugs, the risk of CAV is exacerbated by the concomitant use of corticosteroids.[163] Overall, the choice of calcineurin inhibitor currently seems to be dictated by their adverse-effect profiles, by the results obtained for individual patients, and possibly by institutional preference. The 2005 ISHLT report indicates that tacrolimus has just surpassed cyclosporine as the most commonly used calcineurin inhibitor.[17]

Azathioprine

An imidazole derivative from 6-mercaptopurine, azathioprine is an antimetabolite that inhibits DNA synthesis during the crucial synthetic (S) phase of cell replication. This leads to the inhibition of the antigen-stimulated proliferation of lymphocytes.[164] Dosage adjustments are made to maintain the leukocyte count at between 4000 and 5000/mm^3. Azathioprine causes a dose-related bone marrow suppression that can be profound if it is administered concurrently with allopurinol.[165]

Mycophenolate mofetil (MMF)

MMF (Cellcept), an ester prodrug of mycophenolic acid, inhibits a key step in the de novo biosynthesis of purines, selectively affecting cells (such as lymphocytes) that are unable to use salvage pathways.[166] In the latest reported randomized, double-blind, controlled trial comparing MMF with azathioprine, the MMF groups had reduced mortality and graft loss up to 3 years after transplantation (11.8% versus 18.3%, $p < .01$).[167] Time to retransplantation or patient death was significantly shorter for azathioprine- than for MMF-treated patients ($p = .029$). Congestive heart failure, atrial arrhythmia, and leukopenia were more common in the azathioprine group, whereas diarrhea, esophagitis, herpes simplex, herpes zoster, and CMV tissue invasion were more common in MMF-treated patients. Several other studies in the past also demonstrated the superiority of MMF.[168] Furthermore, MMF has novel properties that may contribute to the prevention of cardiac allograft rejection and also provide benefits in reducing the progression of CAV. In a study by Pethig and colleagues, cardiac transplant patients receiving MMF had lower levels of high-sensitive C-reactive protein, a marker of inflammation having a strong association with cardiovascular disease, than did patients receiving azathioprine.[169] However, there was no significant difference in intimal hyperplasia, although there was a weak trend toward vascular enlargement by intravascular ultrasound in the MMF group. MMF largely has replaced azathioprine and currently is the predominant antiproliferative agent, used in more than 75% of heart transplant recipients.[17]

Sirolimus and everolimus

Sirolimus (Rapamycin), which is another antibiotic from *Streptomyces,* and its derivative everolimus (Certican; formerly SDZ-RAD) are potent proliferation signal inhibitors that have made major breakthroughs in the field of coronary stenting. They act by blocking several events downstream of the IL-2 receptor. Interestingly, these drugs bind to the same binding proteins as tacrolimus (primarily FKBP-12), but rather than inhibiting calcineurin, they inhibit cytoplasmic proteins collectively termed *target-of-Rapamycin* (TOR) proteins. These proteins are required for cell cycle progression from G_1 to S phase in response to IL-2 stimulation, and hence sirolimus and everolimus are able to block the proliferative response of T cells after immune activation.[170,171]

In a randomized, open-label multicenter study conducted in Australia and New Zealand, sirolimus was compared with azathioprine in combination with cyclosporine (Neoral) and steroids administered from the time of cardiac transplantation.[172] One-hundred and thirty-six first cardiac allograft recipients were randomly assigned (2:1) to sirolimus ($n = 92$; 5 or 3 mg/d maintenance dose) or azathioprine ($n = 44$). At 6 months, the proportion of patients with grade 3a or greater acute rejection was 32.4% for sirolimus 3 mg/d ($P = .027$), 32.8% for sirolimus 5 mg/d ($P = .013$), and 56.8% for azathioprine. The trial was not powered to detect differences in mortality; however, survival rates at 12 months did not differ significantly. Intravascular ultrasound at 6 weeks, 6 months, and 2 years demonstrated highly significant progression of transplant vasculopathy in azathioprine-treated patients. A small single-center randomized trial of patients who already had CAV showed that treatment with sirolimus slowed its progression.[173] The use of sirolimus in heart transplant has doubled from 7% in 2002 to 14% in 2004.[17]

The efficacy and safety of everolimus (1.5 or 3.0 mg/d) was compared with azathioprine (1.0 to 3.0 mg/kg per day) in a large 2-year phase III, multicenter, randomized study in 634 recipients of primary heart transplants receiving concomitant full-dose cyclosporine microemulsion (Neoral), corticosteroids, and statins.[174–176] Rates of acute rejection (grade $\geq$ 3a) were significantly lower for patients receiving everolimus than for those receiving azathioprine and maintained at 24 months (22.7% versus 48.1%; $p \leq .001$), indicating a 52.8% reduction. Furthermore, everolimus-treated patients had a significantly lower incidence of CMV infection at 12 months than azathioprine-treated patients (7.7% and 7.6% versus 21.5%; $P < .001$). Both average coronary artery intimal thickness assessed by intravascular ultrasonography and the incidence of CAV were significantly lower in patients receiving everolimus than in those receiving azathioprine at both 12[174] and 24 months.[175] Patient survival was excellent in this study,

with no significant differences noted between the everolimus 1.5 and 3 mg/d groups (88.6% and 91.4%) and the azathioprine group (92.1%) at 12 and 24 months (90.0%, 86.3%, and 88.8%, respectively). At 24 months, overall safety and survival rates were better with everolimus dosed at 1.5 mg/d than at 3 mg/d.[176] There was a high discontinuation rate, especially in the group receiving 3.0 mg of everolimus (nearly 40%). Thrombocytopenia and elevated lipid levels (despite the administration of statins) were seen more frequently in the everolimus groups.

Since CAV is the main risk factor for mortality after the first year posttransplantation and acute rejection and CMV infection play a key role in its development, this pivotal study suggests that primary immunosuppression including everolimus could provide important benefits for heart transplant patients.[177] Coadministration with calcineurin inhibitors (CNIs) can exacerbate CNI-related nephrotoxicity, but evidence suggests that everolimus administered with reduced-exposure cyclosporine in the maintenance phase preserves renal function without loss of immunosuppressive efficacy.[178] Notably, the preceding trials compared sirolimus or everolimus with azathioprine and not with MMF. However, MMF has not been associated with a significant reduction in intravascular ultrasound–defined vasculopathy.[141]

Polyclonal antibodies

Polyclonal antibodies (e.g., antithymocytes and antilymphocytes) are produced by animals following immunization with human lymphocytes. Their mechanisms of action include complement-dependent cytolysis of the recipient lymphocytes, opsonization with destruction of immune cells by the reticuloendothelial system, and induction of apoptosis following binding to surface antigens.[179] These antibodies thereby can decrease the level of circulating T cells to less than 10% of normal. Thymoglobulin, an injectable solution of purified IgG immunoglobulins with pronounced lymphocytotoxic antibody activity, is obtained by hyperimmunization of rabbits with human thymocytes. ATG-Fresenius, which is produced in rabbits after hyperimmunization with an immortalized cellular line (Jurkat), contains various immunoglobulin fractions with high antilymphocyte activity. Antithymocyte sera (ATS) and equine antibodies also are used. These antibody preparations have been introduced for perioperative prophylaxis as part of induction therapy protocols to delay administration of cyclosporine, thus avoiding acute nephrotoxicity during the immediate postoperative period and to permit reduction in early corticosteroid doses.[141,180] Several retrospective series have shown the efficacy of this strategy to achieve low rates of early acute rejection episodes without significantly increasing the incidence of infection or malignancy.[181,182] The antibodies also are used for rescue therapy for acute rejection refractory to corticosteroids.

OKT3

The first monoclonal antibody (mAb) available for therapeutic use in the treatment and prevention of allograft rejection was OKT3. It is a murine mAb directed against the ϵ chain of CD3 molecule, which is part of the T-cell recognition (TCR) complex and functions to modulate the receptor and inactivate T-cell function. By engaging the TCR complex, OKT3 blocks not only the function of naive T cells but also the function of established cytotoxic T cells.[183] As with polyclonal preparations, administration of OKT3 also can eliminate almost all circulating T lymphocytes, although its monoclonal specificity prevents it from having a cytolytic effect on other circulating cells.[184] Monitoring of T3 subpopulation cell counts can be used to determine adequacy of therapy. While it has been used for induction therapy, OKT3 has demonstrated its greatest benefit on rescue therapy.[185,186] Studies comparing the results obtained with OKT3 versus horse or rabbit polyclonal antibodies have yielded conflicting results.[187–189] OKT3 appears to be more aggressive therapy and has been associated with serious adverse effects, which include the following: (1) the development of a cytokine release syndrome owing to the ability of OKT3 to activate T cells, ranging in severity from a mild febrile illness to a syndrome of severe volume overload and hemodynamic compromise,[190] (2) the appearance of human antimouse antibodies that decrease the efficacy or preclude the use of subsequent OKT3 courses and can mediate humoral rejection,[191] (3) the increased incidence of opportunistic infections such as those caused by CMV,[189,192] and (4) the increased incidence of posttransplant lymphoproliferative disorders.[193] Interestingly, the 2005 ISHLT report showed that patients receiving OKT3 as part of an induction protocol have higher rejection rates during the first year after transplant than those receiving polyclonal or IL-2 antibody induction and those receiving no antibody induction. Overall, the perioperative use of OKT3 as an induction agent continues to decrease (only 4% of heart transplant procedures in 2001–2004).[17]

Daclizumab and basiliximab

The preceding limitations of OKT3 have spurred the development of mAbs that have a greater human component and achieve a more selective suppression of the immune system.[194] Because only activated T cells express the Tac antigen (IL-2Rα chain or CD25 antigen), anti-Tac IL-2R mAbs are expected to target graft-reactive lymphocytes immediately after transplantation in an induction or sequential immunosuppression therapy protocol. There are two new anti-Tac mAbs, which generally are known as IL-2 receptor (IL-2R) blockers, and they became available in 1998. Basiliximab (Simulect) is a chimeric antibody retaining the murine elements of the variable portion of the immunoglobulin chain. Daclizumab (Zenapax) is more completely humanized, retaining a smaller region of the murine antibody.[183] The immunogenicity of these molecules, as measured by in vivo circulating half-life and by the appearance of antibodies against the agents, is reduced significantly compared with strictly murine anti-CD25 mAbs. Although these agents are given only for a limited period after transplantation, effective IL-2R blockade is achieved for several weeks after the last

dose, thereby covering the critical period when acute rejection is most common.

In a randomized, single-center evaluation of 55 heart transplant recipients, there was a striking decrease in the rate of rejection, by a factor of 2.8, among patients receiving daclizumab, with no increase in the rate of infection.[195] Hershberger and colleagues recently reported on 434 first heart transplant recipients recruited from 31 transplantation centers in the United States, Canada, Germany, and Sweden.[196] Patients were assigned randomly in a double-blind manner to receive either daclizumab or placebo in combination with cyclosporine, MMF, and corticosteroids. The risk of their primary composite endpoint of histologic rejection, graft dysfunction, a second transplantation, or death within 6 months was reduced by treatment with the mAb daclizumab (47.7% versus 35.6%; $P = .007$). The rate of rejection was lower in the daclizumab group than in the placebo group (41.3% versus 25.5%). Among patients reaching the primary endpoint, the median time to the endpoint was almost three times as long in the daclizumab group at 6 months (61 versus 21 days) and at 1 year (96 versus 26 days). However, the efficacy benefit of the active drug was solely accounted for by the histologic rejection component of the composite endpoint. A worrisome finding was that overall mortality was greater in the daclizumab group than in the placebo group (6.5% versus 3.2%) at 6 months, and this trend continued at 1 year ($P = .11$). Most of the deaths were due to infections and occurred in patients who received both daclizumab and a second monoclonal or polyclonal preparation of antilymphocyte antibody. Also worrisome was the higher incidence of graft dysfunction in the daclizumab group.[197]

A small 1-year double-blind, randomized, placebo-controlled study evaluated the safety, tolerability, and pharmacokinetics of basiliximab with cyclosporine, MMF, and steroids in 56 adult first heart transplant recipients.[198] Basiliximab generally was well tolerated. There were no significant differences between treatment groups with respect to adverse-event profiles, serious adverse events, or infections. The mean number of days to first biopsy-proven acute rejection was longer with basiliximab (73.7 $\pm$ 59.68 days) than placebo (40.6 $\pm$ 53.30 days) at 6 months but not statistically significant. Further studies will be needed to clearly define the role that daclizumab and basiliximab will play in heart transplant immunosuppressive therapy.

ACUTE REJECTION

Cardiac allograft rejection is the normal host response to cells recognized as nonself. The vast majority of cases are mediated by the cellular limb of the immune response through an elegant cascade of events involving macrophages, cytokines, and T lymphocytes. Humoral-mediated rejection (also called *vascular rejection*) is less common. The highest risk factors are allografts from younger and female donors (irrespective of recipient sex).[199] Although about 85% of episodes can be reversed with corticosteroid therapy alone,[200] rejection is still a major cause of morbidity in cardiac transplant recipients.[17,201]

Diagnosis of Acute Rejection

In the precyclosporine era, the classic clinical manifestations of acute rejection included low-grade fever, malaise, leukocytosis, pericardial friction rub, supraventricular arrhythmias, low cardiac output, reduced exercise tolerance, and signs of congestive heart failure. In the cyclosporine era, however, most episodes of rejection characteristically are insidious, and patients can remain asymptomatic even with late stages of rejection. Thus routine surveillance studies for early detection are crucial to minimize cumulative injury to the allograft. Right ventricular endomyocardial biopsy remains the "gold standard" for the diagnosis of acute rejection. The most frequently used technique for orthotopic allografts is a percutaneous approach through the right internal jugular vein.[202] Interventricular septal specimens are fixed in formalin for permanent section, although frozen sections are performed occasionally if urgent diagnosis is necessary. Hemodynamic parameters also may be obtained with a pulmonary artery catheter. Complications are infrequent (1 to 2%) but include venous hematoma, carotid puncture, pneumothorax, arrhythmias, heart block, and right ventricular perforation and injury to the tricuspid valve. The exact schedule for endomyocardial biopsies varies among institutions but reflects the greater risk of rejection during the first 6 months following transplantation. Biopsies are performed initially every 7 to 10 days in the early postoperative period and eventually tapered to 3- to 6-month intervals after the first year. Suspicion of rejection warrants additional biopsies.

Evaluation of sample adequacy for the ISHLT grading scheme requires a minimum of four good endomyocardial tissue fragments, with less than 50% of each fragment being fibrous tissue, thrombus, or other noninterpretable tissues (e.g., crush artifact or poorly processed fragments).[203] The pattern and density of lymphocyte infiltration, in addition to the presence or absence of myocyte necrosis in the endomyocardial biopsy, determine the severity grade of cellular rejection.[204] Further elaboration of the pathologic features and identification of antibody-mediated rejection were addressed more recently.[205] In 2004, the ISHLT Pathology Council proposed simplification of the 1990 diagnostic categories for cellular rejection to mild, moderate, and severe and identification of the histologic characteristics of antibody-mediated rejection.[206] The new grading scale is supposed to better address the challenges and inconsistencies in use of the old grading system.[207] Tables 65-9 and 65-10 show the new 2004 ISHLT grading scale.[206]

Noninvasive studies for the diagnosis of acute rejection have been unreliable. Electrocardiographic voltage summation and E-rosette assay techniques were useful adjuncts in the early cardiac transplant experience[208]; however, they currently are of no value in patients receiving cyclosporine.[209] More recent attempts with signal-averaged electrocardiography,[210]

Table 65–9.

ISHLT Standardized Cardiac Biopsy Grading: Acute Cellular Rejection, 2004*

Grade 0 R†	No rejection
Grade 1 R (Mild)	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
Grade 2 R (Moderate)	Two or more foci of infiltrate with associated myocyte damage
Grade 3 R (Severe)	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis

**The presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required (see Table 65-10).*
†Where R denotes revised grade to avoid confusion with 1990 scheme.
ISHLT = International Society of Heart and Lung Transplantation.
Source: Modified with permission from Stewart et al.[206]

echocardiography,[211] or the combination[212] and magnetic resonance imaging,[213] technetium ventriculography,[214] and a variety of immunologic markers[215] have not provided sufficient sensitivity and specificity to warrant widespread use.[216] Peripheral blood gene expression profiling is an exciting new field that may provide the answer to noninvasive discrimination of rejection in cardiac allograft recipients.[217,218]

Treatment of Acute Rejection

Corticosteroids are the cornerstone for antirejection therapy. The treatment of choice for any rejection episode occurring during the first 1 to 3 postoperative months or for an episode considered to be severe is a short course (3 days) of intravenous methylprednisolone (1000 mg/d). Virtually all other episodes are treated initially with increased doses of oral prednisone (100 mg/d) followed by a taper to baseline over several weeks.[219] Although not yet universally accepted, many centers have reduced the doses of these corticosteroids successfully with reversal rates of rejection similar to traditional dosing.

Repeat endomyocardial biopsy should be performed 7 to 10 days after the cessation of antirejection therapy to assess adequacy of treatment. If the biopsy does not show significant improvement, a second trial of pulse-steroid therapy is recommended; if rejection has progressed (or if the patient becomes hemodynamically unstable), rescue therapy is indicated.

Substitution of tacrolimus for cyclosporine may obviate the need for admission in patients with steroid-refractory persistent rejection.[220] Alternatively, sirolimus may be substituted for mycophenolate or azathioprine.[221] The use of OKT3, antithymocyte globulin, and thymoglobulin generally is reserved for severe rejection with hemodynamic compromise.[222] Methotrexate has been particularly successful in eradicating chronic low-grade rejection.[223,224] Total lymphoid irradiation and photopheresis also have demonstrated success in some cases of refractory rejection.[224] Cardiac retransplantation is the ultimate therapeutic option for patients who do not respond to the aforementioned interventions. However, the results of retransplantation for rejection are dismal, and in most centers, it is no longer performed for this indication.

Asymptomatic mild rejection (grade 1) usually is not treated but is monitored with repeat endomyocardial biopsies because only 20 to 40% of mild cases progress to moderate rejection.[225] On the other hand, the presence of myocyte necrosis (grades 3b and 4) represents a definite threat to allograft viability and is a universally accepted indication for therapy. Management of moderate rejection (grade 3a) is controversial and requires consideration of multiple variables.[226,227] Notably, Stoica and colleagues recently demonstrated that acute moderate to severe cellular rejection has a

Table 65–10.

ISHLT Recommendations for Acute Antibody-Mediated Rejection (AMR), 2004

AMR 0	Negative for acute antibody-mediated rejection No histologic or immunopathologic features of AMR
AMR 1	Positive for AMR Histologic features of AMR Positive immunofluorescence or immunoperoxidase staining for AMR (positive CD68, C4D)

Source: Modified with permission from Stewart et al.[206]

cumulative impact on CAV onset.[228] Regardless of the biopsy results, allograft dysfunction is an indication for hospitalization, antirejection therapy, and if severe, invasive hemodynamic monitoring and inotropic support.

Acute Vascular Rejection

Vascular rejection is mediated by the humoral limb of the immune response.[229] Unlike cellular rejection, hemodynamic instability often necessitating inotropic support is common in cases of vascular rejection.[230] Diagnosis requires evidence of endothelial cell swelling on light microscopy and immunoglobulin-complement deposition by immunofluorescence techniques.[231] Aggressive treatment of patients with allograft dysfunction consists of plasmapheresis, high-dose corticosteroids, heparin, IgG, and cyclophosphamide.[232] Despite these interventions, symptomatic acute vascular rejection is associated with a high mortality.[230,232] Repeated episodes of acute vascular rejection or chronic low-grade vascular rejection are believed to play a dominant role in the development of allograft coronary artery disease.[233]

INFECTIOUS COMPLICATIONS IN HEART TRANSPLANTATION

Organisms and Timing of Infections

Infection is a leading cause of morbidity and mortality in the cardiac transplant population.[17,234] The introduction of new chemoprophylactic regimens and the prevention of serious disease caused by CMV have resulted in significant reductions in the number of infectious episodes and a delay in presentation after heart transplantation.[234,235] Patients are at greatest risk of life-threatening infections in the first 3 months after transplantation and following increases in immunosuppression for acute rejection episodes or retransplantation.[234] Table 65-11 illustrates the most common organisms causing infections in the cardiac recipient.

Preventive Measures and Prophylaxis against Infection

Transmission of infections such as CMV, *Toxoplasma gondii,* HBV, HCV, and HIV after organ transplantation is well documented.[236,237] Prevention of postoperative infection begins with pretransplant screening of the donor and recipient.[238] Current suggested guidelines are outlined in Table 65-12. Perioperative and postoperative antimicrobial prophylaxis, as well as immunizations, are also outlined.

Specific Organisms Causing Infection Following Heart Transplantation

Bacteria

Gram-negative bacilli are the most common cause of bacterial infectious complications following heart transplantation. Furthermore, *Escherichia coli* and *Pseudomonas aeruginosa* are the most prevalent organisms and usually cause urinary tract infections and pneumonias, respectively.[235] *Staphylococcus* species have been shown to cause the majority of gram-positive related infections.

Viruses

CMV remains the single most important cause of infectious disease morbidity and mortality in the heart transplant patient.[239] CMV not only results in infectious disease syndromes but also is indirectly associated with acute rejection episodes, acceleration of CAV, and posttransplant lymphoproliferative disease.[239] Furthermore, the reduction in leukocytes associated with CMV infection predisposes the patient to superinfection with other pathogens (e.g., *Pneumocystis carinii* pneumonia).[240] Infections develop secondary to donor transmission, reactivation of latent recipient infection, or reinfection of a CMV-seropositive patient with a different viral strain.[239] Variable regimens for CMV prophylaxis with ganciclovir are being used by different centers.[241] The standard of care for symptomatic CMV disease is 2 to 3 weeks of intravenous ganciclovir (at a dose of 5 mg/kg twice daily, with dosage adjustment for renal dysfunction). For tissue-invasive disease, particularly pneumonia, many centers add anti-CMV hyperimmune globulin to this regimen.[242] Preemptive treatment strategies employ periodic surveillance using techniques such as plasma polymerase chain reaction (PCR) and CMV antigenemia, a rapid diagnostic test that detects viral protein in peripheral blood leukocytes at a significant interval before clinical disease.[243] Valganciclovir (Valcyte) is an oral prodrug of ganciclovir with a 10-fold greater bioavailability than oral ganciclovir. It has been shown to be effective for prophylaxis and preemptive treatment of CMV and allows for more convenient use.[244,245]

Although not a cure for herpes simplex or zoster viruses, acyclovir can reduce recurrences and the discomfort associated with the vesicular lesions. Epstein-Barr virus infection may be associated with posttransplant lymphoproliferative disorders in immunocompromised hosts.[246]

Fungi

Mucocutaneous candidiasis is common and usually can be treated with topical antifungal agents (nystatin or clotrimazole). Fluconazole is indicated for candidiasis refractory to this therapy or involving the esophagus.[247] It is also useful for therapy of candidemia. One important caveat in the treatment of *Candida* infection with fluconazole is that certain species such as *C. krusei* and *C. glabrata* have a low susceptibility in vitro.[240]

Among patients undergoing heart transplantation, *Aspergillus* is the opportunistic pathogen with the highest attributable mortality.[248] It causes a serious pneumonia in 5 to 10% of recipients during the first 3 months after transplantation. Dissemination of *Aspergillus* to the central nervous system is almost uniformly fatal.[249] Because aspergillosis is highly lethal in the immunocompromised host, even in the

Table 65–11.

Infections in Cardiac Transplant Recipients

Early infections (first month)

I. Pneumonia: Gram negative bacilli (GNB)

II. Mediastinitis and sternal wound infections:
Staphylococcus epidermidis
Staphylococcus aureus
GNB

III. Catheter-associated bacteremia:
S. epidermidis
S. aureus
GNB
Candida albicans

IV. Urinary tract infections:
GNB
Enterococcus
C. albicans

V. Mucocutaneous infections:
Herpes simplex virus (HSV)
Candida spp.

Late infections (after first month)

I. Pneumonia:
A. Diffuse interstitial pneumonia:
Pneumocystis carinii
Cytomegalovirus (CMV)*
HSV
B. Lobar or nodular (cavitary) pneumonia:
Cryptococcus
Aspergillus
Bacteria (community-acquired, nosocomial)
Nocardia asteroides
Mycobacterium spp.

II. Central nervous system infections:
A. Abscess or meningoencephalitis
Aspergillus
*Toxoplasma gondii**
Meningitis
Cryptococcus
Listeria

III. Gastrointestinal (GI) infections:
A. Esophagitis
C. albicans
HSV
B. Diarrhea or lower GI hemorrhage
Aspergillus
Candida spp.

IV. Cutaneous infections:
A. Vesicular lesions
HSV
Varicella-zoster
B. Nodular or ulcerating lesions
Nocardia
Candida (disseminated)
Atypical *Mycobacterium* spp.
Cryptococcus

**Known donor-transmitted pathogens.*

face of therapy, work-up must be prompt and aggressive, and therapy may need to be initiated on suspicion of the diagnosis without definitive proof. Amphotericin B, itraconazole, and recently, voriconazole are acceptable therapy.[250,251]

Protozoa

In heart transplant recipients, the reported incidence of *P. carinii* pneumonia ranges from less than 1% to 10%.[235,252] Since the organism resides in the alveoli, bronchoalveolar lavage usually is necessary for diagnosis.[253] In the case of lung biopsy specimens, histopathologic examination is also helpful. *P. carinii* pneumonia is treated with high-dose trimethoprim-sulfamethoxazole or intravenous pentamidine.[240]

Toxoplasmosis following heart transplantation usually is the result of reactivation of latent disease in the seropositive donor heart because of the predilection of the parasite to invade muscle tissue.[254] *T. gondii* infection may be acquired from undercooked meat and cat feces.[255] The diagnosis is made with certainty only by histologic demonstration of trophozoites with surrounding inflammation in biopsy tissue; PCR also has been used.[256] *T. gondii* usually causes central nervous system infections and is treated with pyrimethamine with sulfadiazine or clindamycin.[240]

CHRONIC COMPLICATIONS FOLLOWING HEART TRANSPLANTATION

Cardiac Allograft Vasculopathy

CAV is a unique, rapidly progressive form of atherosclerosis in transplant recipients that is characterized in its early stages by intimal proliferation and in its later stages by luminal stenosis of epicardial branches, occlusion of smaller arteries,

Table 65–12.

Guidelines for Routine Screening and Prophylaxis of Infections in Heart Transplantation

I. Preoperative Screening
- A. Donor
  1. Clinical assessment
  2. Serologic studies (HIV, HBV, HCV, CMV, *Toxoplasma gondii*)
- B. Recipient
  1. History and physical examination
  2. Serologic studies (HIV, HBV, HCV, CMV, *Toxoplasma gondii*, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, endemic fungi)
  3. PPD (tuberculin) skin test
  4. Urine culture
  5. Stool for ova and parasites (*Strongyloides sterocoralis*; center-specific)

II. Antimicrobial prophylaxis
- A. Perioperative
  1. First-generation cephalosporin (or vancomycin)
- B. Postoperative
  1. Trimethoprim-sulfamethoxazole or pentamidine (for *Pneumocystis carinii*)
  2. Nystatin or clotrimazole (for *Candida* spp)
  3. Ganciclovir followed by acyclovir once dischared (for all patients except CMV-negative recipient and donor)
  4. Acyclovir (for herpes simplex and zoster; routine use is controversial)
  5. Standard endocarditis prophylaxis
- C. Postoperative immunizations
  1. Pneumococcal (booster every 5 to 7 years)
  2. Influenza A (yearly; center-specific)
  3. Exposure to measles, varicella, tetanus, or hepatitis B by a nonimmunized recipient often warrants specific immunoglobulin therapy (e.g., varicella-zoster immune globulin, VZIG)

and myocardial infarction.[257] Long-term survival of cardiac transplant recipients is limited primarily by the development of CAV, the leading cause of death after the first year post-transplantation.[17,37] Angiographically detectable CAV is reported in approximately 40 to 50% of patients by 5 years after transplantation.[258] Although CAV resembles atherosclerosis, there are some important differences that are illustrated in Fig. 65-10.[259] In particular, intimal proliferation is concentric rather than eccentric, and the lesions are diffuse, involving both distal and proximal portions of the coronary tree. Calcification is uncommon, and the elastic lamina remains intact.

The detailed pathogenesis of CAV is unknown, but there are strong indications that immunologic mechanisms that are regulated by nonimmunologic risk factors are the major causes of this phenomenon.[260] The immunologic mechanisms include acute rejection and anti-HLA antibodies, and some of the implicated risk factors relating to the transplant itself or the recipient are donor age, hypertension, hyperlipidemia, and preexisting diabetes. The side effects often associated with immunosuppression with calcineurin inhibitors or corticosteroids, e.g., CMV infection, nephrotoxicity, and new-onset diabetes, after transplantation also play significant roles.[261–265]

It is generally believed that the initiating event of CAV is subclinical endothelial cell injury in the coronary artery of the allograft, which leads to a cascade of immunologic processes involving cytokines, inflammatory mediators, complement activation, and leukocyte adhesion molecules. These changes produce inflammation and, ultimately, thrombosis, smooth muscle cell proliferation, and vessel constriction. The initial endothelial injury may be the result of ischemia-reperfusion damage or the host-versus-graft immune response.[264,265]

CAV may begin within several weeks posttransplantation and progress insidiously at an accelerated rate to complete obliteration of the coronary lumen with allograft failure secondary to ischemia. The clinical diagnosis of CAV is difficult and complicated by allograft denervation resulting in silent myocardial ischemia. Ventricular arrhythmias, congestive heart failure, and sudden death are commonly the initial presentation of significant CAV.[266] An annual coronary angiogram usually is performed for CAV surveillance.[267] Intravascular ultrasound (IVUS) is better equipped to provide important quantitative information regarding vessel wall morphology and the degree of intimal thickening.[268,269]

Since angiography and IVUS are invasive tests, they pose increased risks for patients. Noninvasive tests (e.g.,

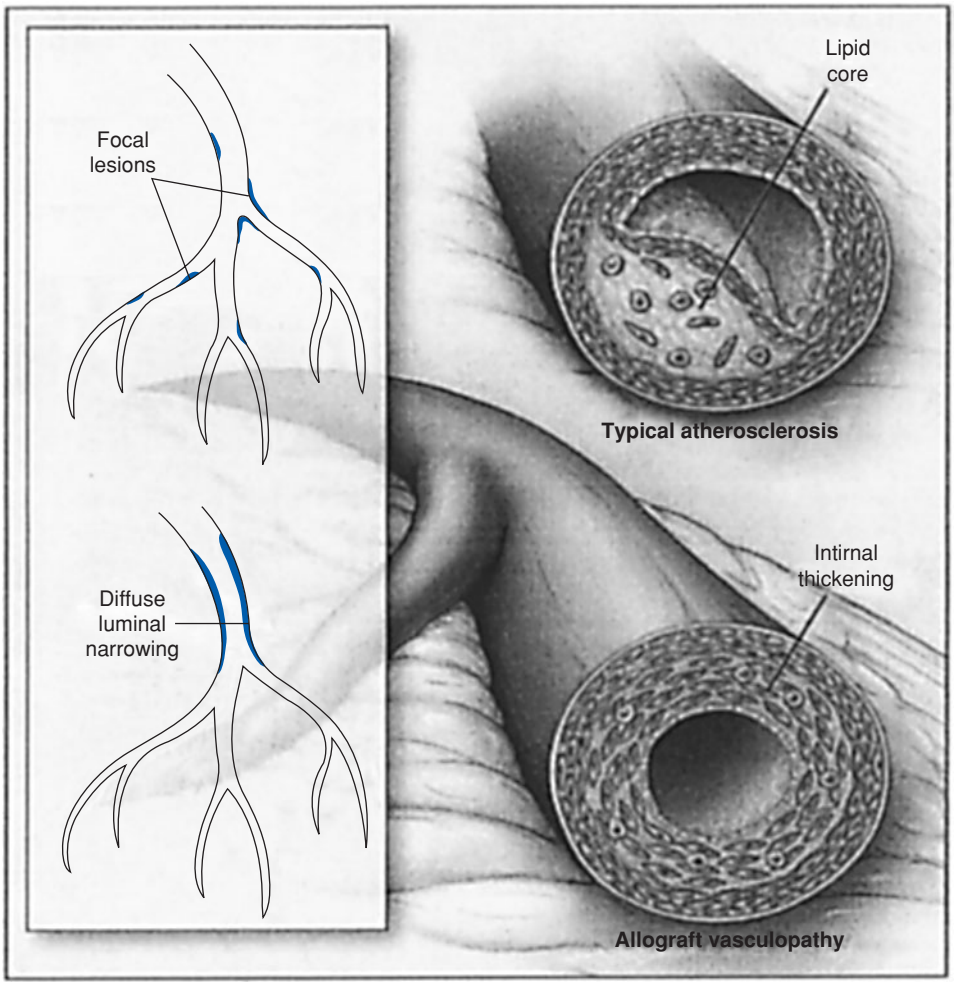

Figure 65-10. Schematic illustration of typical atherosclerosis and cardiac allograft vasculopathy. *(Source: Reprinted with permission from Avery RK.[259])*

thallium scintigraphy and dobutamine stress echocardiography), however, have not been sensitive or specific enough to be a reliable screen for CAV.[270] Other possible modalities include pulse-wave tissue Doppler imaging, electron beam computed tomography (CT), fast CT scanning, and MRI. These modalities may replace invasive procedures in the future.[271]

Currently, the only definitive treatment for advanced CAV is retransplantation, which has risks for the patient and poses problems associated with scarcity of donor organs.[266] Owing to the diffuse and distal nature of the disease, procedures such as stenting and angioplasty are inherently less effective than in nontransplant patients and result in a higher need for repeated procedures.[272] Prophylactic management therefore is of paramount importance. Prior to transplantation, the focus should be on preventing endothelial injury at brain death, reducing cold ischemia time, and improving myocardial preservation during storage and transportation.[266] Postransplantation care focuses on empirical risk factor modification (e.g., dietary and pharmacologic reduction of serum cholesterol, cessation of smoking, hypertension control, etc.). Several studies have demonstrated a decrease in CAV in patients treated with a calcium channel blocker and angiotensin-converting enzyme (ACE) and HMG-CoA reductase inhibitors.[273,274]

Newer immunosuppressive drugs, specifically the proliferation signal inhibitors (e.g., everolimus and sirolimus), may be useful in reducing the incidence and severity of CAV and slowing disease progression.[173–178]

Renal Dysfunction

The 2005 ISHLT registry reported that only 60% of heart transplant recipients are free of severe renal dysfunction (defined as a creatinine concentration of more than 2.5 mg/dL and the need for dialysis or renal transplantation) by Kaplan-Meier estimates at 9.5 years.[17] Furthermore, the risk of death after heart transplantation is markedly increased by the development of end-stage renal failure.[275,276]

Cyclosporine nephrotoxicity after heart transplantation is well recognized and well documented.[277] The improved bioavailability of cyclosporine microemulsion (Neoral) compared with the conventional formulation has led to investigations into monitoring of cyclosporine levels 2 hours after

dosing (C2).[278] Neoral C2 monitoring may be a better indictor of immunosuppression efficacy than trough levels and a better measure to avoid nephrotoxicity and other cyclosporine-associated side effects.[279] Lowering cyclosporine dose may be helpful in slowing the progression of renal disease, especially with concomitant use of newer immunosuppressive regimens such as mycophenolate mofetil and sirolimus (Rapamycin).[280,281] Calcineurin-free immunosuppression is also being implemented by some centers.[282]

Hypertension

Moderate to severe systemic hypertension afflicts 50 to 90% of cardiac transplant recipients.[17,283] Peripheral vasoconstriction in combination with fluid retention seems to play the greatest role. Although the exact mechanisms are unclear, it likely involves a combination of cyclosporine-induced tubular nephrotoxicity and vasoconstriction of renal and systemic arterioles mediated by sympathetic neural activation.[284] Tacrolimus is associated with a lower incidence of hypertension than is cyclosporine.[159] No single class of antihypertensive agents has proven uniformly effective, and treatment of this refractory hypertension remains empirical and difficult. In a prospective, randomized trial, titrated monotherapy with either diltiazem or lisinopril controlled the condition in fewer than 50% of patients.[285] Diuretics should be used cautiously because the balance between edema/hypertension and volume depletion/hypotension can be tenuous in a subset of these patients. Overzealous diuresis can potentiate the apparent nephrotoxicity of cyclosporine by further reducing renal blood flow and altering cyclosporine pharmacokinetics.[286] Beta blockers also should be used with caution because they may further blunt the heart-rate response to exercise.[287]

Malignancy

Chronic immunosuppression is associated with an increased incidence of malignancy ranging from about 4 to 18%, which is 100-fold greater than in the general population.[288] Improved graft and patient survival owing to pharmacologic advances in the area of immunosuppressive therapy has determined an increase in the incidence of neoplasms.[289] Malignant neoplasias have become, along with graft vasculopathy, a significant limiting factor for the long-term survival of heart transplant recipients.[17,139] Lymphoproliferative disorders and carcinoma of the skin are the most common malignancies found in heart transplant recipients.[289–291] Attenuation of T-lymphocyte control over Epstein-Barr virus (EBV)–stimulated B-lymphocyte proliferation appears to be the primary mechanism for the development of lymphoproliferative disorders.[292] The risk of these malignancies is increased further following monoclonal and polyclonal antibody therapy.[193,293] Treatment options in transplantation include a reduction in immunosuppression and high-dose acyclovir (to attenuate EBV replication), in addition to conventional therapies for carcinoma (e.g., chemotherapy, radiation therapy, and surgical resection), which are associated with very high risk and limited success.

Other Chronic Complications

Hyperlipidemia eventually develops in the majority of recipients and is managed with dietary restrictions, exercise, and lipid-lowering agents.[294] Other complications that commonly contribute to posttransplant morbidity include osteoporosis, obesity, cachexia, and gastrointestinal complications, notably cholelithiasis.[295,296]

CARDIAC RETRANSPLANTATION

Retransplantation accounts for fewer than 3% of the cardiac transplants currently performed.[12] Primary indications for retransplantation are early graft failure, allograft coronary artery disease, and refractory acute rejection.[297,298] The operative technique and immunosuppressive regimen are similar to those employed for the initial transplantation. Despite reduced mortality in the cyclosporine era, actuarial survival remains markedly reduced. Analysis of the ISHLT registry for retransplantations performed between 1987 and 1998 reveals survival to be 65%, 59%, and 55% for 1, 2, and 3 years, respectively. Intertransplant interval of 6 months or less was associated with a dismal 1-year survival of 50% in this analysis. Conversely, when the interval between primary and retransplantation was more than 2 years, 1-year survival after retransplantation approached that of primary transplantation.[298] Likewise, in the 2005 registry report, when the subset of recipients in the more recent era between 1996 and 2003 was analyzed, patients undergoing retransplantation at 12 months or more after initial transplantation have 1-year survival rates of approximately 82% (similar to the contemporary cohort of primary transplants at 83%).[17] Advanced donor age also was a predictor of increased mortality among these recipients.[298] These data suggest that although cardiac retransplantation is associated with significant morbidity and mortality, careful selection of patients, especially those who are younger and with longer intertransplant intervals, may be associated with more favorable outcome. Nonetheless, the disparity between the demand and supply for donor hearts makes cardiac retransplantation an ethical issue.[299]

RESULTS OF HEART TRANSPLANTATION

Although no direct comparative trials have been or are likely to be performed, survival following heart transplantation remains favorable if compared with both the medical and device arms of the REMATCH trial.[13,18] The superiority of heart transplantation is more clearly evident in the medium- and high-risk patients with end-stage heart failure.[300] The overall results actually are improving despite increasing risk profiles.[123] Remarkably, transplants performed in 2002 experienced an 18% lower risk of 1-year mortality than those performed in 2000.[17] The reported operative (i.e., 30-day) mortality for cardiac transplantation ranges from 5 to 10%.[301] Overall 1-year survival is up to 85%.[17,123] After the steep fall in survival during the first 6

months, survival decreases at a very linear rate (approximately 3.4% per year), even well beyond 15 years posttransplantation.[17] Graft failure (primary and nonspecific), multiorgan-system failure, and infection account for most deaths within the first 30 days. Infection, graft failure, and acute rejection are the leading causes of death during the first year; thereafter, cardiac allograft vasculopathy and malignancy are the major causes of death.[17,123,302] Studies examining the health-related quality of life (HRQOL) in patients following cardiac transplantation demonstrate marked improvement, particularly in the absence of complications, and approaches the general population by 10 years after transplantation.[303,304]

THE FUTURE

As a result of a series of unprecedented advances over the past decade, the clinical outcome of heart transplantation has improved dramatically. Although cardiac replacement remains the best therapeutic option for patients with end-stage heart failure, a number of challenges await future investigators to further improve survival and reduce transplant-related morbidity. A major factor limiting long-term survival of recipients is allograft rejection and the untoward effects of immunosuppression. Development of reliable, noninvasive diagnostic studies will permit more frequent evaluations for the early detection of rejection and for monitoring the effectiveness of therapy. Ultimately, this will allow more precise control of immunosuppression and, in turn, a reduction in cumulative allograft injury and infectious complications. Molecular tests and gene expression profiling could be available soon and may provide the best noninvasive option.[207,216,217]

Immunosuppressive strategists will continue their efforts to establish specific unresponsiveness to antigens of transplanted organs in hopes of preserving much of the recipient's immune responses. Proliferative signal inhibitors such as sirolimus and everolimus are showing promising results. Alternatively, donor organs may be made less susceptible to immunologic attack through genetic engineering techniques by altering the expression of cell membrane–bound molecules. This approach is being used currently in the pursuit of clinically applicable xenotransplant sources. Xenografts eventually may be an additional source of donor organs, although extended xenograft survival remains an elusive goal.[305] Complicating this alternative are unresolved ethical issues concerning transgenic experimentation and the potential for transmission of veterinary pathogens to an immunosuppressed recipient.

Future improvements in organ preservation permitting extension of the storage interval will have several benefits. In addition to a modest increase in the donor pool, extension of storage times would permit better allocation of organs with respect to donor-recipient immunologic matching. Assist devices are being used currently both as a bridge to transplantation and as a destination therapy. It appears that as the technology of assist devices continues to improve, it is only a matter of time before they become a long-term solution for patients with severe congestive heart failure. Finally, surgical ventricular restoration is gaining increasing application in patients with end-stage heart failure with acceptable results.[306,307]

The concept of regenerating the failing heart using cardiomyocytes of different sources, autologous smooth muscle cells, and dermal fibroblasts is in the experimental stage. Lineage-negative bone marrow cells or bone marrow–derived endothelial precursor cells are also being studied to induce new blood vessel formation after experimental myocardial infarction.[308,309] Cardiac transplantation remains a remarkable achievement of the twentieth century and has revolutionized therapy for end-stage heart failure. Further investigations are needed to overcome the current obstacles to long-term graft function and patient survival.

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CHAPTER 66

Heart-Lung and Lung Transplantation

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The birth and evolution of thoracic organ transplantation have occurred over the past 60 years. With improvement of operative techniques, organ preservation, and immunosuppressive regimens, combined heart-lung and isolated lung transplantation have emerged as life-saving procedures for patients with end-stage cardiopulmonary or pulmonary disease. To date, 3154 combined heart-lung transplants, 10,223 single lung transplants, and 8268 bilateral lung transplants have been reported worldwide.[1] While the number of heart-lung transplants performed annually has declined in recent years, the number of single lung transplantation procedures remains stable, accompanied by a steady increase in bilateral lung transplant procedures. Clinical progress in thoracic organ transplantation has been considerable, yet significant barriers that limit the scope of these procedures still remain. These include donor organ shortage, limited preservation techniques, graft rejection, and infectious complications. This chapter summarizes the state of the art in combined heart-lung and isolated lung transplantation.

HISTORICAL BACKGROUND

History of Heart-Lung Transplantation

Long before the first successful human heart-lung transplants were reported, thoracic organ transplantation flourished in the laboratory. In the 1940s, Demikhov developed the first successful method of en bloc heart-lung transplantation in dogs. In his series of 67 dogs, the longest survivor lived for 6 days postoperatively.[2] These remarkable studies demonstrated the technical feasibility of heart and lung replacement, yet remained largely unknown in the West until the 1960s. In 1953, Marcus and colleagues at the Chicago Medical School described a technique for heterotopic heart-lung grafting to the abdominal aorta and inferior vena cava in dogs (Fig. 66-1).[3] Later studies in the 1960s and early 1970s examined the physiologic effect of total denervation on heart and lung function. Studies by Webb and Howard in 1957 proved discouraging, as they showed failure to resume normal spontaneous respiration following heart-lung replacement in dogs.[4] This physiologic phenomenon was confirmed by several other groups utilizing canine models, including Lower and colleagues in 1961.[5] Fortunately, later studies in primates by Haglin,[6] Nakae,[7] and Castaneda[8,9] and their colleagues showed that unlike dogs, primates resume a normal respiratory pattern following complete denervation with cardiopulmonary replacement. The 1970s saw the development of improved immunosuppressive medications, particularly cyclosporine, which prevented rejection of primate heart-lung allografts after transplantation. Studies from Stanford University showed survival for well over 5 years after heart-lung allografting in primates.[10] In the 1980s, Reitz and colleagues reported a modification to the standard technique of heart-lung replacement, using a retained portion of the right atrium for a single inflow anastomosis instead of separate caval anastomoses (Fig. 66-2).[11] This technique preserved the donor sinoatrial node and eliminated the potential for caval anastomotic stenosis. These studies laid the groundwork for a clinical trial of heart-lung transplantation at Stanford University. On March 9, 1981, Reitz and colleagues performed the first successful human heart-lung transplant in a 45-year-old woman with end-stage primary pulmonary hypertension.[12]

History of Lung Transplantation

Experimental lung transplantation developed in parallel with heart-lung transplantation. In 1949, Henry Metras described important technical concepts, including preservation of the left atrial cuff for the pulmonary venous anastomoses and reimplantation of an aortic patch containing the origin of the bronchial arteries to prevent bronchial dehiscence.[13] Airway dehiscence was a major obstacle in

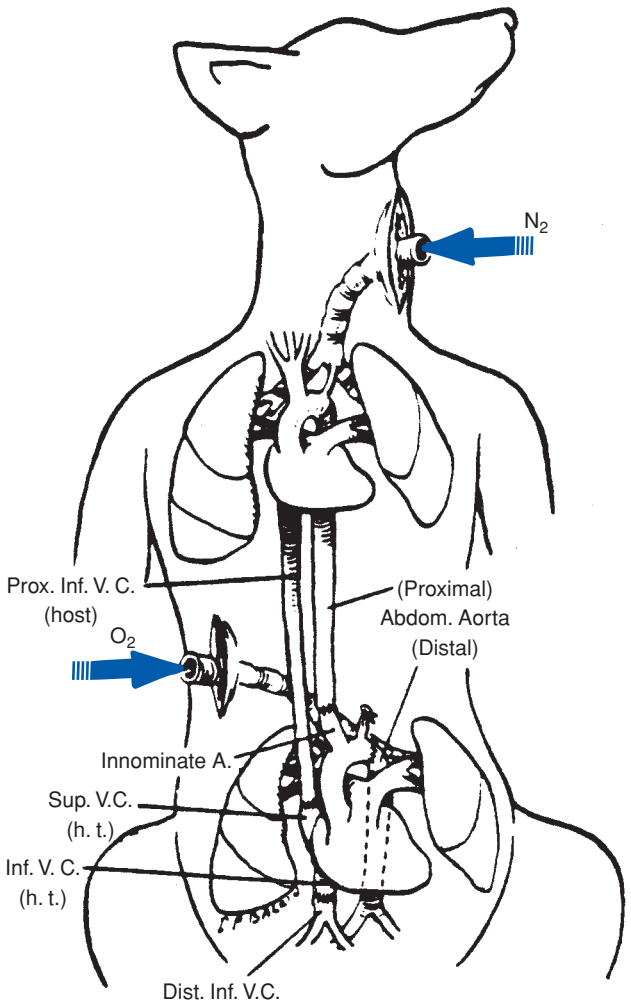


Figure 66-1. Heterotopic heart-lung transplantation in canines as reported by Marcus and associates in 1953. (*From Marcus E, Wong SNT, Luisada AA: Homologous heart grafts. Arch Surg 1953; 66:179. Copyright © 1953, American Medical Association, used with permission.*)

experimental lung transplantation, and he proposed that preservation of the bronchial arterial supply was critical to airway healing. Unfortunately, this technique was technically cumbersome and never gained widespread popularity. In the 1960s, Blumenstock and colleagues advocated transection of the transplant bronchus close to the lung parenchyma to prevent ischemic bronchial necrosis.[14] Additional surgical modifications were developed to prevent bronchial anastomotic complications, including telescoping of the bronchial anastomosis, described by Veith and Richards in 1970,[15] and coverage of the anastomosis with an omental pedicle flap, described by the Toronto group in 1982.[16] Corticosteroids were found to be another contributor to poor bronchial healing,[17] a problem ameliorated by the introduction of cyclosporine immunosuppression. Thus by the 1970s, the stage was set for successful clinical lung transplantation.

The first human lung transplant was described in 1963 by Hardy and colleagues at the University of Mississippi.[18] The patient, a 58-year-old man with lung cancer, survived 18 days postoperatively. Over the next two decades, nearly forty lung transplants were performed without long-term success. In 1986, the Toronto Lung Transplant Group reported the first successful series of single lung transplants with long-term survival.[19] Improved immunosuppression, along with careful recipient and donor selection, were pivotal to their success. For patients with bilateral lung disease, en bloc double lung replacement was introduced by Patterson and associates in 1988.[20] This technique was later replaced by sequential bilateral lung transplantation, described by Pasque and colleagues in 1990.[21] More recent operative innovations include living lobar transplantation, an alternative to cadaveric bilateral lung transplantation.

INDICATIONS AND EVALUATION FOR HEART-LUNG AND LUNG TRANSPLANTATION

Indications for Heart-Lung Transplantation

Upon its introduction in 1982, heart-lung transplantation provided a life-saving therapeutic option for patients with end-stage cardiopulmonary and septic lung disease. Since that time, the techniques of single and double lung transplantation have improved considerably, with fewer indications for combined heart-lung replacement. Moreover, donor organ distribution algorithms, which appropriately distribute donor hearts to critical heart recipients, have also limited the availability of heart-lung blocs.

Heart-lung transplant volumes peaked in the late 1990s, and in 2003 only 74 operations were reported worldwide.[1] The most common indications include congenital heart disease with Eisenmenger syndrome, primary pulmonary hypertension, and cystic fibrosis. The diagnostic profile of heart-lung transplant recipients reported to the Registry of the International Society for Heart & Lung Transplantation (ISHLT) is shown in Fig. 66-3.

Congenital heart disease (atrial and ventricular septal defects and patent ductus arteriosus) with secondary pulmonary hypertension (Eisenmenger syndrome) is the most frequent indication, found in over one-third of patients. Congenital cardiac lesions that may lead to Eisenmenger syndrome include atrial and ventricular septal defects, patent ductus arteriosus, and truncus arteriosus. Other complex congenital heart defects have also been treated successfully with heart-lung transplantation, including univentricular heart with pulmonary atresia, truncus arteriosus, and hypoplastic left heart syndrome.

Data regarding the long-term survival benefit of heart-lung transplantation in patients with Eisenmenger syndrome remain unclear.[22] Some data suggest that pulmonary hypertension in these patients has a more favorable prognostic course than other types of pulmonary hypertension. There is clear evidence, however, that quality of life is improved by transplantation.[23] In patients with simpler cardiac defects,

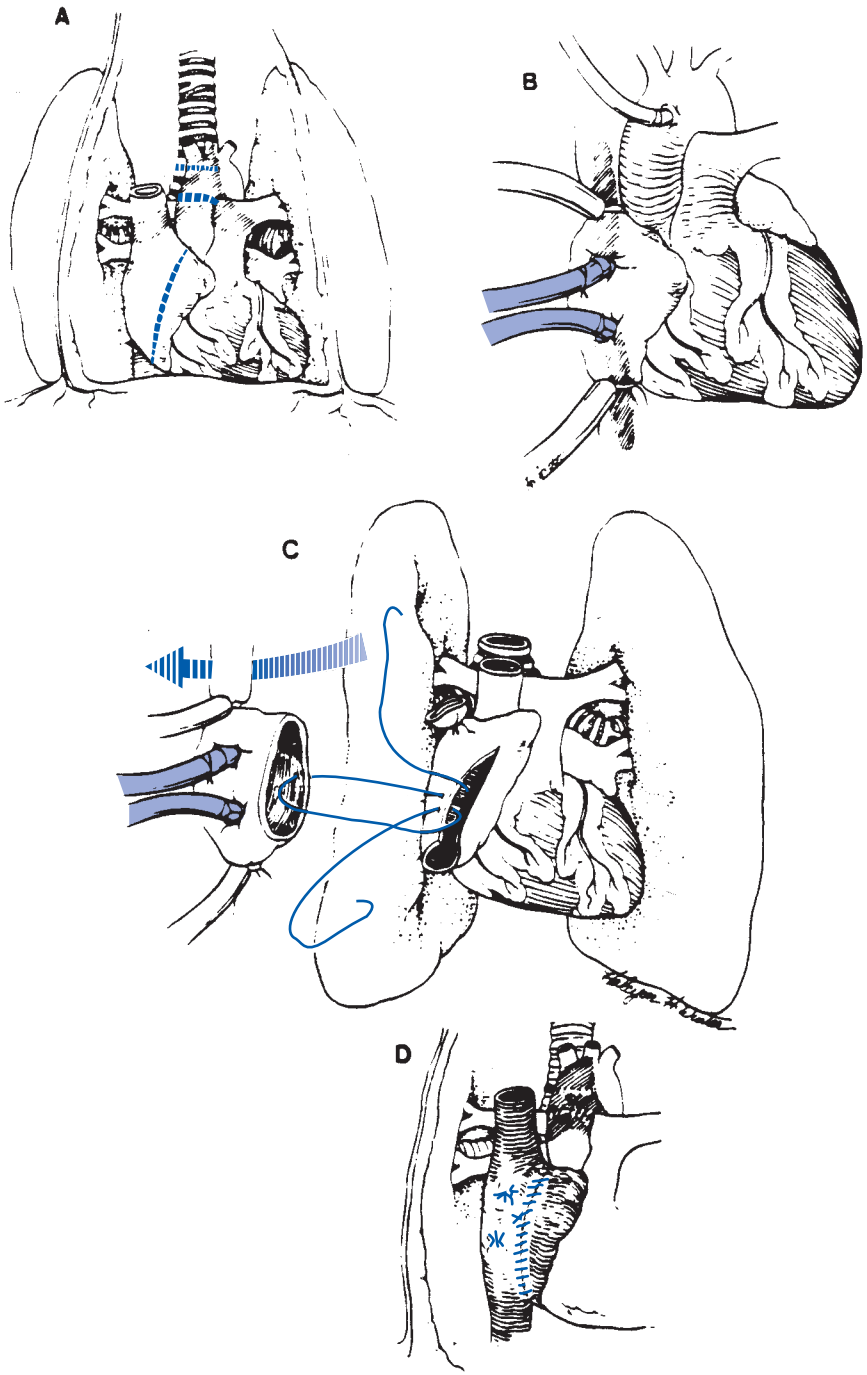


Figure 66-2. Simplified technique for heart-lung transplantation as described by Reitz and colleagues in 1981. (A) Native heart-lung en bloc dissection with preservation of phrenic nerves on pedicles and lines of transection along the right atrium, aorta, and trachea. (B) Cannula configuration for recipient cardiopulmonary bypass with venous cannulas placed in the lower right atrium and arterial cannula in the ascending aorta. (C) Inflow (right atrial) anastomosis. The graft right atrial cuff is constructed by ligating the superior vena cava and opening the right atrium from the inferior vena caval orifice toward the appendage. Note that the right lung is passed behind the vena cava and right phrenic nerve pedicle. (D) Completed transplantation with right atrial, aortic, and tracheal anastomoses shown. (*From Reitz BA, Pennock JL, Shumway NE: Simplified operative method for heart and lung transplantation. J Surg Res 1981; 31:1. Used by permission from Academic Press, Inc.*)

repair of the cardiac defect combined with single or bilateral lung transplantation is an alternative option.

Primary pulmonary hypertension with right-sided heart failure is the second most common diagnosis in heart-lung transplant recipients. Nearly one-quarter of patients in the ISHLT registry carry this diagnosis. Recently there has been a shift toward single and bilateral lung transplantation in this population.[24] This new paradigm is based on the finding that normalization of pulmonary pressures following lung transplantation often allows for recovery of right heart function. However, in patients with severe right-sided heart failure and primary pulmonary hypertension, heart-lung transplantation is clearly the operation of choice.

The balance of heart-lung transplants are performed for a variety of cardiac and pulmonary diseases. These include cystic fibrosis and other septic lung diseases, severe coronary artery disease with intercurrent end-stage lung disease, and primary parenchymal lung disease with severe right-sided heart failure (e.g., idiopathic pulmonary fibrosis, lymphangioleiomyomatosis, sarcoidosis, and desquamative interstitial pneumonitis).

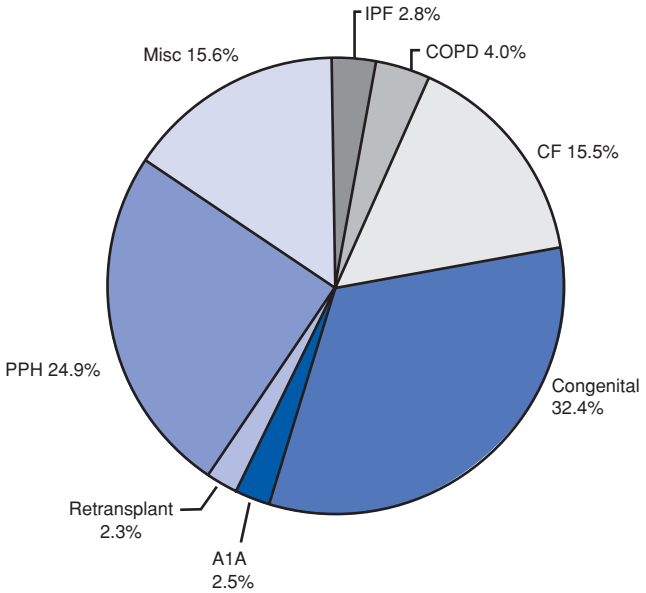


Figure 66-3. Distribution of indications for patients requiring heart-lung transplantation. A1A = alpha$_1$-antitrypsin deficiency; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; Misc = miscellaneous; PPH = primary pulmonary hypertension. (*Adapted from Trulock EP, Edwards LB, Taylor DO, et al: Registry of the International Society for Heart & Lung Transplantation: Twenty-second official adult lung and heart-lung transplant report—2005. J Heart Lung Transplant 2005; 24:956. Used with permission from Elsevier Science.*)

Septic lung disease was a historically significant indication for heart-lung transplantation. The domino procedure, which emerged in the late 1980s, took explanted hearts from these patients and offered them to a second recipient in need of heart transplantation.[25–27] While studies show equivalent survival in recipients of domino heart grafts, the domino procedure is now rarely performed. Instead, bilateral lung transplantation has become the procedure of choice for end-stage septic lung disease.[28,29] Bilateral transplants avoid the pitfalls of cardiac denervation and graft coronary artery disease associated with heart-lung transplantation.

Indications for Lung Transplantation

In recent years, the number of lung transplant procedures performed annually has plateaued. Worldwide, 1703 lung transplants were reported in 2003. In recent years, the number of bilateral lung transplants has surpassed that of single lung transplants, accounting for nearly 55% of all lung transplant procedures. A small number of living lobar transplants are also being performed annually.[1]

The primary indications for single lung transplantation are emphysema and pulmonary fibrosis (Fig. 66-4A). Patients with emphysema comprise over half of single lung transplant recipients. In some cases, hyperinflation of the native emphysematous lung may lead to compressive atelectasis and restriction of the donor lung. This may result in a significant ventilation-perfusion mismatch. In such cases, native lung volume reduction can be used to preserve allograft function.[30] Some evidence demonstrates that late allograft function may be superior in emphysematous patients treated with bilateral rather than single lung transplantation.[31] However, given the donor organ shortage, single lung transplantation remains the preferred therapeutic option.

The principal indications for bilateral lung transplantation are septic lung disease, emphysema, primary pulmonary hypertension, and pulmonary fibrosis (see Fig. 66-4B).[30] While

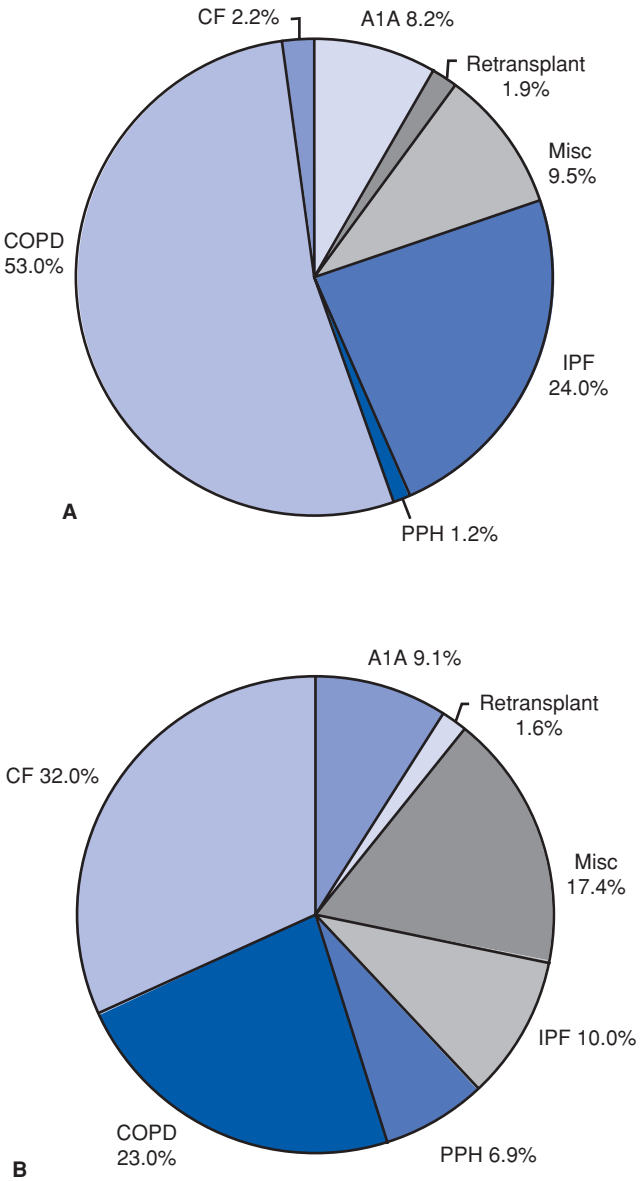


Figure 66-4. Distribution of indications for patients requiring single (A) and bilateral (B) lung transplantation. A1A = alpha$_1$-antitrypsin deficiency; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; Misc = miscellaneous; PPH = primary pulmonary hypertension. (*Adapted from Trulock EP, Edwards LB, Taylor DO, et al: Registry of the International Society for Heart & Lung Transplantation: Twenty-second official adult lung and heart-lung transplant report—2005. J Heart Lung Transplant 2005; 24:956. Used with permission from Elsevier Science.*)

single lung transplantation may be performed for emphysema, primary pulmonary hypertension, and pulmonary fibrosis, it is not an option for septic lung disease. In these patients, bilateral sepsis mandates removal of both native lungs. Primary pulmonary hypertension can be treated with both bilateral and single lung transplants, though most centers advocate bilateral lung transplantation. There is evidence from long-term survivors demonstrating that the effects of bronchiolitis obliterans are better tolerated in bilateral lung transplant recipients. However, in a single-center, retrospective study of 58 patients undergoing either single lung or bilateral lung transplantation for pulmonary hypertension, Gammie and colleagues found equivalent survival at 1 and 4 years.[24] While Gammie's group advocates the preferential application of single lung transplantation in this patient population, this indication will remain controversial until larger clinical trials are conducted.

Less than 2% of all single and bilateral lung transplants are retransplantations.[1] Overall, survival is poor compared to first-time transplantation, though certain subsets of patients perform better than others. In fact, the Pulmonary Retransplant Registry has collected data from 230 patients at over 40 centers and found that 1-year survival of ambulatory, nonventilated patients undergoing retransplantation after 1991 is comparable to that of first-time transplants.[32]

Finally, lobar transplantation is another option for end-stage lung disease. Living lobar transplantation was developed by Starnes and colleagues and has its greatest application in children with cystic fibrosis. The left and right lower lobes from two separate donors are transplanted into the recipient. The procedure is most applicable to children and adults of small stature. In children, lobar transplantation affords improved long-term survival and freedom from bronchiolitis obliterans syndrome compared to cadaveric transplants. In the adult population, however, results have been comparable to those of cadaveric transplants.[33–35]

Recipient Selection Criteria

The primary objective in recipient evaluation is to select individuals with progressively disabling cardiopulmonary or pulmonary disease who still possess the capacity for full rehabilitation after transplantation. Notably, early attempts at thoracic transplantation were thwarted by selection of critically ill recipients, and it was not until the development of strict recipient selection criteria that heart-lung and lung transplantation achieved success.

Candidates should have a projected life expectancy of less than 18 to 24 months despite appropriate medical or alternative surgical strategies. On average, waiting times can range from 6 to 36 months. Unfortunately, mortality while on the waiting list remains nearly 20% for both lung and heart-lung transplant candidates. Therefore it is imperative that recipients be identified as early as possible within the "transplant window."[36]

Disabling symptoms prompting consideration for transplantation typically include dyspnea, cyanosis, syncope, and hemoptysis. Most recipients for heart-lung transplantation also fall within New York Heart Association functional classes III or IV.[37] Potential recipients are identified by their local primary physicians and referred to transplantation centers for further evaluation. This includes a complete history, physical exam, laboratory tests, specialized studies, and a psychosocial evaluation.

Among most heart-lung transplant programs, the upper recipient age limit is 50 years. For bilateral lung transplantation the limit is 55 years, and for single lung transplantation 60 years. These values represent a relaxation of previous age limits, reflecting the ongoing evolution of recipient selection criteria. Unfortunately, the expansion of recipient eligibility further exacerbates the problem of donor organ shortage.

There are well-established contraindications to lung and heart-lung transplantation (Table 66-1). Significant

Table 66–1.

Recipient Contraindications to Heart-Lung and Lung Transplantation

Age >50 years (heart-lung), >55 years (bilateral lung), and >60 years (single lung)
Significant systemic or multisystem disease (e.g., peripheral or cerebrovascular disease, portal hypertension, or poorly controlled diabetes mellitus)
Significant irreversible hepatic or renal dysfunction (e.g., bilirubin >3.0 mg/dL or creatinine clearance <50 mg/mL/min)
Active malignancy
Corticosteroid therapy (>10 mg/d)
Panresistant respiratory flora
Cachexia or obesity (<70% or >130% of ideal body weight)
Current cigarette smoking
Psychiatric illness or history of medical noncompliance
Drug or alcohol abuse
Previous cardiothoracic surgery (considered on a case-by-case basis)
Severe osteoporosis
Prolonged mechanical ventilation
Human immunodeficiency virus infection
Hepatitis B surface antigen positivity
Hepatitis C infection with biopsy-proven liver disease

multisystem disease is a contraindication, though multiorgan transplants have occasionally been performed. Renal dysfunction, active malignancy, infection with human immunodeficiency virus (HIV), hepatitis B antigen positivity, hepatitis C infection with biopsy-proven liver disease, and infection with panresistant respiratory flora are absolute contraindications. Relative contraindications include active extrapulmonary infection, symptomatic osteoporosis, recent history of active peptic ulcer disease, cachexia or obesity, drug or alcohol abuse, and psychiatric illness or history of medical noncompliance. Cigarette smokers must quit smoking and remain abstinent for several months before transplantation. Patients with histories of previous thoracic surgery are evaluated on a case-by-case basis. For patients who require systemic corticosteroids, tapering to the lowest tolerable level, preferably below 10 mg/d, is critical to prevent airway healing complications. Finally, mechanical ventilation is generally considered a contraindication to transplantation; repeated studies have shown that these patients have significantly worse immediate and long-term survival after transplantation.[38] In addition to meeting these criteria, a stable and supportive socioeconomic environment is an important criterion. Recipients should be carefully evaluated by social workers and psychologists. It is important that recipient candidates be educated about lifestyle modifications necessary for the success of a transplant, and willingness to comply with immunosuppression regimens and extensive posttransplant medical and surgical follow-up is a must.

Clinical and Laboratory Criteria for Listing

Tests required for transplant listing are reviewed in Table 66-2. Diagnostic studies that are particularly useful in evaluating potential recipients include full pulmonary function tests, an exercise performance test, electrocardiogram, echocardiogram, 24-hour creatinine clearance, and liver function tests.

Certain patient populations may require additional evaluation. For example, cystic fibrosis recipients should have an otolaryngologic evaluation before being placed on an active waiting list. Most of these patients will require endoscopic maxillary antrostomies for sinus access and monthly antibiotic irrigation to decrease the bacterial load of the upper respiratory tract. This measure has decreased the incidence of serious posttransplant bacterial infections.[39] Former smokers must undergo screening to exclude smoking-related illnesses, such as peripheral vascular disease and malignancy. A negative sputum cytology, thoracic computed tomography scan, bronchoscopy, otolaryngologic evaluation, and carotid duplex scan are required. In addition, left heart catheterization and coronary angiography should be performed in recipient candidates who have a history of smoking.

Patients deemed suitable for transplantation during the initial evaluation are subjected to a final phase of testing (see Table 66-2). If accepted by the transplant review committee, they are listed on the national transplant registry on the basis of clinical urgency, time on the waiting list, ABO

Table 66–2.

Typical Laboratory Tests and Studies Obtained During Recipient Evaluation for Heart-Lung and Lung Transplantation

Suitability for transplantation (phase I)

Required laboratory tests and studies

- Complete blood cell count with differential, platelet, and reticulocyte count
- Blood type and antibody screen (ABO and Rh)
- Prothrombin and activated partial thromboplastin time
- Bleeding time
- Immunology panel (fluorescent antinuclear antibody and RF)
- Electrolytes, including Mg^{2+}
- Creatine kinase with isoenzymes
- Serum protein electrophoresis
- Urinalysis
- Viral serologies
  - Compromised host panel (cytomegalovirus, adenovirus, varicella-zoster, herpes simplex, and Epstein-Barr virus)
  - Hepatitis A, B, and C antibodies and hepatitis B surface antigen
  - Cytomegalovirus (quantitative antibodies and IgM)
  - Human immunodeficiency virus
- Electrocardiogram
- Chest x-ray

Studies obtained as indicated

- Echocardiogram with bubble study
- Multiple-gated acquisition (MUGA) scan for right and left ventricular ejection fraction
- Cardiac catheterization with coronary angiogram
- Thoracic computed tomography scan
- Quantitative ventilation-perfusion scans
- Carotid duplex scan
- Mammogram
- Colonoscopy
- Sputum for Gram stain, acid-fast bacillus smear, potassium hydroxide test, and routine bacterial, mycobacterial, and fungal cultures

Required for listing (phase II)

- Human leukocyte antigen (HLA) and HLA-DR typing
- Transplant antibody
- Quantitative immunoglobulins
- *Histoplasma, Coccidioides,* and *Toxoplasma* titers
- Purified protein derivative tuberculin test
- Pulmonary function tests with arterial blood gases
- 12-Hour urine collection for creatinine clearance and total protein
- Urine viral culture

blood group, and thoracic cage dimensions. Listed candidates should be seen every 3 to 6 months at the transplant center and regularly by their primary physicians in order to maintain optimal medical condition. If appropriate, a period of exercise rehabilitation and nutritional modification may be initiated. Most transplant centers will require patients to reside within several hours of the center by automobile or air charter.

ABO compatibilities are strictly adhered to, because isolated cases of hyperacute rejection have been reported in transplants performed across ABO barriers. Donor-to-recipient lung volume matching is based on the vertical (apex to diaphragm along the midclavicular line) and transverse (level of diaphragmatic dome) radiologic dimensions on chest x-ray, as well as body weight, height, and chest circumference. Matching donor and recipient height seems the most reproducible method for selection of appropriate donor lung size, and donor lung dimensions should not be greater than 4 cm more than those of the recipient. If need be, donor lungs may be downsized by lobectomy.

In a series of 82 heart-lung transplants at Papworth Hospital, Tamm and associates recorded recipient lung volumes posttransplantation followed by a comparison to preoperative and predicted volumes to evaluate the influence of donor lung size and recipient underlying disease.[40] The investigators demonstrated that by 1 year after surgery, total lung capacity and dynamic lung volume returned to values predicted by the patient's sex, age, and height. They proposed that the simplest method of matching donor lung size to that of the recipient is to use their respective predicted total lung capacity values. Moreover, they concluded that recipients should attain their predicted lung volumes by 1 year posttransplantation, and failure to do so suggests possible complications within the transplanted lungs.

In contrast to renal transplantation, human leukocyte antigen (HLA) matching is not a criterion for thoracic organ allocation. Because only short ischemic times are tolerated by lung and heart-lung blocs, it is not possible to perform this tissue typing preoperatively.[41] However, several retrospective studies have been performed evaluating the influence of HLA matching on long-term graft survival and development of obliterative bronchiolitis. Wisser and colleagues examined the relationship between HLA matching and long-term survival in 78 lung transplant recipients, finding improved graft survival with matching at the HLA-B locus.[42] In a retrospective study of 74 lung transplant patients, Iwaki and associates also correlated matching at the HLA-B and HLA-DR loci with improved graft survival.[43] Harjula and coworkers at Stanford evaluated the relationship between HLA matching and outcomes in heart-lung transplantation.[44] Among 40 heart-lung transplant recipients evaluated, they found a significant increase in graded obliterative bronchiolitis with total mismatch at the HLA-A locus. These studies all suggest a relationship between HLA matching and long-term graft function.

Once an appropriate donor-recipient pairing is made, the recipient is screened for preformed antibodies against a panel of random donors. A percent reactive antibody level greater than 25% prompts a prospective specific cross-match between the donor and recipient. A positive cross-match indicates the presence of anti-donor circulating antibodies in the recipient that would likely lead to hyperacute rejection. In the event of a positive cross-match, the donor organ cannot be accepted for that recipient.

RECIPIENT MANAGEMENT AFTER LISTING

It is essential that a candidate's medical condition be optimized prior to heart-lung and lung transplantation. Standard medical measures should be aggressively employed by the patient's local physician, and the patient should have routine follow-up at the transplant center.

Supplemental oxygen is recommended for any patient exhibiting arterial hypoxemia, defined as either an arterial oxygen saturation $<90\%$ or an arterial partial oxygen pressure <60 mm Hg at rest, during exertion, or while asleep.

For patients with heart failure, standard therapeutic measures are applied, including dietary restrictions, diuretics, and vasodilators. Restriction of dietary water and salt combined with diuretic therapy facilitates intravascular fluid management. Particular care must be exercised when using loop diuretics in patients with underlying pulmonary disease. These potent diuretics can result in metabolic alkalosis, thereby depressing the effectiveness of plasma carbon dioxide as a stimulus for breathing. Vasodilators reduce afterload, improve functional capacity, and prolong survival in patients suffering from severe cardiac failure.[45] Commonly used vasodilators include nitrates, hydralazine, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

Although primary pulmonary hypertension may stem from a broad range of etiologies, conventional medical therapy targets the sequelae of pulmonary vascular derangements associated with this disease. In cases of arterial hypoxemia, supplemental oxygen therapy is recommended to prevent hypoxia-induced pulmonary vasoconstriction and secondary erythropoiesis. This eases the burden placed on the right side of the heart and diminishes the likelihood of cardiac arrhythmias. Pulmonary vasodilator therapy is important in the treatment of primary pulmonary hypertension, and includes the use of calcium channel blockers and continuous prostacyclin infusions.[46] As most standard vasodilators have potent systemic effects, careful dosing and follow-up is essential. Approximately 20% of patients with primary pulmonary hypertension will respond to calcium channel blockers. Often a favorable response to short-acting vasodilators during cardiac catheterization is predictive of a successful response to calcium channel blocker therapy. In contrast, response to an acute vasodilator challenge does not always predict the response to long-term prostacyclin infusion.

Interstitial lung disease in patients awaiting transplantation results from a wide variety of diffuse inflammatory processes such as sarcoidosis, asbestosis, and collagen vascular

diseases. Increases in pulmonary vascular resistance leading to right-sided heart failure are thought to arise from interstitial inflammatory infiltrates that entrap and eventually destroy septal arterioles, thus reducing the distensibility of the remaining pulmonary vessels.[47] This process, coupled with closure of peripheral bronchioles, results in arterial hypoxemia, further aggravating pulmonary hypertension. Corticosteroids are the mainstay of treatment in this class of diseases. The adverse effects of steroids on airway healing are well-established[17,48] and mandate significant dose reductions in anticipation of heart-lung and isolated lung transplantation.

The multisystem manifestations of cystic fibrosis, particularly chronic bronchopulmonary infection, malabsorption, malnutrition, and diabetes mellitus, pose difficult management problems in potential transplant recipients. These patients require aggressive chest physiotherapy, antibiotics, enteral or parenteral nutritional supplementation, and tight serum glucose control.[49]

Certain underlying diagnoses are associated with increased rates of pulmonary and systemic thrombosis and embolization. These include patients with dilated cardiomyopathy, congestive heart failure, and primary pulmonary hypertension,[47] and most centers recommend routine prophylactic anticoagulation with heparin, warfarin, or antiplatelet agents.

ORGAN PROCUREMENT AND PRESERVATION

Donor Selection

Standard criteria have been established for donor selection (Table 66-3).[50,51] Donors must have sustained irreversible brain death, but due to the susceptibility of the lungs to edema and infection, particularly in the setting of brain death and trauma, suitable heart-lung and lung blocs are more difficult to obtain than other organs. Less than 20% of organ donors possess lungs suitable for transplantation.

Table 66–3.

Heart-Lung and Lung Donor Selection Criteria

Age <40 years (heart-lung), <50 years (lung)
Smoking history less than 20 pack-years
Arterial partial oxygen pressure of 140 mm Hg on a fraction of inspired oxygen (F_{IO_2}) of 40% or 300 mm Hg on an F_{IO_2} of 100%
Normal chest x-ray
Sputum free of bacteria, fungi, or significant numbers of white blood cells on Gram and fungal staining
Bronchoscopy showing absence of purulent secretions or signs of aspiration
Absence of thoracic trauma
Human immunodeficiency virus negative

Initial donor evaluation consists of a directed history and physical examination, chest x-ray, 12-lead electrocardiogram, arterial blood gases, and serologic screening (including HIV, hepatitis B surface antigen, hepatitis C antibodies, herpes simplex virus, cytomegalovirus [CMV], *Toxoplasma*, and rapid plasma reagin). A donor age of less than 50 is preferred. The chest x-ray should be clear and the arterial partial oxygen pressure (P_{O_2}) should exceed 140 mm Hg on a fraction of inspired oxygen (F_{IO_2}) of 40% or 300 mm Hg on an F_{IO_2} of 100%. Lung compliance can be estimated by measuring peak inspiratory pressures, which should be less than 30 cm H_2O. Bronchoscopy should ensure the absence of purulent secretions or signs of aspiration. Combined heart-lung donors must have no significant cardiac history, be free of coronary atherosclerosis, and possess normal heart function by echocardiography. Coronary angiography may also be indicated in donors with cardiac risk factors. Finally, direct inspection and palpation of the heart and lungs at explantation is an essential part of the donor organ evaluation.

Absolute contraindications to lung and heart-lung donation include prolonged cardiac arrest, arterial hypoxemia, active malignancy (excluding basal cell and squamous cell carcinoma of the skin), and positive HIV status. For heart-lung donation, severe coronary or structural heart disease and prior myocardial infarction are additional contraindications. Relative contraindications to both lung and heart-lung donation include thoracic trauma, sepsis, significant smoking history, prolonged severe hypotension (i.e., less than 60 mm Hg for over 6 hours), hepatitis B surface antigen or hepatitis C antibodies, multiple resuscitation attempts, and a prolonged high inotropic requirement (e.g., dopamine in excess of 15 μg/kg per minute for 24 hours). It is important to rule out correctable metabolic or physiologic causes of cardiac rhythm disturbances and electrocardiographic anomalies (e.g., brain herniation, hypothermia, or hypokalemia).

Over the last decade, there has been a trend toward liberalization of standard donor selection criteria. This strategy, initiated in response to the shortage of donor organs, is employed at a large number of transplant centers.[52–56] Donors ranging from age 50 to 64 have been used in thoracic transplantation, with good long-term graft survival.[55] However, reports from the ISHLT document worse outcomes in recipients of lung allografts from donors over 55 that had ischemic times over 6 to 8 hours.[57] In this group of recipients, long-term survival is impaired and the risk of developing bronchiolitis obliterans is increased. A limitation on smoking history is another criterion that has been liberalized. Conventional guidelines limit smoking history to less than 20 pack-years, but modified criteria allow for a more extensive smoking history, assuming there is no evidence of chronic obstructive pulmonary disease or other lung disease

on screening tests. Other extended criteria include use of lungs from donors whose sputum Gram stains show presence of bacteria. In such cases, treatment with antimicrobials is initiated in the donor and continued post transplantation in the recipient. In general, the presence of fungus in donor sputum samples is a contraindication to donation. Some groups have accepted donors with small pulmonary infiltrates on chest x-ray, though clinical correlation is necessary. Others have selectively used donor lungs in patients with partial arterial oxygen pressure (Pa_{O_2}) less than 300 mm Hg on F_{IO_2} of 100%.

Gabbay and associates in Australia have adopted an aggressive approach to donor management and "organ resuscitation."[53] By manipulating donors with antibiotic therapy, chest physiotherapy, careful fluid management, ventilator adjustments, and pulmonary toilet, 34% of donors with an initial Pa_{O_2} less than 300 mm Hg on F_{IO_2} of 100% had increases in their Pa_{O_2}, becoming acceptable donors.

Areas of investigation in the field of donor organ procurement include the use of non-heart-beating donors. In 2001, Steen and colleagues reported transplantation of lungs from a non-heart-beating donor into a 54-year-old woman with chronic obstructive pulmonary disease,[58] with good functional results during the first 5 months of follow-up. However, ethical, logistic, and scientific questions remain on the use of non-heart-beating donors, and this strategy is far from being widely applicable.

It is essential that each donor be evaluated on a case-by-case basis. While certain selection criteria remain absolute, others must be considered in the context of the individual donor and recipient. Moreover, as knowledge in the field of thoracic transplantation grows, selection criteria will likely require further modification.

Donor Management

The overriding goal in managing the thoracic organ donor is to maintain hemodynamic stability and pulmonary function. Patients suffering from acute brain injury are often hemodynamically unstable due to neurogenic shock, excessive fluid losses, and bradycardia. Donor lungs are prone to neurogenic pulmonary edema, aspiration, nosocomial infection, and contusion. Continuous arterial and central venous pressure monitoring, judicious fluid resuscitation, vasopressors, and inotropes are usually required.

Meticulous fluid management prevents intraoperative blood pressure instability and minimizes the need for inotropes and vasopressors that stress the myocardium. Intravascular volume replacement should be given to maintain the central venous pressure between 5 and 8 mm Hg, though fluids should not be administered at rates that far exceed hourly urine output. In general, crystalloid fluid boluses are to be avoided. Diabetes insipidus is common in donors and requires the use of intravenous vasopressin (0.8 to 1.0 U/h) to prevent excessive urine loss.

Dopamine is the standard inotropic agent used to maintain adequate perfusion pressures, although alpha agonists (e.g., phenylephrine) are often appropriate. Blood transfusions should be used sparingly to maintain a hemoglobin concentration of approximately 10 g/dL, ensuring adequate myocardial oxygen delivery. CMV-negative and leukocyte-filtered blood should be used whenever possible. Hypothermia should be avoided, as it predisposes to ventricular arrhythmias and metabolic acidosis.

With regard to mechanical ventilation, F_{IO_2} values in excess of 40%, especially 100% oxygen "challenges," should be avoided, since these oxygen levels may be toxic to the denervated lung. Ventilator settings should include positive end-expiratory pressure (PEEP) between 3 and 5 cm H_2O to prevent atelectasis.

Donor Operation

The donor operation is performed via a median sternotomy (Fig. 66-5A). After the sternum is divided, a standard chest retractor is placed, and both pleural spaces are opened followed by immediate inspection of the lungs and pleural spaces, particularly in cases involving trauma. The lungs are briefly deflated, and the pulmonary ligaments are divided inferiorly using electrocautery. After completely excising the thymic remnant, the pericardium is opened vertically and laterally on the diaphragm and cradled during dissection of the great vessels and trachea. The ascending aorta, pulmonary artery, and venae cavae are dissected. Umbilical tapes are placed around the ascending aorta and venae cavae (Fig. 66-5B). The pericardium overlying the trachea is incised vertically, and the trachea is encircled with an umbilical tape between the aorta and superior vena cava at the highest point possible and at least four rings above the carina (see Fig. 66-5B). The entire anterior pericardium is excised back to each hilum (Fig. 66-5C).

Approximately 15 minutes prior to applying the aortic cross-clamp, prostaglandin E_1 (PGE_1) is infused intravenously, initially at a rate of 20 ng/kg per minute, followed by incremental increases of 10 ng/kg per minute to a target rate of 100 ng/kg per minute (Fig. 66-5D). During PGE_1 infusion, the mean arterial blood pressure should be maintained at or above 55 mm Hg. Ventilation is continued with an F_{IO_2} of 40% and a PEEP of 3 to 5 cm H_2O. The donor is heparinized. The superior vena cava is ligated and a straight Potts clamp is placed across the inferior vena cava. After the heart is allowed to empty, the aortic cross-clamp is applied, and 10 mL/kg of cold crystalloid cardioplegia, commonly the Stanford formulation, is rapidly infused into the aortic root. The inferior vena cava is incised, and the left atrial appendage is amputated to avoid cardiac distension. While the antegrade cardioplegia is being delivered, Perfadex (Vitrolife Inc., Englewood, Colo) is rapidly flushed into the main pulmonary artery at a rate of 15 mL/kg per minute for 4 minutes. Ice-cold saline or Physiosol solution (Abbott Laboratories, North Chicago, Ill) is immediately poured over the heart and lungs. During the cardioplegic and Perfadex infusions, ventilation is maintained with half-normal tidal volumes of room air. Upon completion of the infusions and

topical cold application, all solutions are aspirated from the thoracic cavity and the lungs are fully deflated.

For combined heart-lung blocs, the bloc is dissected free from the esophagus commencing at the level of the diaphragm and continuing cephalad to the level of the carina. Dissection is kept close to the esophagus, and care is taken to avoid injury to the trachea, lung, or great vessels. The posterior hilar attachments are divided. The lungs are inflated to a full normal tidal volume, and the trachea is stapled at the highest point possible with a TA-55 stapler (U.S. Surgical, Norwalk, Conn), at least four rings above the carina (Fig. 66-5E). The trachea is then divided above the staple line, and the entire heart-lung bloc is removed from the chest.

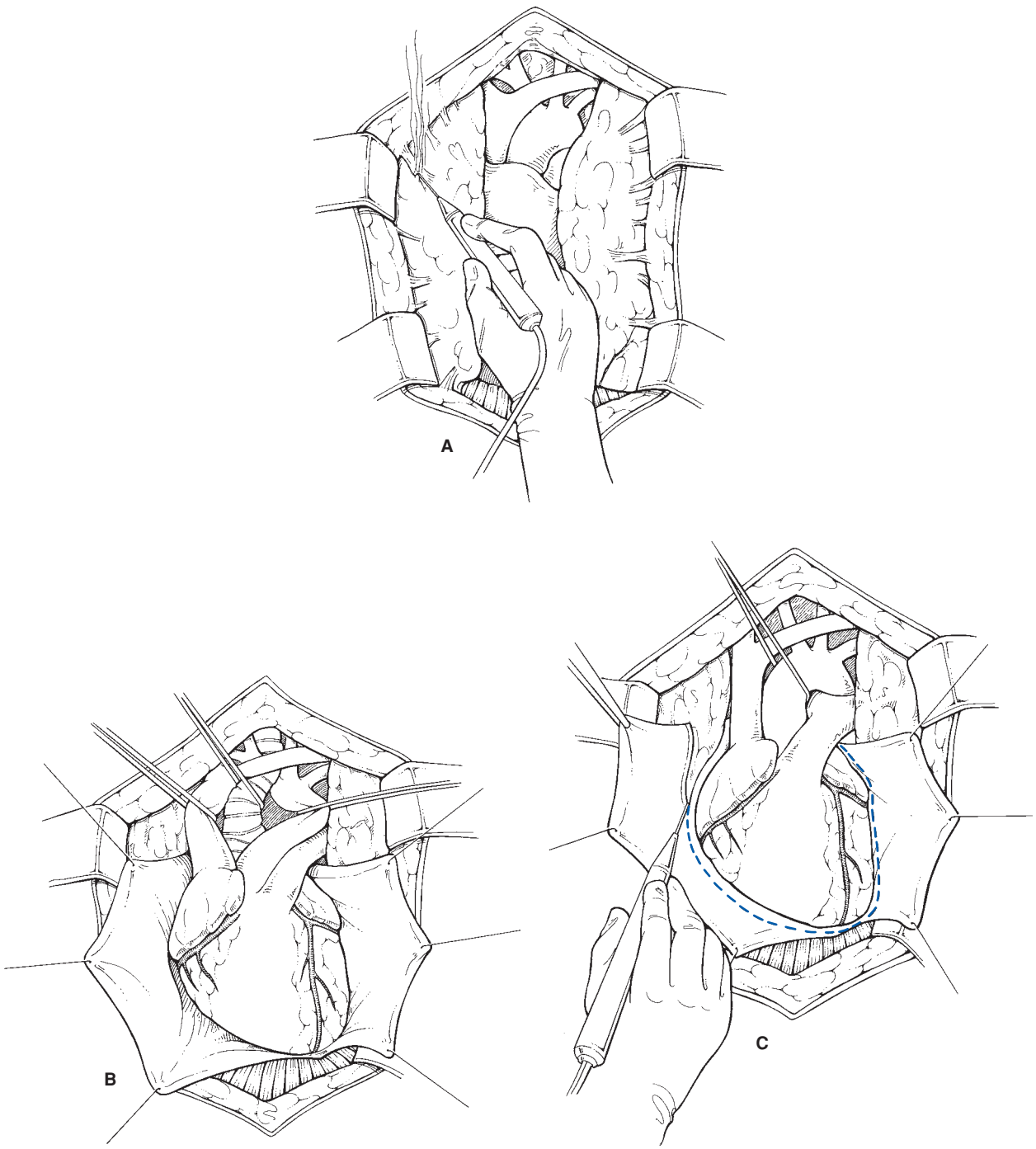
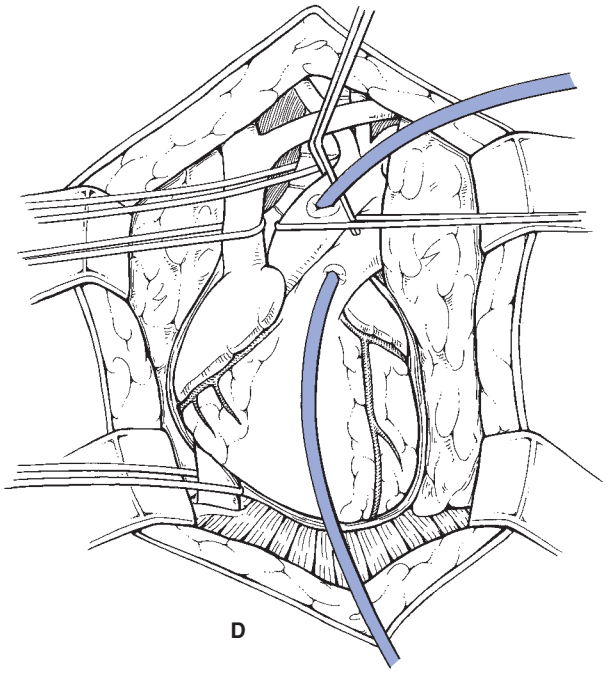


Figure 66-5. Donor operation for heart-lung transplantation. (A) Through a median sternotomy, adhesions are lysed and the pulmonary ligaments are divided inferiorly. (B) The pericardium is opened and cradled followed by dissection of the ascending aorta, venae cavae, pulmonary artery, and trachea. (C) The entire anterior pericardium is excised back to each hilum.



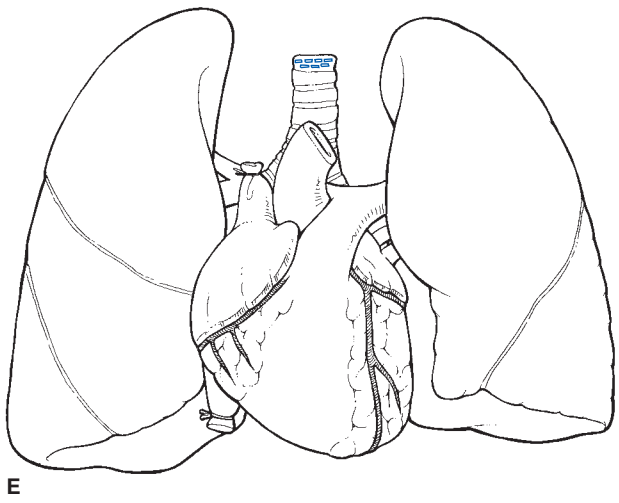


Figure 66-5. (*Continued*) (D) Cardioplegia and pulmonoplegia are infused simultaneously into the aorta and main pulmonary artery after aortic cross-clamping. Application of topical cold Physiosol follows immediately. (E) The venae cavae and aorta are divided, and the heart-lung bloc is dissected free from the esophagus and posterior hilar attachments. After the trachea is stapled and divided at the highest point possible, the entire heart-lung bloc is removed from the chest.

For separate heart and lung blocs, the donor operation is modified slightly, allowing for in situ separation of the heart from the lungs. After delivery of plegic solutions, the great vessels are divided. The heart is reflected anteriorly and a left atriotomy is performed, leaving a 2-cm cuff of atrium around the pulmonary vein orifices. Once this division is complete, the heart is removed from the chest. The lung bloc is then dissected free along the pre-esophageal plane above the level of the carina. The lungs are inflated and the trachea is stapled at the highest possible point. If needed, the bilateral lung bloc can be further separated into left and right lung blocs. The left atrial cuff containing the orifices of the pulmonary veins is divided in half vertically. The left and right pulmonary arteries are divided at their junction. Finally, the left main stem bronchus is stapled near its junction with the trachea.

Once removed from the donor, grafts are wrapped in sterile gauze pads and immersed in ice-cold saline at 2 to 4°C in several sterile plastic bags placed within a sterile plastic container. This, in turn, is placed in an ice-filled chest and transported to the transplant center.

Organ Preservation and Transport

On-site lung procurement was considered essential between 1981 and 1984 due to inadequate lung preservation techniques.[59] Since then, research and clinical experience have resulted in several different preservation protocols permitting distant procurement. Most centers currently tolerate a maximum of 6 to 8 hours of ischemia in lung and heart-lung allografts. This practice is supported by several studies, including independent retrospective studies from the University of Pittsburgh[60] and the University of Virginia,[61] showing comparable long-term survival, rate of acute rejection, and incidence of bronchiolitis obliterans among recipients of grafts with over 6 hours of ischemia compared with those with <4 or 4 to 6 hours of ischemia. In animal studies, successful transplantation of lung allografts with cold ischemia times of up to 18 hours have been reported. Despite such experimental observations, it is believed that beyond a certain threshold, organ ischemia will likely lead to primary graft failure and/or impaired long-term function.

The principal goal of preservation is to minimize injury to the allograft from ischemia and reperfusion.[62] Ischemia-reperfusion injury is mediated by reactive oxygen species, which disrupt the homeostatic mechanisms in myocytes and endothelial cells. As receptors for leukocyte adhesion molecules are upregulated and leukocyte chemotactic factors released, an inflammatory response ensues, leading to cellular injury. Several approaches for minimizing ischemia-reperfusion injury have been developed, including donor pretreatment, use of specialized preservation solutions, and recipient treatments.

Hypothermia is considered by many to be the most important method of organ preservation. It works by reducing tissue metabolic demand by up to 99%. In a small number of centers, hypothermic preservation includes donor core cooling on cardiopulmonary bypass (CPB). Universally, hypothermia is employed during explantation, storage, and

implantation. During explantation, organs are flushed with cold plegic solutions (between 0 and 10°C, depending on the institution and solution employed). Organs are stored at 0 to 10°C, and during implantation they are covered with gauze soaked in saline slush or recipients are cooled through CPB. The optimal temperature for flush and storage of organs remains unknown, but common practice is to rely on the temperature of the ice bath for convenience.

Heart-lung and lung blocs are typically preserved with a cold pulmonary artery flush in conjunction with standard crystalloid cardioplegic arrest. A variety of crystalloid flush solutions are used worldwide, and they can be divided into two categories based on their electrolyte compositions: intracellular and extracellular. Intracellular solutions contain moderate to high concentrations of potassium and little calcium and sodium; Euro-Collins, University of Wisconsin, and Cardiosol are examples. Extracellular solutions contain high concentrations of sodium and low to moderate concentrations of potassium; low-potassium dextran solution is an example (e.g., Perfadex). While Euro-Collins is the most frequently used preservation solution, there is a growing body of evidence in support of low-potassium, dextran-containing extracellular solutions.[63–65] Several centers, including our own, have now moved to using such solutions, but further studies are required to definitively determine the optimal composition of preservation solution.

Prostaglandins are commonly used for donor pretreatment and as an additive in pulmonary flush solutions. The administration of PGE_1 (a potent vasodilator) counteracts reflex pulmonary vasoconstriction induced by the cold flush and permits uniform distribution of perfusate throughout the lung. Studies in large animals also suggest that PGE_1 treatment may minimize reperfusion injury through its anti-inflammatory properties.[66]

Another commonly used pretreatment strategy is steroid treatment. Administration of intravenous methylprednisolone to the donor inactivates lymphocytes, which are thought to mediate ischemic lung graft injury.

Studies suggest that lung graft function is improved when the explanted organ is inflated, 100% oxygen is used for the inflation, and transport is carried out at 10°C.[67] Research in the field of lung preservation has recently focused on the role of various flush and storage solution additives, such as antioxidants, which may act as free radical scavengers. Other additives shown to decrease reperfusion injury in research models include nitric oxide donors and phosphodiesterase inhibitors. Areas of ongoing research include the development of leukocyte depletion strategies, examining the role of gene therapy to modify donor organ susceptibility to ischemia-reperfusion injury, and the development of colloid-based perfusates.

These preservation techniques, coupled with streamlined donor and recipient protocols, have permitted procurements as far as 1000 miles from the transplant center. Extensive communication and coordination must be maintained between the organ procurement agency, donor-recipient operative teams, medical centers, and abdominal procurement teams. Worldwide, the major procurement agencies include the United Network for Organ Sharing in the United States, Multiple Organ Retrieval in Canada, and the EURO Transplant Organization in Europe.

RECIPIENT OPERATION

The recipient operation in heart-lung and lung transplantation proceeds in two phases. The first is excision of the native organ(s) and the second is implantation of the allograft. Cardiopulmonary bypass is mandatory for heart-lung transplantation and occasionally required for single and bilateral lung transplantation. Regardless, CPB should be available as standby at all times. At Stanford, we have favored the use of CPB during bilateral lung transplantation for a variety of reasons. There is improved exposure of the hilar structures, which is particularly helpful in patients with dense adhesions and bronchial collaterals. CPB allows for early pneumonectomies without hemodynamic or respiratory instability, and ischemic time of the second lung is substantially reduced compared to off-CPB bilateral lung transplants. Its use also prevents overperfusion of the first lung graft with the entire cardiac output. In patients with suppurative lung disease, the use of CPB facilitates careful washout of the distal trachea and proximal bronchi to prevent contamination of the first implanted lung. Others prefer to avoid CPB, as it may be associated with increased blood loss, transfusion needs, and reperfusion injury. More detailed experimental and clinical studies are needed to resolve these questions. At present, the need for CBP should be determined on a case-by-case basis.

Anesthetic monitoring includes arterial pressure monitoring, pulse oximetry, continuous electrocardiography, pulmonary artery catheter monitoring, temperature monitoring, and urine output monitoring. The use of double-lumen endotracheal tubes is particularly helpful, allowing for single lung ventilation during certain portions of the dissection. Large-bore intravenous lines are placed for volume infusion. Transesophageal echocardiography is often performed during the procedure.

Heart-Lung Transplantation

The recipient is positioned supine and the chest is entered through a median sternotomy. A sternal retractor is placed, and both pleural spaces are opened anteriorly from the level of the diaphragm to the level of the great vessels (Fig. 66-6A). Electrocautery is used to divide any pleural adhesions. If dense pleural adhesions are anticipated (due to previous thoracotomies or cystic fibrosis, for example), a bilateral "clamshell" thoracotomy is performed. Combined with the use of perioperative antifibrinolytic therapy (e.g., aprotinin) and an argon beam coagulator, this approach improves exposure and facilitates both lysis of adhesions and hemostasis.

The anterior pericardium is excised, and the lateral segments are preserved to support the heart and protect the phrenic nerves. A 3-cm border of the pericardium should be left both anterior and posterior to each phrenic nerve extending from the level of the diaphragm to the level of the

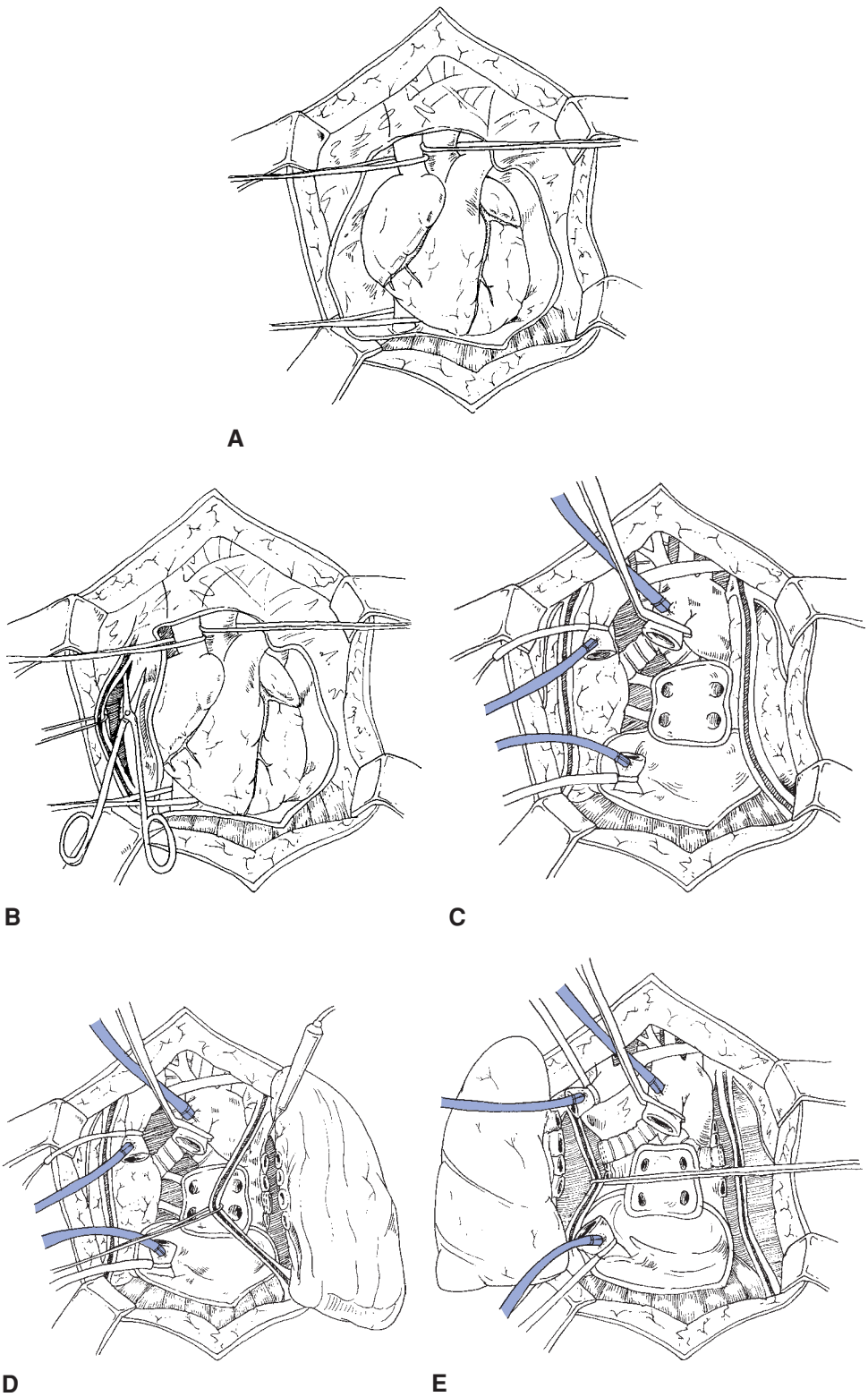


Figure 66-6. Recipient operation for heart-lung transplantation. (A) Through a median sternotomy, the anterior pericardium is partially removed and the ascending aorta and both venae cavae are dissected and encircled with tapes. (B) The right phrenic nerve is carefully separated from the right hilum, providing a space for inserting the right lung of the graft. (C) Cannulation for cardiopulmonary bypass consists of a cannula in the high ascending aorta and separate vena caval cannulas. Once on bypass, the native heart is excised in a manner similar to that for standard cardiac explantation. (D, E) Left and right pneumonectomies are performed by dividing the respective inferior pulmonary ligament, pulmonary artery and veins, and main stem bronchus.

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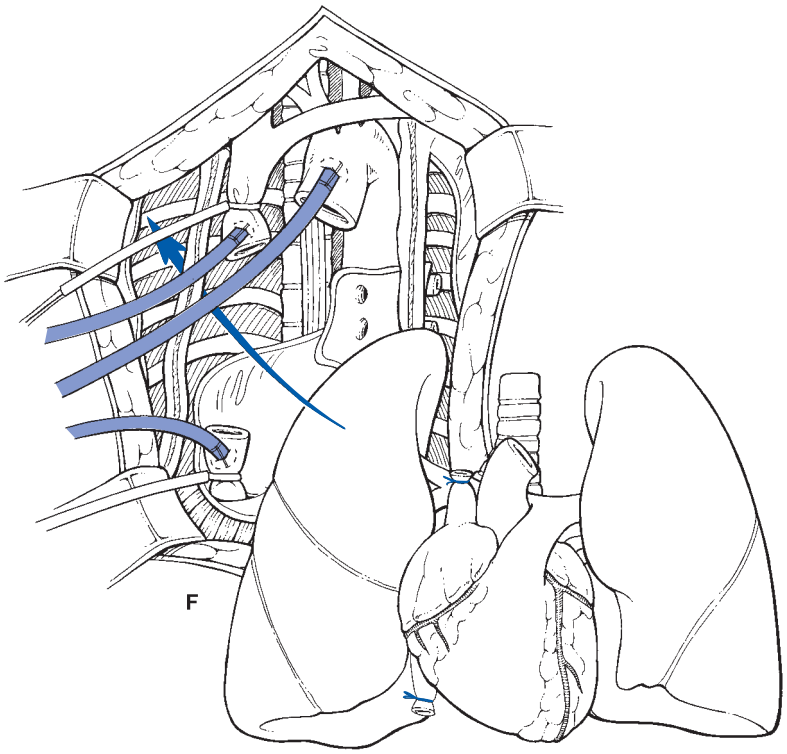


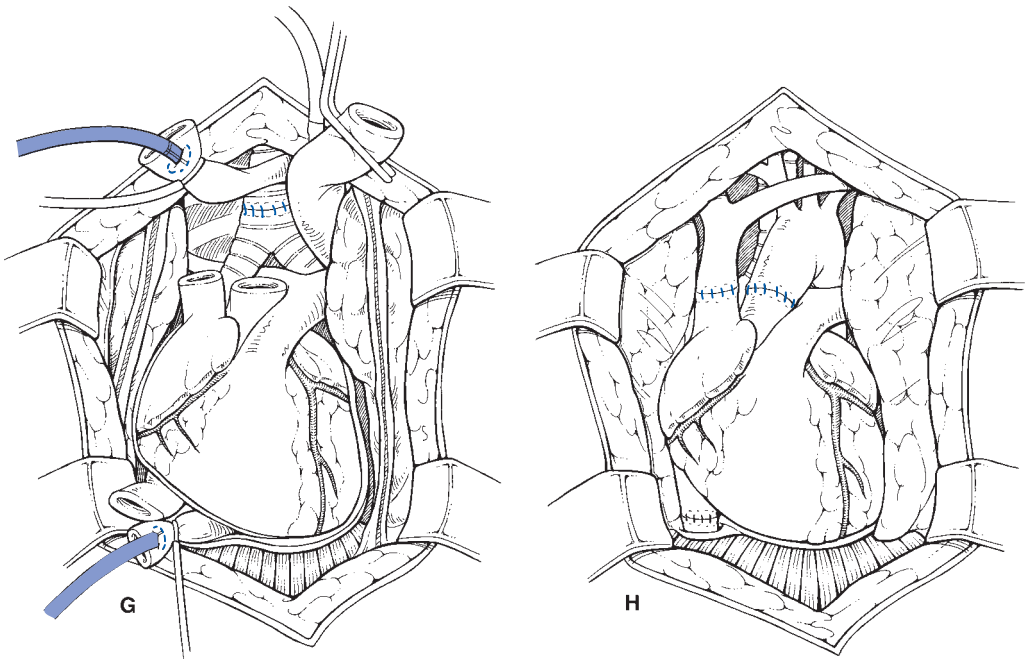


Figure 66-6. (*Continued*) (F) The heart-lung graft is moved into the chest, beginning with passage of the right lung underneath the right phrenic nerve pedicle, followed by manipulation of the left lung beneath the left phrenic nerve pedicle. (G) The tracheal anastomosis is performed with a continuous 3-0 polypropylene suture. (H) The caval and aortic anastomoses are performed with a continuous 4-0 polypropylene suture.

great vessels (Fig. 66-6B). An alternative approach is to create posterior pericardial apertures where the pulmonary veins enter into the pericardium. A border of pericardium is left posterior to the phrenic nerves, while the entire remaining pericardium anterior to the phrenic nerves is left intact.

After fully heparinizing the recipient, the ascending aorta is cannulated near the base of the innominate artery, and the venae cavae are individually cannulated laterally and snared. Cardiopulmonary bypass with systemic cooling to 28 to 30°C is instituted, and the heart is excised at the midatrial

level. The aorta is divided just above the aortic valve, and the pulmonary artery is divided at its bifurcation (Fig. 66-6C). The left atrial remnant is then divided vertically at a point halfway between the right and left pulmonary veins.

The posterior edge of the left atrial and pulmonary venous remnant is developed in a manner allowing the left inferior and superior pulmonary veins to be displaced over into the left chest. Following division of the pulmonary ligament, the left lung is moved into the field, allowing full dissection of the posterior aspect of the left hilum, with care taken to avoid the vagus nerve posteriorly. Once this is completed, the left main pulmonary artery is divided (Fig. 66-6D), and the left main bronchus is stapled with a TA-30 stapler and divided. The same technique of hilar dissection and division is repeated on the right side (Fig. 66-6E), and both lungs are removed from the chest.

The native main pulmonary artery remnant is removed, leaving a portion of the pulmonary artery intact adjacent to the underside of the aorta (near the ligamentum arteriosus) to preserve the left recurrent laryngeal nerve. Attention is then turned to preparing the distal trachea for anastomosis. The stapled ends of the right and left bronchi are grasped and dissection is carried up to the level of the distal trachea. Bronchial vessels are individually identified and carefully ligated. Patients with congenital heart disease and pulmonary atresia or severe cyanosis secondary to Eisenmenger syndrome may have large mediastinal bronchial collaterals that must be meticulously ligated. Perfect hemostasis is necessary in this area of the dissection, because it is obscured once graft implantation is complete. Once absolute hemostasis is achieved, the trachea is divided at the carina with a no. 15 blade. The chest is now prepared to receive the heart-lung graft.

The donor heart-lung bloc is removed from its transport container and prepared by irrigating, aspirating, and culturing the tracheobronchial tree, followed by trimming of the trachea to leave one cartilaginous ring above the carina. The heart-lung graft is then lowered into the chest, passing the right lung beneath the right phrenic nerve pedicle. The left lung is then gently manipulated under the left phrenic nerve pedicle (Fig. 66-6F). The tracheal anastomosis is performed using continuous 3-0 polypropylene suture (Fig. 66-6G). The posterior membranous portion of the anastomosis is performed first, followed by completion of the anterior aspect. Ventilation is then carried out with room air at half-normal tidal volumes to inflate the lungs and reduce atelectasis. Topical cooling with a continuous infusion of cold Physiosol into both thoraces is begun. To augment endomyocardial cooling and to exclude air from the graft, a third cold, "bubble-free" line is placed directly into the left atrial appendage.

Next, the bicaval venous anastomosis is performed. The recipient inferior vena cava is anastomosed to the donor inferior vena cava–right atrial junction with a continuous 4-0 polypropylene suture. At this point the patient is warmed toward 37°C, and the superior vena caval and aortic anastomoses are performed end to end with continuous 4-0 polypropylene sutures (Fig. 66-6H). After the ascending aorta and pulmonary artery are cleared of air, the aortic cross-clamp and caval tapes are removed. The left atrial catheter is removed, and the atrium is allowed to drain. The amputated left atrial stump is oversewn, and the pulmonary artery pulmonoplegia infusion site closed. The heart is defibrillated, and the patient is gradually weaned from cardiopulmonary bypass in the standard fashion. Methylprednisolone (500 mg) is administered to the recipient following heparin reversal with protamine sulfate.

PEEP at 3 to 5 cm H_2O and an F_{IO_2} of 40% is maintained. As in cardiac transplantation, isoproterenol (0.005 to 0.01 μg/kg per minute) is usually initiated on graft reperfusion to increase the heart rate (~100 to 110 bpm) and to lower pulmonary vascular resistance. Temporary right atrial and ventricular pacing wires are placed. Right and left pleural "right angle" chest tubes are placed along each diaphragm, as well as a single mediastinal tube. The chest is closed in the standard fashion. Finally, the double-lumen endotracheal tube is exchanged for a single-lumen tube and the tracheal anastomosis is visualized by bronchoscopy before transporting the patient to the intensive care unit.

Lick and associates describe an interesting alternative to the standard technique in which the pulmonary hila are placed anterior to the phrenic nerves and direct caval anastomoses are used whenever feasible.[68] This modification obviates extensive dissection of the phrenic nerves and posterior mediastinum, decreasing the likelihood of phrenic and vagus nerve injury. Furthermore, the posterior mediastinum can readily be inspected for bleeding after implantation by rotating the heart-lung bloc anteromedially while still on bypass.

Single Lung Transplantation

If possible, the poorer-functioning lung (as determined by preoperative ventilation-perfusion scan) is selected for replacement. The patient is placed in a standard thoracotomy position with access to the groin should CPB be needed. A posterolateral thoracotomy is made at the level of the fourth or fifth intercostal space. Adhesions are lysed and the hilar dissection performed. The pulmonary artery, the superior and inferior pulmonary veins, and the main stem bronchus are isolated. A trial occlusion of the pulmonary artery is used to determine whether the procedure can be conducted without CPB. If the occlusion is tolerated, the pulmonary artery is ligated and divided distal to the upper lobe branch. The pulmonary veins are also ligated and divided. The main stem bronchus is stapled and divided, and the native lung is explanted.

The donor lung is removed from its transport container and prepared for implantation. The donor bronchus is opened and secretions are aspirated and cultured. The bronchus is trimmed, leaving two cartilaginous rings proximal to the orifice of the upper lobe. Any remaining pericardial and lymphatic tissue is removed, and the left atrial cuff is trimmed as needed. The donor lung is then placed in the recipient's chest and covered with saline slush and iced laparotomy pads.

The sequence of anastomoses is a matter of preference, though most perform the deepest anastomosis (the bronchial anastomosis) first and then proceed to the more superficial ones. The bronchial anastomosis is fashioned with 4-0 polypropylene suture. We favor a continuous suture technique for the entire anastomosis, although the membranous portion can be sewn with interrupted suture. Variations on the end-to-end bronchial anastomosis include the use of a telescoping technique, in which the donor bronchus is intussuscepted into the recipient bronchus, and an omental pedicle flap is placed around the anastomosis. These techniques were developed to prevent bronchial anastomotic dehiscence, but are now rarely performed.

Once the bronchial anastomosis is complete, attention is turned to the anastomoses of the pulmonary veins. A side-biting clamp is applied to the left atrium to include the pulmonary veins. The recipient pulmonary vein stumps are opened and the intervening atrial tissue is cut. This creates a cuff which is anastomosed to the donor atrial remnant using continuous 4-0 polypropylene suture (this suture is not tied down until reperfusion). Donor and recipient pulmonary arteries are anastomosed with 5-0 polypropylene suture. Arteries must be trimmed to an appropriate length before fashioning the anastomosis, since kinking can occur upon graft inflation if the vessels are left too long. The pulmonary artery anastomosis is then de-aired. The lung is inflated, and the pulmonary artery clamp is temporarily released to allow flushing of air through the atrial suture line. The left atrial clamp is removed to allow retrograde de-airing of the atrial anastomosis. The pulmonary venous anastomosis is then secured.

After hemostasis is ensured, apical and basal chest tubes are inserted. The ribs are reapproximated and the chest is closed in standard fashion. The double-lumen endotracheal tube is exchanged for a single-lumen tube and bronchoscopy is performed to evaluate the bronchial anastomosis.

Bilateral Lung Transplantation

Bilateral lung transplantation is performed as sequential single lung transplants. The patient is positioned supine and a bilateral anterior thoracosternotomy (clamshell) incision is made at the level of the fourth intercostal space. The lung with the least amount of function (as determined by a preoperative ventilation-perfusion scan) is removed first and replaced with an allograft as described for single lung transplantation above. Once ventilation and perfusion are established in the first allograft, the remaining lung is explanted and the second allograft is implanted. Bilateral chest tubes are placed and the chest is closed. Bronchoscopy is performed to evaluate the bronchial anastomoses.

While single lung transplants are usually performed off CPB, the majority of double lung transplants are still performed on-pump. The use of CPB allows for improved exposure, shorter graft ischemic times, controlled reperfusion, and the use of leukocyte-depleting filters. As the risk of bleeding may be increased with CPB, strategies have been developed to minimize the chance of hemorrhage. These include the routine use of aprotinin and heparin-coated CPB circuits, as well as the availability of an argon beam coagulator. Despite these maneuvers, there remains considerable risk associated with CPB, and many centers prefer to perform all lung transplants off-pump if possible.

POSTOPERATIVE MANAGEMENT

Heart-Lung and Lung Graft Physiology

The structural and functional aspects of transplanted heart-lung or lung blocs are distinct from native cardiopulmonary physiology, as detailed in Table 66-4.

Denervation of the lungs results in a diminished cough reflex and impairment of mucociliary clearance mechanisms. This predisposes recipients to pulmonary infections and necessitates aggressive postoperative pulmonary toilet.[69] Moreover, in the transplanted lung, ischemia-reperfusion injury, along with disrupted pulmonary lymphatics, may result in increased vascular permeability with varying degrees of interstitial edema. For the heart-lung recipient, denervation of the cardiac allograft leads to additional physiologic characteristics. The denervated heart loses its sympathetic and parasympathetic autonomic regulation, and thus recipients of heart-lung grafts do not have normal autonomic regulation of heart rate, contractility, or coronary

Table 66–4.

Structural and Functional Aspects of the Transplanted Heart-Lung and Lung Allograft

Heart-lung only
Denervation from sympathetic and parasympathetic cardiac plexus
Higher resting heart rate
Absence of respiratory sinus arrhythmia and carotid reflex bradycardia
Increased chronotropic and inotropic sensitivity to circulating catecholamines
Slower initial rise in heart rate in response to exercise or stress
Normal coronary flow reserve in the absence of rejection
Heart-lung and isolated lung
Increased pulmonary vascular permeability and interstitial edema (early)
Disrupted pulmonary lymphatics
Diminished cough reflex
Impaired mucociliary airway clearance mechanisms
Hypoxic pulmonary vasoconstriction intact

artery vasomotor tone. The resting heart rate is generally higher due to the absence of vagal input. Respiratory sinus arrhythmia and carotid reflex bradycardia are absent. Interestingly, the denervated heart develops an increased sensitivity to catecholamines due to increased beta-adrenergic receptor density and loss of norepinephrine uptake in postganglionic sympathetic neurons.[70,71] This augmented sensitivity plays an important role in maintaining an adequate cardiac response to exercise and stress. During exercise, the recipient experiences a steady but delayed increase in heart rate, primarily due to a rise in circulating catecholamines. This initial rise in heart rate is subsequently accompanied by an immediate increase in filling pressures resulting from increased venous return. These changes lead to increased stroke volume and cardiac output sufficient to sustain activity. The coronary circulation's ability to dilate, thus increasing blood flow to meet increased myocardial oxygen demand, is normal in cardiac transplant recipients. A similar physiologic response can be expected in recipients of heart-lung grafts. It should be noted, however, that graft coronary vasodilator reserve is abnormal in the presence of rejection, hypertrophy, or regional wall abnormalities.

Clinical Management in the Early Postoperative Period

The acute postoperative management for heart-lung and isolated lung graft recipients centers around careful fluid and ventilatory management. The primary objective in the immediate postoperative period is to maintain adequate perfusion and gas exchange while minimizing intravenous fluid administration, cardiac work, and barotrauma.

Upon completion of the transplant, the patient is transported to the intensive care unit (ICU), where cardiac rhythm, arterial pressures, and central venous pressures are monitored. Strict isolation precautions (previously enforced to reduce the incidence of infection in these immunosuppressed patients) are no longer required. Simple handwashing is now considered sufficient.

Approximately 10 to 20% of heart-lung graft recipients experience some degree of transient sinus node dysfunction in the immediate perioperative period. This often manifests as sinus bradycardia and usually resolves within a week. The use of bicaval venous anastomoses has been reported to lower the incidence of sinus node dysfunction and improve tricuspid valve function.[72] Because cardiac output is primarily rate-dependent after heart-lung transplantation, the heart rate should be maintained between 90 and 110 bpm during the first few postoperative days using temporary pacing or isoproterenol (0.005 to 0.01 μg/kg per minute) as needed. Although rarely seen, persistent sinus node dysfunction and bradycardia may require a permanent transvenous pacemaker. Systolic blood pressure should be maintained between 90 and 110 mm Hg using nitroglycerin or nitroprusside for afterload reduction, if necessary. "Renal-dose" dopamine (3 to 5 μg/kg per minute) is frequently used to augment renal blood flow and urine output. The adequacy of cardiac output is indicated by warm extremities and a urine output greater than 0.5 mL/kg per hour without diuretics. Cardiac function generally returns to normal within 3 to 4 days, at which time inotropes and vasodilators can be weaned.

In the case of heart-lung grafts, several factors may contribute to depressed global myocardial performance during the acute postoperative setting. The myocardium may be subject to prolonged ischemia, inadequate preservation, or catecholamine depletion prior to implantation. Hypovolemia, cardiac tamponade, sepsis, and bradycardia are also potential contributors and should be treated expeditiously if they are present. A Swan-Ganz pulmonary artery catheter should be used in cases of persistently abnormal hemodynamics.

Ventilatory management is a key element in the postoperative management of both heart-lung and isolated lung graft recipients. Barotrauma and high airway pressures can compromise bronchial mucosal flow and should be avoided. Lower tidal volumes and flow rates may be necessary to limit peak airway pressures to less than 40 cm H_2O. Upon arrival in the ICU, an anteroposterior chest x-ray is obtained, and the ventilator is typically set to an Fio_2 of 50%, tidal volume of 10 to 15 mL/kg, an assist-control rate of 10 to 14 breaths per minute, and PEEP of 3 to 5 cm H_2O. These settings are adjusted every 30 minutes to achieve an arterial Po_2 >75 mm Hg on an Fio_2 of 40%, an arterial partial carbon dioxide pressure between 30 and 40 mm Hg, and a pH between 7.35 and 7.45. Pulmonary toilet with endotracheal suctioning is an effective means of reducing mucus plugging and atelectasis. Ventilatory weaning is initiated after the patient is stable, awake, and alert. Usually, weaning is accomplished through successive decrements in the intermittent mandatory ventilation rate, followed by a trial of continuous positive airway pressure. Once ventilatory mechanics and arterial blood gases are deemed acceptable, the patient is extubated. This usually occurs within the first 24 hours after transplantation. Subsequent pulmonary care consists of vigorous diuresis, supplemental oxygen for several days, continued aggressive pulmonary toilet, incentive spirometry, and serial chest x-rays.

A diffuse interstitial infiltrate is often found on early postoperative chest x-rays. Previously referred to as a *reimplantation response*, this finding is better defined as graft edema due to inadequate preservation, reperfusion injury, or early rejection.[73] It appears that the degree of pulmonary edema is inversely related to the quality of preservation. Judicious administration of fluid and loop diuretics is required to maintain fluid balance and minimize this pulmonary edema.

Early lung graft dysfunction occurs in less than 15% of transplants, and is manifest as persistent marginal gas exchange without evidence of infection or rejection.[74] This primary graft failure often results from ischemia-reperfusion injury and is histologically evident as diffuse alveolar damage. Of course, technical causes of graft failure such as pulmonary venous anastomotic stenosis or thrombosis must always be considered. In cases of persistent, severe pulmonary graft

dysfunction refractory to mechanical ventilatory maneuvers, extracorporeal membrane oxygenation[75] and inhaled nitric oxide[76] have been used successfully to stabilize gas exchange. Urgent retransplantation can also be considered if other interventions fail.

The incidence of line sepsis can be reduced by the expedient removal of vascular catheters. Pleural and mediastinal chest tubes are removed when drainage has fallen to <25 mL/h. For heart-lung graft recipients, pacing wires are removed between 7 and 10 days after transplantation, provided no further pacing is required. Barring significant complications, the patient is usually transferred from the ICU to a standard cardiothoracic surgical ward within a few days.

Immunosuppressive Management: Early and Late Postoperative Regimens

For heart-lung and lung graft recipients, immunosuppression begins intraoperatively and is continued for life. The conventional triple-drug combination consists of cyclosporine, azathioprine, and prednisone. Initially, high doses of these drugs are given, and they are later tapered for chronic administration. A typical dosing protocol employed at Stanford University Hospital is outlined in Table 66-5. Cyclosporine is started in the early postoperative period, initially intravenously (0.05 to 0.1 mg/kg per hour) and subsequently orally (5 to 10 mg/kg per day in two divided doses). Dosing is titrated to maintain a trough serum concentration between 150 and 250 ng/mL in the first few weeks after transplantation, and from 100 to 150 ng/mL thereafter. Azathioprine is administered intravenously at 4 mg/kg preoperatively and subsequently maintained at approximately 2 to 3 mg/kg per day. Azathioprine dosages are adjusted to maintain the white blood cell count >4000 cells/mm^3. Methylprednisolone is administered intraoperatively at graft reperfusion (500 mg intravenously) and then continued for the first 24 hours at 125 mg intravenously every 8 hours. Steroids are then suspended for 2 weeks, based on experimental and clinical evidence that they impede bronchial anastomotic healing. After 2 weeks, prednisone is started at a daily oral dose of 0.6 mg/kg and gradually tapered over the next 3 to 4 weeks to 0.1 to 0.2 mg/kg per day.

The conventional triple-drug combination of cyclosporine, azathioprine, and prednisone is modified at some centers. Tacrolimus (FK506) and mycophenolate mofetil are two drugs that have been widely used in kidney and liver transplantation. Experience with use of these drugs in heart-lung and lung transplant recipients is limited. One promising study by Keenan and associates compared triple therapy with tacrolimus, azathioprine, and steroids to triple therapy with cyclosporine, azathioprine, and steroids.[77] Among the 133 lung allograft recipients studied, they found decreased acute rejection episodes and increased freedom from obliterative bronchiolitis at 2 years in the tacrolimus/azathioprine/steroid group. Reichenspurner and colleagues also found lower acute rejection rates and comparable infection rates in lung transplant recipients treated with tacrolimus-based immunotherapy rather than cyclosporine.[78] Larger studies and longer follow-up periods will be needed before conventional immunosuppressive regimens are modified.

Many centers have added prophylactic induction therapy to the standard triple-drug regimen. This includes the use of OKT3, rabbit antithymocyte globulin (RATG) and antithymocyte gamma-globulin (ATGAM), and daclizumab. OKT3 is a murine monoclonal antibody preparation that recognizes the CD3 antigen of human T cells. RATG and ATGAM are polyclonal anti–T-cell anti-

Table 66–5.

Typical Immunosuppression Protocol for Heart-Lung and Lung Transplant Recipients

Immunosuppressant	Early postoperative period	Late postoperative period
Cyclosporine	5–10 mg/kg/d PO*,† or 0.05–1 mg/kg/h IV	3–6 mg/kg/d PO‡
Methylprednisolone	500 mg IV after reperfusion followed by 125 mg IV every 8 hours for three doses	None
Prednisone	0.6 mg/kg/d PO starting on day 15	0.1–0.2 mg/kg/d PO
Azathioprine	2 mg/kg/d PO*	1–2 mg/kg/d PO§
Rabbit antithymocyte globulin	2.5 mg/kg/d IV on days 1, 2, 3, 5, and 7	

* *Intravenous dose only if preoperative serum creatinine >1.5 mg/dL.*
† *Maintain trough serum concentration between 150 and 250 ng/mL.*
‡ *Maintain trough serum concentration between 100 and 150 ng/mL.*
§ *Maintain white blood cell count >4000/mm^3.*

body preparations. Daclizumab is a monoclonal antibody preparation that blocks interleukin-2 (IL-2)-dependent activation of human T cells by binding to their IL-2 receptors. Use of these agents may reduce the rate of acute pulmonary rejection, but may also predispose to infection. Several retrospective and prospective studies have compared the efficacy of all or some of these induction agents. Palmer and coworkers found a decreased incidence of acute rejection in lung transplant recipients receiving RATG induction and conventional triple-drug therapy when compared to patients receiving triple-drug therapy alone.[79] Barlow and associates found that the incidence of acute pulmonary rejection was significantly lower in recipients induced with RATG compared with those induced with OKT3; in addition, there was a trend toward a decreased infection rate in the RATG group when compared to the OKT3 cohort.[80] Brock and colleagues performed a prospective nonrandomized trial comparing OKT3, ATGAM, and daclizumab as induction agents in 87 lung allograft recipients.[81] Across all groups, they found comparable freedom from acute rejection and bronchiolitis obliterans syndrome, with comparable long-term survival. However, daclizumab was associated with a lower rate of infections. Unfortunately, the follow-up for the daclizumab cohort was only 7 months, whereas the other cohorts were followed for 2 years. Long-term follow-up will be important in ascertaining which induction therapy is optimal in heart-lung and lung allograft recipients. Moreover, given that use of certain induction agents increases the risks of infection and/or development of posttransplant lymphoproliferative disorders, these drugs should be used with caution.

Judicious doses of immunosuppressives are usually well tolerated by patients; however, each drug has well characterized side effects. Cyclosporine is commonly associated with nephrotoxicity, hypertension, hepatotoxicity, hirsutism, and an increased incidence of lymphoma. The primary toxicity of azathioprine is generalized bone marrow depression, manifest as leukopenia, anemia, and thrombocytopenia. Steroids are associated with a myriad of side effects, including the development of cushingoid features, hypertension, diabetes, osteoporosis, and peptic ulcer disease. Initial doses of OKT3 and antithymocyte globulin can be associated with a "cytokine release syndrome," characterized by significant hypotension, bronchospasm, and fever. Therefore, patients receiving these induction agents require close monitoring and premedication with acetaminophen, antihistamines, and corticosteroids. Interestingly, daclizumab is not associated with the cytokine release syndrome.

Infection Prophylaxis

Antiviral and antifungal prophylaxis remain important components of the postoperative management strategy in heart-lung and lung transplant recipients. Many centers employ cytomegalovirus prophylaxis with ganciclovir for any CMV-positive recipient and in any CMV-negative recipient receiving an allograft from a CMV-positive donor. Ganciclovir is typically given for a several-week course and can be associated with leukopenia. Some patients may require granulocyte colony-stimulating factor if their white blood cell count falls below 4000/mm^3. Fungal prophylaxis against mucosal *Candida* infection includes use of daily nystatin swish and swallow. *Pneumocystis carinii* prophylaxis consists of trimethoprim-sulfamethoxazole or aerosolized pentamidine. In the immediate postoperative period, *Aspergillus* colonization is inhibited by the use of aerosolized amphotericin B. For *Toxoplasma*-negative recipients of grafts from *Toxoplasma*-positive patients, pyrimethamine prophylaxis is maintained for the first 6 months after transplantation.

Graft Surveillance: Patient Follow-Up Schedule

Routine clinical follow-up for heart-lung and lung allograft recipients is required to monitor graft function and modify immunosuppressive regimens. Regular surveillance protocols developed to monitor graft function typically consist of serial pulmonary function tests, arterial blood gases, and bronchoscopic evaluation. Surveillance is usually conducted at 2, 4 to 6, and 12 weeks, followed by 6 months after transplantation and yearly thereafter. Transbronchial biopsies are obtained from each transplanted lung, and lavage specimens are submitted for staining (i.e., Gram, fungal, acid-fast bacillus, and silver), culture, and cytology. Surveillance endomyocardial biopsies are performed at 3 months and then annually in heart-lung graft recipients.

In addition to routine surveillance, follow-up is often needed to address changes in clinical status. Complications related to transplantation are many, and these must be addressed carefully and expediently to prevent long-term graft failure.

POSTOPERATIVE COMPLICATIONS

Early morbidity and mortality after heart-lung and lung transplantation (within 30 days of operation or before initial discharge from hospital) are most commonly caused by primary graft failure or infection. Late mortality is most commonly caused by obliterative bronchiolitis or infection.[1] Causes of death at various time points after transplantation have been compiled by the ISHLT and are presented in Figs. 66-7 and 66-8.

Hemorrhage

Perioperative hemorrhage is an infrequent but significant cause of early death in heart-lung and lung transplantation. The majority of perioperative hemorrhagic complications stem from operating in the midst of dense adhesions caused by previous operations or inflammation from chronic lung

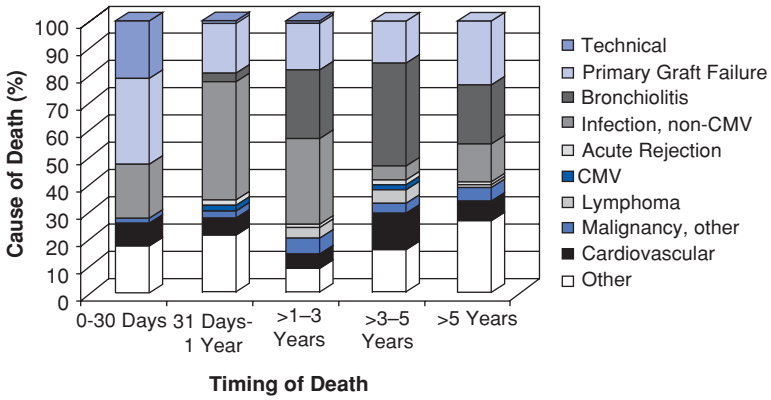


Figure 66-7. Causes of death at various periods after heart-lung transplantation. CMV = cytomegalovirus. (*Adapted from Trulock EP, Edwards LB, Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-second official adult lung and heart-lung transplant report—2005. J Heart Lung Transplant 2005; 24:956. Used with permission from Elsevier Science.*)

infection. As mentioned previously, meticulous attention to hemostasis is mandatory, and all available means should be used to achieve a dry field upon completion of the operation.

Hyperacute Rejection

ABO matching of donor and recipient has decreased the rate of hyperacute rejection. This complication, which is almost universally fatal, is mediated by preformed antibodies in the recipient which recognize antigens on the donor vascular endothelium. This humoral immune response results in activation of inflammatory and coagulation cascades, resulting in extensive thrombosis of graft vessels and subsequent graft failure.[68] To reduce the incidence of hyperacute rejection, a prospective cross-match should be performed in recipients with a percent reactive antibody >25%.

Early Graft Dysfunction and Primary Graft Failure

Graft dysfunction in the first few days after transplantation is common. It is often referred to as the "reimplantation response," manifest by abnormal lung function, pulmonary edema, and pulmonary infiltrates on chest x-ray. This phenomenon is thought to be linked to ischemia and reperfusion. Other contributing factors may also include allograft contusion, inadequate preservation, or use of cardiopulmonary bypass during transplantation. While most cases are mild and resolve with supportive care, some progress to primary graft failure. Reported rates of primary graft failure following lung and heart-lung transplantation range between 10 and 15%. Treatment may include the use of extracorporeal membrane oxygenation and inhaled nitric oxide. Unfortunately, primary graft failure is associated with a mortality of over 60%.[74]

Acute Rejection

As in cardiac transplantation, the majority of acute rejection episodes occur within the first year after transplant. From 1981 through 1994 at Stanford University, acute lung rejection (either isolated or simultaneous with heart rejection) occurred in more than 67% of heart-lung patients within the first year.[82] Similar rates of acute rejection have been reported among isolated lung transplant recipients. Despite its prevalence, death is very rarely a direct consequence of acute rejection. It is recognized, however, that the number and severity of acute rejection episodes is a risk factor for ultimately developing obliterative bronchiolitis.

Diagnosis of acute rejection in the early posttransplant period is often based on clinical parameters. Symptoms and signs of rejection include fever, dyspnea,

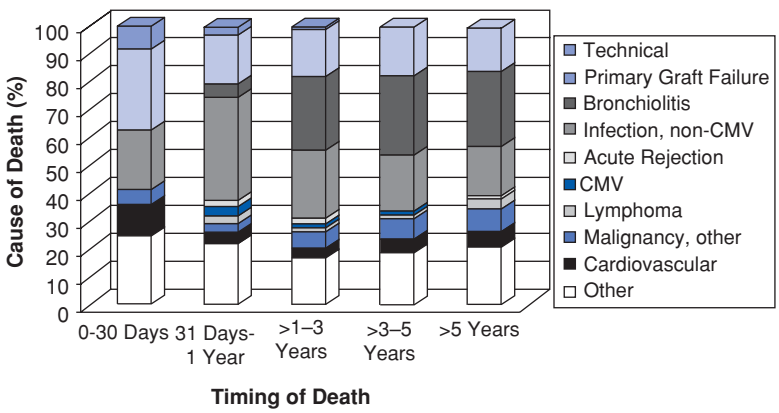
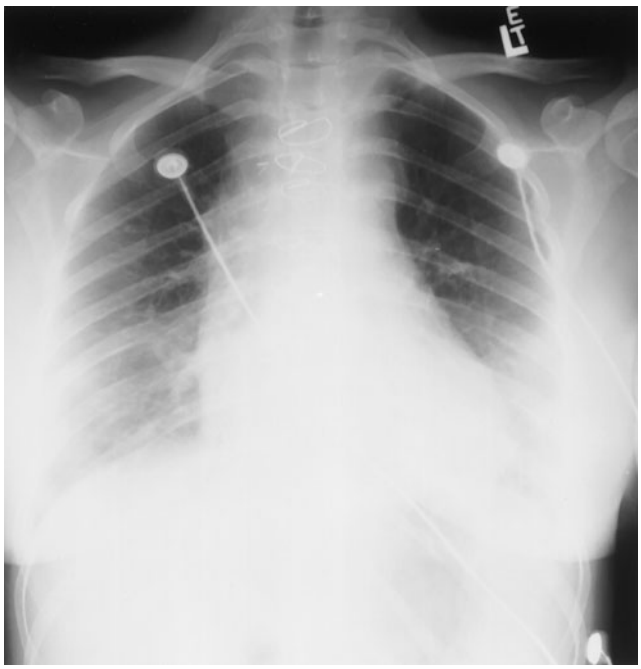
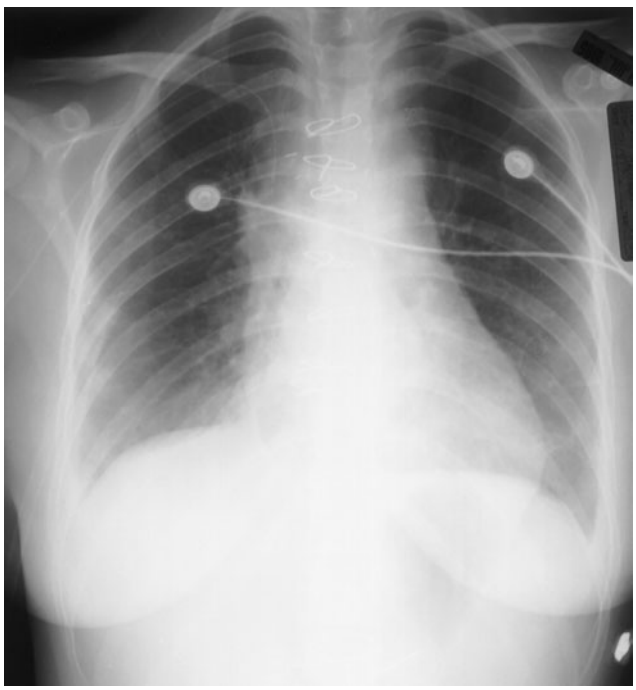


Figure 66-8. Causes of death at various periods after isolated lung transplantation. CMV = cytomegalovirus. (*Adapted from Trulock EP, Edwards LB, Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-second official adult lung and heart-lung transplant report—2005. J Heart Lung Transplant 2005; 24:956. Used with permission from Elsevier Science.*)

impaired gas exchange (manifest as a decrease in arterial P_{O_2}), a diminished forced expiratory volume in 1 second (FEV_1, a measure of airway flow), a fall in vital capacity, and the development of characteristic bilateral interstitial infiltrates on chest x-ray (Fig. 66-9A). After the first postoperative month, the chest x-ray is frequently normal during episodes of acute rejection, placing greater emphasis on other clinical parameters characteristic of rejection.



A



B

Figure 66-9. Acute and resolving lung rejection. (A) Chest radiograph illustrates bilateral infiltrates characteristic of acute pulmonary rejection. (B) Follow-up radiograph after pulsed methylprednisolone treatment of acute rejection demonstrating resolution of infiltrates.

It is often difficult to distinguish between the diagnosis of acute lung rejection and pulmonary infection based on clinical findings alone. It is of paramount importance to distinguish between acute rejection and infection prior to initiating therapy. Fiberoptic bronchoscopy (with transbronchial parenchymal lung biopsy and bronchoalveolar lavage) is the gold standard for the diagnosis of acute lung rejection and pulmonary infection. At least five biopsy specimens are taken from the lung allografts along with bronchoalveolar lavage which is evaluated for cytology, undergoes microbial staining, and cultured.[83] In addition to performing bronchoscopy with transbronchial biopsy in response to changes in clinical status and graft performance, most centers maintain a schedule of surveillance biopsies for lung and heart-lung allograft recipients. Interestingly, surveillance bronchoscopy reveals occult rejection or infection in 17 to 25% of transbronchial biopsy specimens from asymptomatic heart-lung and lung allograft recipients. For patients undergoing bronchoscopy due to a change in clinical condition, 50 to 72% of biopsy specimens have shown evidence of rejection or infection. In most cases, positive biopsies directly guide successful treatment of rejection or infection.[84,85]

Acute lung rejection is histologically characterized by lymphocytic perivascular infiltrates (Fig. 66-10). A grading scheme for acute lung rejection was developed by Clelland[86]

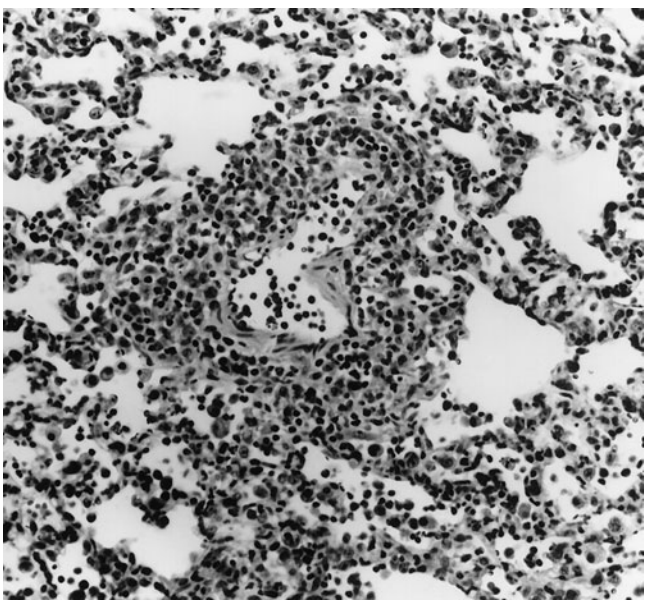


Figure 66-10. Moderate acute lung rejection. Moderate rejection is characterized by perivascular mononuclear cell infiltrates with extension into the adjacent alveolar septa (H&E stain; ×200).

Table 66–6.

Grading System for Acute Lung Rejection

Grade	Histologic appearance (transbronchial biopsy)
0	No significant inflammation; normal specimen
1	Small, infrequent perivascular infiltrates with or without bronchiolar lymphocytic infiltrates
2	Larger, more frequent perivascular lymphocytic infiltrates with or without moderate bronchiolar lymphocytic inflammation; occasional neutrophils and eosinophils
3	Extension of infiltrates into alveolar septa and alveolar spaces with or without bronchiolar mucosal ulceration

and is presented in Table 66-6; a similar scheme was also developed by the Lung Rejection Study Group.[83]

In heart-lung transplantation, experimental and clinical evidence suggests that pulmonary and cardiac rejections occur independently of one other. Higenbottam and associates at Papworth Hospital reported a surprisingly low diagnostic yield from routine endomyocardial biopsies in heart-lung recipients compared with functional or histologic tests of pulmonary rejection. Thus, the authors advanced that transbronchial biopsy eliminates the need for routine endomyocardial biopsies in heart-lung transplant recipients.[87] These findings were confirmed by Sibley and colleagues at Stanford University, who demonstrated discordance between findings on endomyocardial and transbronchial biopsies during episodes of acute rejection. Endomyocardial biopsies are most often normal despite findings of pulmonary rejection on transbronchial biopsy.[85] Combined, these results have led to modifications in surveillance biopsy programs. At Stanford, surveillance endomyocardial biopsies have been abandoned in patients in whom transbronchial biopsies can be reliably performed.

As in cardiac transplantation, efforts are being made to develop noninvasive ways of diagnosing early acute lung rejection. Loubeyre and coworkers at the Hôpital Cardiovasculaire et Pneumologique report an association between "ground-glass" density areas seen on high-resolution computed tomography and histologically confirmed acute lung rejection in heart-lung transplant recipients.[88] They found that ground-glass opacities on high-resolution computed tomography had a sensitivity of 65% for detecting lung rejection and a specificity of 85% for detecting an acute lung complication.

Treatment strategies for rejection involve augmentation of immunosuppression. At most institutions, the timing and severity of rejection episodes dictate therapy. A typical algorithm is shown in Fig. 66-11. Rejection episodes that are

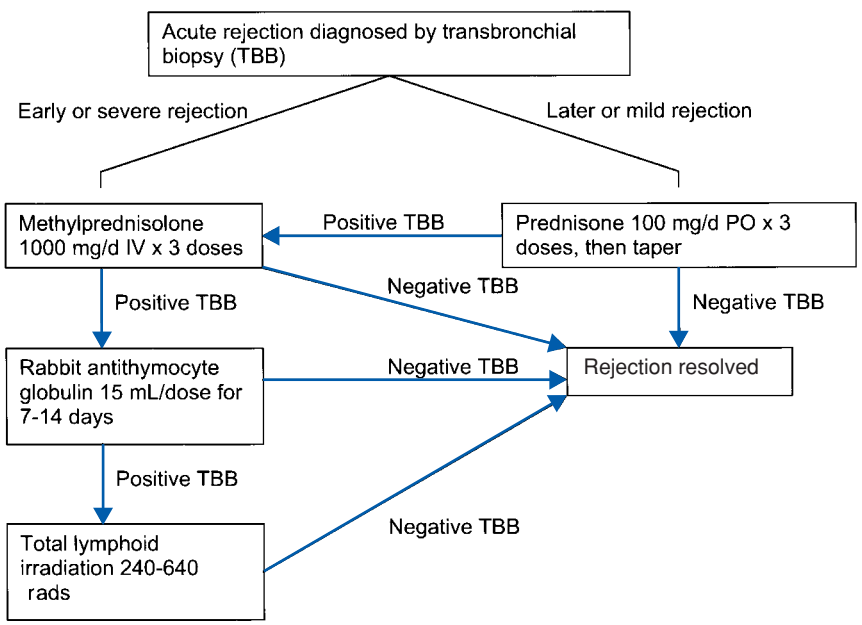


Figure 66-11. Typical algorithm for treating acute rejection in heart-lung and lung transplant recipients.

graded moderate or severe are treated with a "steroid pulse" (intravenous methylprednisolone 500 to 1000 mg/d for 3 consecutive days), followed by augmentation of the oral prednisone maintenance dose to 0.6 mg/kg per day. This maintenance dose is then tapered to 0.2 mg/kg per day over 3 to 4 weeks. Clinical and radiographic improvement (see Fig. 66-9B) following steroid therapy is often dramatic, rapid, and considered confirmatory of rejection. Mild episodes are initially treated by increasing oral prednisone dose, followed by a gradual taper over 3 to 4 weeks. Transbronchial biopsies are repeated 10 to 14 days following antirejection therapy to assess efficacy. Recurrent rejection episodes may be treated by a second steroid pulse and taper. Acute rejection refractory to steroid therapy may be treated with antilymphocyte preparations. Alternatively, primary immunosuppression may be switched from cyclosporine-based therapy to tacrolimus-based therapy. Finally, in especially difficult cases of persistent rejection, total lymphoid irradiation may be useful.[89]

Chronic Rejection

Chronic lung allograft rejection poses the greatest limitation to the long-term benefits of lung and heart-lung transplantation. Chronic lung rejection most commonly presents as obliterative bronchiolitis (OB). It was first noted as a pulmonary corollary to chronic cardiac rejection (cardiac graft atherosclerosis) in recipients of heart-lung transplants.[90] Later, OB was shown to occur in recipients of isolated lung transplants as well. The onset of OB typically occurs after the first 6 months to 1 year after transplantation, with a steadily increasing incidence thereafter. Recent data demonstrate that 70% of heart-lung and lung graft recipients are diagnosed with OB by the fifth postoperative year.[91]

Transbronchial biopsies remain the gold standard for diagnosing OB. The sensitivity of transbronchial biopsy for detecting OB has been reported between 17 and 87%.[85,92] Diagnostic yield of the biopsy procedure is related to the number of specimens taken, and current recommendations advise taking at least five specimens from each transplanted lung. Clearly, OB is a patchy process and therefore a large number of samples will be falsely negative due to sampling error.

OB is a histologic diagnosis and is characterized by dense eosinophilic, submucosal scar tissue that partially or totally obliterates the lumen of small (2 mm) airways, particularly the terminal and respiratory bronchioles (Fig. 66-12). The physiologic consequences are decreased arterial P_{O_2}, FEV_1, $FEF_{25–75}$ (forced expiratory flow at 25 to 75% [midrange] of lung volumes), and FEF_{50}:FVC (ratio of FEF_{50} to forced vital capacity). A characteristic "bowing" of the expiratory limb of the flow-volume loop has also been associated with OB. Clinical symptoms may be nonspecific and include cough and dyspnea with or without exertion. The term *bronchiolitis obliterans syndrome* (BOS) was developed to refer to patients who have clinical manifestations of OB with or without proven histologic characteristics (Table 66-7). A standardized working formulation for the clinical staging of BOS was established by the ISHLT and is based on the ratio of the current FEV_1 to the best posttransplant FEV_1. Patients with a decline of 20% or greater in their FEV_1 (in the absence of infection or other process) are diagnosed with BOS, irrespective of pathologic evidence of OB.[93]

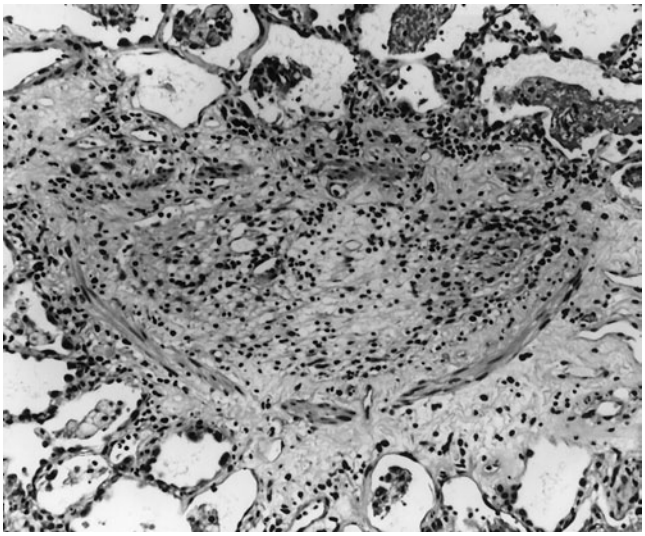


Figure 66-12. Bronchiolitis obliterans. Chronic airway rejection is characterized by luminal narrowing or replacement by dense eosinophilic collagenous scar tissue. Inflammatory cells may be seen in this case (H&E stain; ×150).

Valentine and the Stanford group reported that measurements of small airway function (i.e., $FEF_{25–75}$ and FEF_{50}:FVC) are more sensitive indicators of BOS than the FEV_1 in heart-lung and bilateral lung transplant recipients.[91] An FEF_{50}:FVC persistently below 0.7 for 6 consecutive weeks was the most sensitive predictor of OB. Approximately 50%

Table 66–7.

Working Formulation for Bronchiolitis Obliterans Syndrome

$0_{a \text{ or } b}$	No significant abnormality: FEV_1 80% of baseline
$1_{a \text{ or } b}$	Mild bronchiolitis obliterans syndrome: FEV_1 66–80% of baseline
$2_{a \text{ or } b}$	Moderate bronchiolitis obliterans syndrome: FEV_1 51–65% of baseline
$3_{a \text{ or } b}$	Severe bronchiolitis obliterans syndrome: FEV_1 50% of baseline

FEV_1 = forced expiratory volume in 1 second.
Note: a = without pathologic evidence of bronchiolitis obliterans; b = with pathologic evidence of bronchiolitis obliterans.

of heart-lung and bilateral lung recipients with biopsy-proven OB developed a fall in their FEF_{50}:FVC nearly 4 months prior to fulfilling the ISHLT working group criteria for BOS.

Experimental and clinical evidence suggests that the etiology of OB stems from the injury of the bronchial epithelium by one or more mechanisms. These include infection (particularly CMV), chronic inflammation due to impaired mucociliary clearance, and immunologic mechanisms.[73] These insults result in airway epithelial damage and subsequently an exaggerated healing response. Along with this injury, there is increased expression of major histocompatibility complex class II antigens in the bronchial epithelium. In a recent meta-analysis, Sharples and associates found that acute rejection is a risk factor for later development of OB.[94] In keeping with this finding is the association between BOS and decreased levels of immunosuppression (as may occur with noncompliance). Lymphocytic bronchitis and bronchiolitis were also closely associated with development of OB. CMV pneumonitis, other pulmonary infections, and HLA mismatching are also linked to the development of OB in small retrospective studies. Novick and colleagues recently reported on the relationship between OB, donor age, and graft ischemic times.[57] Using data from the ISHLT registry, they found a higher rate of OB at 3 years in recipients of grafts from donors over 55 that were also subjected to 6 to 8 hours of ischemia.

The current management of OB hinges on prevention, close surveillance, and immediate therapeutic intervention when patients become symptomatic or when asymptomatic physiologic changes occur. Patients are encouraged to perform incentive spirometry to prevent microatelectasis of lungs that are deprived of native innervation, lack bronchial circulation, and have impaired mucociliary clearance mechanisms. Moreover, all recipients are instructed to contact their transplant center or primary care physician upon development of respiratory tract symptoms so that pulmonary function tests can be performed. Any alterations in $FEF_{25–75}$, FEF_{50}:FVC, or specific changes in the flow-volume loop are indications for bronchoscopy with bronchoalveolar lavage and transbronchial biopsy, especially in the absence of infectious bronchitis or pulmonary edema.

Augmentation of immunosuppression is the mainstay of therapy for BOS. The prednisone dose is increased to 0.6 to 1.0 mg/kg per day and slowly tapered to 0.2 mg/kg per day while concomitantly optimizing cyclosporine and azathioprine dosing. Ganciclovir is reinstituted during treatment for those patients at risk of reactivation of CMV infection, and antimicrobial therapy is directed against any organisms isolated from bronchoalveolar lavage. Follow-up pulmonary function tests are performed. Pulmonary function can be stabilized in most patients, but significant improvement is uncommon. Unfortunately, relapse rates are >50% and progressive pulmonary failure or infection due to increased immunosuppression are the most common causes of death in lung transplant patients after the second year. Among 89 heart-lung and 13 bilateral lung recipients who underwent transplantation at Stanford University between 1981 and 1995, a 5-year survival rate of 49% among recipients diagnosed with OB (n = 59) was noted compared to 74% among recipients without OB (n = 43). The 1-, 3-, 5-, 8-, and 10-year actuarial survival rates following the diagnosis of OB were 74, 50, 43, 23, and 11%, respectively, with a median survival of 3 years following diagnosis.

Retransplantation is the only option for terminal respiratory failure secondary to OB. While survival for patients undergoing retransplantation for OB is better than for those undergoing retransplantation for other reasons, it is still worse than survival of first-time transplant recipients. Among heart-lung recipients with OB, Adams and associates at Harefield Hospital noted that retransplant survival rates were worse for those undergoing combined heart-lung replacement compared to patients who underwent isolated lung replacement.[95] The group also noted that the following factors were associated with improved survival after retransplant: absence of preformed antibodies, retransplantation at least 18 months after the original transplantation, and negative preoperative sputum cultures. Novick and colleagues recently reported results from the Pulmonary Retransplant Registry.[32] They reviewed survival rates in 237 patients who underwent pulmonary retransplantation between 1985 and 1996. At 1, 2, and 3 years after retransplantation, survival was 47, 40, and 33%, respectively. Survival was higher in nonventilated ambulatory patients and their freedom from OB was comparable to that of first-time transplant recipients. The authors conclude that pulmonary retransplantation should only be performed in carefully selected recipients who have a reasonable likelihood of long-term survival.

Accelerated graft coronary artery disease (CAD) or graft atherosclerosis is another major obstacle to long-term survival in heart-lung transplant recipients. Significant graft CAD resulting in diminished coronary artery blood flow may lead to arrhythmias, myocardial infarction, sudden death, or impaired left ventricular function with congestive heart failure. Classic angina due to myocardial ischemia is usually not noted in transplant recipients because the cardiac graft is not innervated. Multiple etiologies for graft CAD have been proposed, all focusing on chronic, immune-mediated damage to the coronary vascular endothelium. In fact, elevated levels of anti-endothelial antibodies have been correlated with graft CAD. Unlike coronary artery occlusive disease in the native heart, which tends to be a more focal process, transplant atherosclerosis is a more diffuse vascular narrowing extending symmetrically into distal branches. Histologically, transplant arteriopathy is characterized by concentric intimal proliferation with smooth muscle hyperplasia (Fig. 66-13).

Coronary angiograms are performed on a yearly basis to identify recipients with accelerated CAD. Angiography is limited, however, to assessment of luminal diameter. Intracoronary ultrasound, by contrast, can assess both vascular wall morphology and luminal diameter, making it a more sensitive tool to detect the diffuse coronary intimal thickening typical of graft atherosclerosis. Interestingly, graft CAD occurs at a

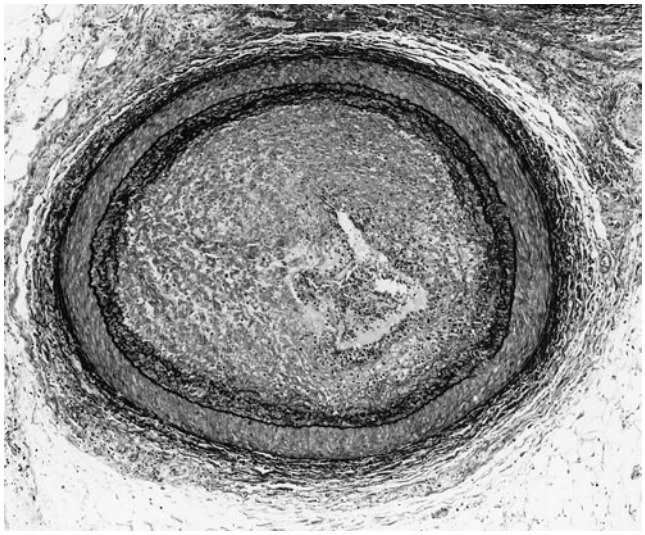


Figure 66-13. Cardiac graft atherosclerosis. Complete luminal obliteration by a concentric fibrointimal proliferation was observed postmortem in this heart-lung transplant patient (Elastin van Gieson stain; ×60).

reduced incidence in heart-lung recipients compared with the cardiac transplantation population.[96] A retrospective survey at Stanford revealed that 89% of heart-lung recipients were free from graft CAD at 5 years compared to 73% of heart transplant recipients. Clinically observed risk factors for developing this condition in heart transplant recipients include donor age >35 years; incompatibility at the HLA-A1, A2, and DR loci; hypertriglyceridemia (serum concentration >280 mg/dL); frequent acute rejection episodes; and documented recipient CMV infection. It is not clear whether these risk factors can be extended to the heart-lung transplant population.

Percutaneous transluminal coronary angioplasty and coronary artery bypass grafting have been used to treat discrete proximal lesions in some cases of graft CAD. However, the only definitive therapy for diffuse graft CAD is retransplantation. Effective prevention of graft CAD will rely on development of improved immunosuppression, recipient tolerance induction, improved CMV prophylaxis, and inhibition of vascular intimal proliferation.

Airway Complications

Improvements in surgical technique and posttransplant management have resulted in a relatively low incidence of airway complications after heart-lung and lung transplantation. Kshettry and colleagues at the University of Minnesota report an airway complication rate of 15% in lung transplant recipients.[97] The avoidance of perioperative steroids has long been considered important in preventing airway complications. However, recent experimental and clinical evidence suggests that the detrimental effect of steroids may be overestimated.[98] The most common airway complications are partial anastomotic dehiscence and stricture. Such complications are usually diagnosed by bronchoscopy. Airway dehiscence is treated by reoperation or close observation and supportive care. Strictures are treated by balloon or bougie dilatation, often with stent placement.

Infection

Bacterial, viral, and fungal infections are leading causes of morbidity and mortality in both heart-lung and lung transplant recipients. The rate of infection is higher in this transplant group compared to other solid organ transplant recipients. This may be related to the lung allograft's direct exposure to airway colonization and aspiration, as well as its impaired cough reflex and mucociliary clearance. The risk of infection and infection-related death peaks in the first few months after transplantation, declining to a low persistent rate thereafter. Between 1981 and 1994 at Stanford, only 20% of heart-lung transplant recipients were free from infection 3 months after transplantation. In a retrospective analysis of 200 episodes of serious infections occurring in 73 heart-lung recipients at Stanford between 1981 and 1990, Kramer and associates[99] found that half of all infections were caused by bacteria, whereas fungal infections accounted for only 14% of total infections. The most common viral agent was CMV, occurring primarily in the second month after transplantation and comprising 15% of all viral infections. Other viral infections (e.g., herpes simplex, adenovirus, and respiratory syncytial virus) were less common. Five percent of infections were attributed to *Pneumocystis jiroveci* (formerly *carinii*), typically occurring 4 to 6 months after transplantation, and 2% were due to *Nocardia*, generally appearing after the first year. There was no significant difference in the incidence of infections between patients receiving triple-drug or double-drug (cyclosporine and prednisone) immunosuppression. Infectious mortality comprised 40% of all deaths.

Posttransplant infections can be classified broadly into those that occur early or late after transplantation. Early infections, occurring within the first month after transplantation, are commonly bacterial (especially gram-negative bacilli) and manifest as pneumonia, mediastinitis, urinary tract infections, catheter-related sepsis, and skin infections. In the late posttransplant period, opportunistic viral, fungal, and protozoan pathogens become more prevalent. The lungs, central nervous system, gastrointestinal tract, and skin are the usual sites of invasion.

Bacterial infections, particularly those caused by gram-negative bacteria, predominate during the early postoperative period. Between 75 and 97% of bronchial washings obtained from donor lungs before organ retrieval culture at least one organism.[100] Posttransplant invasive infections are frequently caused by organisms cultured from the donor. Conversely, bacterial infections developing in patients with septic lung disease, particularly cystic fibrosis, most commonly originate from the recipient's airways and sinuses. Treatment of bacterial infections generally involves characterization of the infective agent (e.g., cultures and antibiotic sensitivities), source control (e.g., catheter removal and débridement), and appropriate antibiotic regimens.

CMV infection occurs most often at 1 to 3 months after transplantation and presents either as a primary infection or as reactivation of a latent infection. By definition, primary infection results when a previously seronegative recipient is infected through contact with tissue or blood from a seropositive individual. The donor organ itself is thought to be the most common vector of primary CMV infections. Reactivation infection occurs when a recipient who is seropositive prior to transplant develops clinical CMV infection during immunosuppressive therapy. Seropositive recipients are also subject to infection by new strains of CMV. Primary infection in previously seronegative recipients is generally more serious than reactivation or reinfection in seropositive patients.

Clinically, CMV infection has protean manifestations, including leukopenia with fever, pneumonia, gastroenteritis, hepatitis, and retinitis. CMV pneumonitis is the most lethal of these, with a 13% mortality, and retinitis remains the most refractory to treatment. Diagnosis of CMV infection is made by direct culture of the virus from blood, urine, or tissue specimens, by a fourfold increase in antibody titers from baseline, or by characteristic histologic changes (i.e., markedly enlarged cells and nuclei containing basophilic inclusion bodies). Most cases respond to ganciclovir and hyperimmune globulin.

The significance of CMV as an infective agent becomes clear when one realizes that it is implicated as a trigger for accelerated graft CAD[101] and OB,[94] as well as an inhibitor of cell-mediated immunity. CMV-negative donors comprise <20% of the donor organ pool, and due to organ scarcity most transplant centers perform transplants across CMV serologic barriers using ganciclovir and/or hyperimmune globulin prophylactic protocols in CMV-positive donors and/or recipients. A recent study by Valantine and associates in 80 heart-lung and lung transplant recipients found that the combined use of ganciclovir and hyperimmune globulin was superior to ganciclovir alone as prophylaxis against CMV. Moreover, the ganciclovir/hyperimmune globulin cohort had longer survival at 3 years and greater freedom from OB.[102]

Invasive fungal infections peak in frequency between 10 days and 2 months after transplantation. Treatment consists of fluconazole, itraconazole, or amphotericin B. Reichenspurner and associates have reported that the actuarial incidence and linearized rate of fungal infections after heart, heart-lung, and lung transplants performed at Stanford University were significantly reduced in recipients who received inhaled amphotericin prophylaxis.[103]

The institution of prophylaxis with oral trimethoprim-sulfamethoxazole (or inhalational pentamidine for sulfa-allergic patients) has effectively prevented *Pneumocystis jiroveci* pneumonia in lung and heart-lung transplant patients. The risk of *Pneumocystis* infection is highest during the first year after transplant. However, as infections can also occur late after transplant, most centers recommend that prophylactic therapy be continued for life.

Infection prophylaxis in heart-lung and lung recipients is comprised of vaccinations, perioperative broad-spectrum antibiotics, and long-term prophylactic antibiotics. Pretransplant inoculations with pneumococcal and hepatitis B vaccines, as well as diphtheria-pertussis-tetanus boosters, are recommended. All transplant recipients should receive annual influenza vaccinations. Although perioperative antibiotic regimens vary widely between transplant centers, first-generation cephalosporins (e.g., cefazolin) or vancomycin are commonly used. Long-term prophylaxis typically includes nystatin mouthwash, trimethoprim-sulfamethoxazole, aerosolized amphotericin B, and antivirals such as acyclovir or ganciclovir.

Neoplasm

Transplant recipients have a higher incidence of neoplasia than that of the general population.[104] This is undoubtedly due to chronic immunosuppression. Recipients are predisposed to a variety of tumors, including skin cancer, B-cell lymphoproliferative disorders, carcinoma in situ of the cervix, carcinoma of the vulva and anus, and Kaposi's sarcoma. On average, tumors appear approximately 5 years after transplantation.[1]

The incidence of B-cell lymphoproliferative disorders in transplant patients is a staggering 350 times greater than that of the normal age-matched population. Posttransplant lymphoproliferative disorder has been reported in 6% of lung transplant recipients.[105] These most commonly occur within the first year after transplantation and are associated with Epstein-Barr virus infection. Treatment consists of reducing immunosuppression and administration of an antiviral agent such as acyclovir or ganciclovir. A response rate of 30 to 40% can be expected, and recurrence is uncommon. Chemotherapy and radiotherapy have been used successfully in some cases. During therapy, close monitoring of the graft, along with clinical assessment of tumor status, is essential.

LONG-TERM RESULTS IN HEART-LUNG AND LUNG TRANSPLANTATION

The Stanford long-term survival for heart-lung and lung transplant recipients is shown in Figs. 66-14 and 66-15, respectively. Similar results are recorded in the ISHLT registry (Figs. 66-16 and 66-17). At Stanford, 1-, 5-, 10-, 15-, and 20-year survival rates after heart-lung transplantation are 72, 50, 32, 25, and 14%, respectively. Lung transplantation survival at 1, 5, 10, and 15 years posttransplantation are 82, 49, 28, and 17%, respectively. Most recipients are able to resume active lifestyles without supplemental oxygen and demonstrate significant increases in exercise capacity posttransplant. Pulmonary function measured by spirometry and arterial blood gases is markedly improved within several months after transplantation, with a normalization of ventilation and gas exchange after 1 to 2 years.[106]

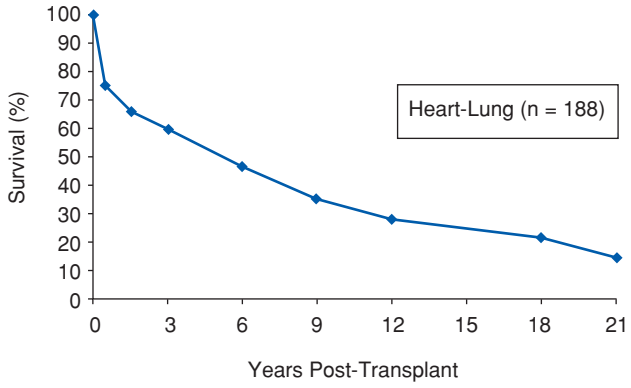


Figure 66-14. Survival for Stanford heart-lung transplantation, 1981 through 2003.

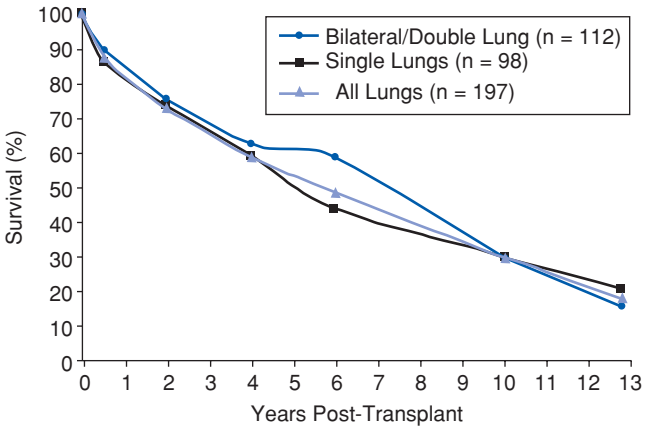


Figure 66-15. Survival for Stanford lung transplantation, 1989 through 2003.

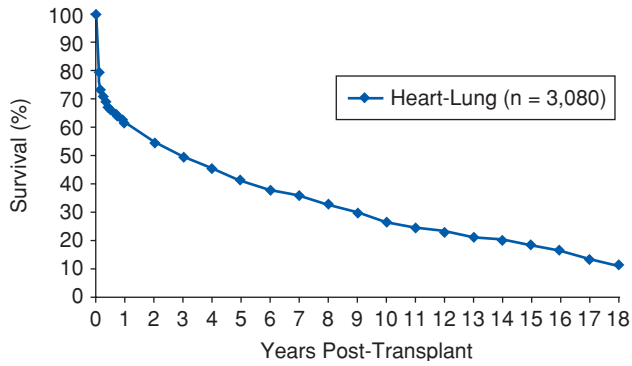


Figure 66-16. Actuarial survival for heart-lung transplantation, 1982 through 2003. (*Adapted from Trulock EP, Edwards LB, Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-second official adult lung and heart-lung transplant report—2005. J Heart Lung Transplant 2005; 24:956. Used with permission from Elsevier Science.*)

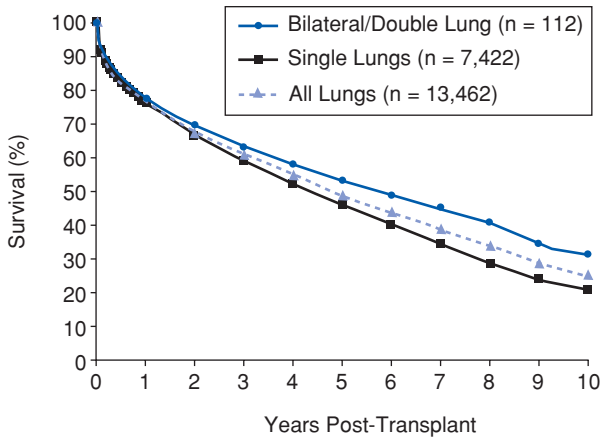


Figure 66-17. Actuarial survival after isolated lung transplantation, 1983 through 2003. (*Adapted from Trulock EP, Edwards LB, Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-second official adult lung and heart-lung transplant report—2005. J Heart Lung Transplant 2005; 24:956. Used with permission from Elsevier Science.*)

CONCLUSION

The evolution of heart-lung and lung transplantation from rudimentary laboratory experimentation to its current prominence as an accepted therapy for end-stage cardiopulmonary disease is a product of ingenuity, perseverance, skill, and courage. Many debilitated patients, both adult and pediatric, now have an opportunity to resume full and active lifestyles after heart-lung and lung transplantation. Nevertheless, significant hurdles have yet to be overcome, including issues of graft rejection, infection, and a limited donor pool. Important advances on the horizon include cross-species transplantation, improved immunosuppression, the induction of immunologic tolerance to foreign tissue, and improved organ preservation techniques.

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CHAPTER 67

Long-Term Mechanical Circulatory Support

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Heart failure continues to be an ever-growing public health concern facing our country today. The continued aging of the population has contributed to the increasing incidence and prevalence of heart failure. Presently, approximately 5 million people are affected, with over 500,000 new cases diagnosed annually. Economically, this represents over 30 billion dollars in health care spending each year.[1,2]

Despite advances in the understanding of the neurohormonal changes involved in the progression of heart failure and improvements in medical management, the natural history of the disease dictates a dismal prognosis. In the Framingham Study cohort, overt congestive heart failure led to a median survival of 1.7 years in men and 3.2 years in women, with 5-year survival rates in men and women of 25% and 38%, respectively.[3] Overall, it is estimated that congestive heart failure is responsible for approximately 250,000 deaths per year.[4] Cardiac transplantation has been regarded as the gold standard treatment for heart failure. However, limitations on availability of donor organs have made transplantation a viable option for only a very small percentage of this growing population. Over the past decade, the number of transplants being performed annually has remained between 3000 and 4000 worldwide, with a decreasing trend noted in recent years.[5]

Mechanical support of the cardiopulmonary system was first introduced clinically by John Gibbon in 1953, when he successfully employed cardiopulmonary bypass for the repair of an atrial septal defect.[6] In 1963, DeBakey implanted the first ventricular assist device in a patient suffering a cardiac arrest following aortic valve replacement. The patient subsequently died on postoperative day 4. In 1966, DeBakey reported the first successful bridge to recovery with implantation of a pneumatically driven ventricular assist device in a patient suffering from postcardiotomy shock. The patient was supported for 10 days, and ultimately survived to discharge.[7] Soon thereafter, Cooley reported the first successful bridge to transplantation using a pneumatically driven implantable artificial heart.[8] During this time, the National Heart, Lung, and Blood Institute began funding initiatives to further the development of ventricular assist devices and a total artificial heart. DeVries and colleagues reported the successful implantation of the Jarvik-7-100 total artificial heart in 1984.[9] Despite initial success, a high incidence of thromboembolic and infectious complications led to a moratorium on the use of the total artificial heart in 1991. During this period, however, continued advances in the development of left ventricular assist devices culminated in Food and Drug Administration (FDA) approval of a left ventricular assist device as a bridge to transplantation in 1994.

The feasibility of a mechanical-based approach to the treatment of end-stage heart failure was validated by the REMATCH trial in 2004.[10] This prospective randomized trial demonstrated a marked survival benefit in patients receiving mechanical ventricular assistance for the treatment of end-stage heart failure when compared to medical management alone. At the same time, the limitations of current device technology were highlighted by the incidence of adverse events related to mechanical support, such as infection, device failure, and thromboembolic events. Continued technological developments and improvements in device design are necessary for mechanical circulatory support to become an effective means of long-term destination therapy.

INDICATIONS FOR DEVICE SUPPORT

With advances in device technology and improvements in patient selection criteria, the indications for mechanical circulatory support continue to evolve. In general terms, patients considered for mechanical circulatory support can no longer sustain adequate systemic oxygen delivery to maintain normal end-organ function despite maximal medical therapy. Traditional hemodynamic criteria for device implantation include a systolic blood pressure less

than 80 mm Hg, mean arterial pressure less than 65 mm Hg, cardiac index less than 2.0 L/min/m^2, pulmonary capillary wedge pressure greater than 20 mm Hg, and a systemic vascular resistance greater than 2100 dynes-sec/cm.[11,12] The decision to implement mechanical circulatory support must be made with consideration of the ultimate goal of therapy. Devices can be used as a bridge to transplantation, as a bridge to myocardial recovery, or as destination therapy in patients not eligible for cardiac transplantation. The range of disease processes treated with ventricular assist device (VAD) therapy includes both acute and chronic forms of cardiac failure, and will likely continue to expand.[13,14]

Cardiogenic Shock Associated with Acute Myocardial Infarction

It is estimated that cardiogenic shock complicates the clinical presentation of between 6 and 20% of patients suffering from acute myocardial infarction. Cardiogenic shock results from either a loss of more than 40% of the left ventricular myocardium, or is due to isolated right ventricular infarction and subsequent hemodynamic compromise secondary to right ventricular failure.[15] Myocardial infarction complicated by cardiogenic shock has a reported mortality rate of between 70 and 80%.[16,17] In recent years, the trend toward more aggressive and early coronary reperfusion strategies such as intra-aortic balloon counterpulsation, percutaneous coronary interventions, and coronary artery bypass grafting have resulted in a modest decline in the mortality rate of this condition.[17] Early experience with use of left ventricular assist device (LVAD) therapy in the setting of acute myocardial infarction resulted in high mortality rates.[18–20] As experience with the implantation and management of LVADs has grown, there has been a renewed interest in recent years in the use of mechanical circulatory support in the acute setting. Chen and associates have advocated the early implementation of LVAD therapy following acute myocardial infarction as a means of providing a greater chance for ventricular recovery and subsequent device weaning.[21] A more recent series by Leshnower and colleagues retrospectively examined the results of LVAD support in 49 patients suffering from infarction-related cardiogenic shock.[22] Mechanical support in this setting was able to successfully bridge 74% of patients to transplant, with an overall in-hospital mortality of 33%, a marked improvement over historical controls. LVAD therapy will likely play an increasingly important role in the treatment of such patients.

Postcardiotomy Cardiogenic Shock

Approximately 2 to 6% of patients undergoing coronary or valvular cardiac procedures will suffer from postcardiotomy cardiogenic shock.[23] Mehta and colleagues reported the results of 1279 cases of postcardiotomy cardiogenic shock.[24] Forty-five percent of patients were weaned from support, with only 25% surviving to discharge. The mean duration of support was 4 days, with use of both centrifugal and pneumatically driven devices. Similar survival-to-discharge rates in this ill group of patients were found in the New York State cardiac surgery database.[25]

We have advocated the early implementation of mechanical circulatory assistance in the setting of postcardiotomy shock to provide mechanical unloading of the ventricle and rapid restoration of normal end-organ perfusion, with improved survival rates.[26] The creation of regional networks allows for patients to receive bridge-to-bridge therapy with short-term devices implanted early at "spoke" facilities and then subsequent transfer to a specialized "hub" center for either management as bridge to recovery or device exchange to a more permanent implantable VAD. In a series of 44 patients treated in this way, 66% survived to hospital discharge.[27,28]

Special consideration should be given to patients with severely impaired ventricular function undergoing high-risk cardiac procedures. If possible, transplant evaluation is initiated preoperatively and the procedure performed with LVAD back-up. In this way, postcardiotomy failure can be dealt with expeditiously with LVAD implantation either as a bridge to recovery or as a bridge to transplantation.

Chronic Heart Failure

Patients in chronic decompensated heart failure generally fall into one of two categories: those who are eligible for cardiac transplantation and those who are not. Mechanical circulatory support can be instituted in this group of patients as a bridge to transplantation or as destination therapy. Patients who are listed for transplant with a long anticipated waiting time due to limited donor availability, blood type, patient size, or immunologic sensitization with the need for prospective cross-matching may benefit from elective LVAD placement to maintain or restore normal end-organ function. The normalization of hemodynamics and end-organ function with mechanical support in pretransplant patients has been shown to decrease posttransplant mortality rates.[29,30]

Myocarditis

Acute myocarditis typically affects a younger cohort of patients and is characterized by an unpredictable clinical course. Mechanical circulatory support in this setting offers the chance for bridge to recovery. Determining which group of patients will recover and which will require support as a bridge to transplant remains a challenge.[31,32] Due to the frequent involvement of both the right and left ventricles in the disease process, early consideration should be given to instituting biventricular support to achieve optimal clinical outcomes.[33,34]

Ventricular Arrhythmia

There have been several successful reports of device implantation in patients suffering from ventricular arrhythmias refractory to medical therapy.[35–38] While some patients may have ventricular arrhythmias arising in the setting of acute

myocardial infarction with compromised cardiac function, many have de novo arrhythmias with relatively normal cardiac function and hemodynamics. The natural course of the arrhythmia following LVAD implantation is variable, with some patients demonstrating resolution and others having persistent arrhythmias. When persistent, they are usually well tolerated. The impairment in right ventricular function with prolonged ventricular arrhythmias has led some to advocate early biventricular support in these patients.

PATIENT SELECTION AND RISK ASSESSMENT

Appropriate patient selection represents one of the most critical determinants of successful outcomes with VAD therapy. The operative risk of device implantation must be weighed against the potential lifestyle and survival benefit with mechanical support. Patient selection criteria must not be so stringent as to exclude ill patients who may benefit from device therapy, while at the same time avoiding high perioperative mortality rates by the inclusion of patients who have prohibitive risk.

Several reports have sought to identify significant preoperative variables that may predict risk and impact outcomes. The revised Columbia screening scale published in 2003 offers a way of stratifying the risk for LVAD therapy based on several clinical factors: mechanical ventilation; postcardiotomy; prior LVAD insertion; central venous pressure >16 mm Hg; and prothrombin time >16 seconds (Table 67-1).[39] Each factor is given a weight, with a cumulative score of >5 predicting an operative mortality of 46%, versus a mortality rate of 12% for a score ≤5. This scoring system is a revision of a prior scale developed in conjunction with The Cleveland Clinic Foundation.[40] The revised scoring scale was the result of analysis of 130 patients undergoing implantation of the Heartmate vented electrical device. In the new scoring scale, preoperative oliguria (urine output <30 mL/h) and reoperative surgery were not statistically significant factors in predicting postoperative mortality as they were in the old model. McCarthy and colleagues previously reported the results of 100 patients undergoing LVAD implantation.[41] In this group of patients, preoperative factors that increased the risk of death by univariate analysis included the need for mechanical ventilation or extracorporeal membrane oxygenation, low pulmonary arterial pressures, and elevations in bilirubin, blood urea nitrogen, and creatinine. Deng and associates reported the results of 464 patients undergoing implantation of the Novacor left ventricular assist system (LVAS). Sepsis associated with respiratory failure, preoperative right heart failure, age >65 years, acute postcardiotomy state, and acute infarction were independent risk factors for death by multivariate analysis.[42]

Table 67–1.

Revised Risk Factor Summation Score

Variable	Relative risk	Weighting
Ventilated	5.3	4
Postcardiotomy	3.3	2
Prior LVAD insertion	3.3	2
CVP >16 mm Hg	2.1	1
PT >16 seconds	2.1	1

Variables excluded by multivariate analysis: prior right ventricular assist device, coronary artery disease, acute myocardial infarction, urine output <30 mL/h, reoperative surgery.
CVP = central venous pressure; LVAD = left ventricular assist device; PT = prothrombin time.
Source: Reproduced with permission from Rao et al.[39]

The timing of intervention is also an important determinant of clinical outcomes. Optimization of the patient's clinical status with diuresis, correction of coagulation abnormalities, pulmonary rehabilitation, and intra-aortic balloon counterpulsation are important, but should not delay institution of support in critically ill patients with severe ventricular failure and ongoing end-organ malperfusion. In the acute setting of postcardiotomy shock, data from the Abiomed registry demonstrated that delays in instituting mechanical support beyond 6 hours led to a marked increase in mortality.[43,44] Urgency of device implantation also has an impact on overall survival. Deng and coworkers reported the results of patients undergoing device implantation as a bridge to transplantation, showing a decreased rate of survival to transplantation in those receiving LVADs for emergent indications such as acute myocardial infarction, postcardiotomy failure, and acute heart failure when compared to patients receiving devices on an elective basis.[45]

Although inclusion criteria for mechanical support have expanded in recent years, there still exist generally agreed upon contraindications for device implantation. Patients with irreversible end-organ damage, particularly renal, hepatic, or respiratory failure, uniformly demonstrate poor clinical outcomes. Severe and unrecoverable neurologic injury also represents a contraindication to device implantation. Systemic sepsis or bacteremia poses a high risk of device contamination after implantation and should be controlled prior to LVAD insertion.

DEVICE SELECTION

A wide variety of devices exists today, with many more in development. Several factors must be considered when choosing a specific device. These include the anticipated endpoint of treatment (i.e., destination therapy, bridge to transplantation, or bridge to myocardial recovery), the expected duration of support, the type of ventricular support needed (i.e., right, left, or biventricular), and patient

factors such as body size and habitus, blood type, and preexisting contraindications to anticoagulation therapy. Surgeon experience and institutional bias also factor into device selection. The Food and Drug Administration has approved certain devices for particular clinical situations. Some of the most commonly used devices will be reviewed in the next section.

Short-Term Mechanical Support

Several modalities exist for providing short-term mechanical circulatory support. These include counterpulsation and centrifugal, axial, and pneumatic pumps. These devices have the advantage of relative ease of implementation with the hope of providing either a short-term bridge to recovery or a short-term bridge to more permanent ventricular assistance.

The first clinical application of an intra-aortic balloon pump (IABP) was reported by Kantrowitz and colleagues in 1968 for the treatment of postinfarction cardiogenic shock.[46] Since that time, IABP placement has become one of the most common forms of mechanical circulatory assistance. Counterpulsation, which is synchronized to either electrocardiogram or arterial waveforms, provides balloon inflation within the descending thoracic aorta during diastole with deflation at the onset of systole. The result is a reduction in myocardial work through afterload reduction, and improvement in myocardial oxygen supply through augmentation of diastolic blood pressure and coronary perfusion pressure.[47,48] IABP counterpulsation is used today in a variety of clinical settings, including cardiogenic shock associated with myocardial infarction, postcardiotomy shock, mechanical complications of infarction such as acute mitral regurgitation and ventricular septal defect, postinfarction angina, and for the treatment of ventricular arrhythmias in the setting of ongoing ischemia. IABP has also been used preoperatively as an adjunct to high-risk percutaneous interventions or coronary artery bypass grafting.[49,50]

Centrifugal pumps have been used both for intraoperative cardiopulmonary bypass and as a means of providing either right, left, or biventricular mechanical circulatory support. They have the advantage of wide availability, ease of use, and relative low cost compared to other devices.[51–53] Disadvantages include the need for systemic anticoagulation with resultant bleeding complications. Progressive development of interstitial edema secondary to capillary leak and the inability to ambulate and rehabilitate these patients limits this technology to short-term support. Three of the most commonly used pumps in the United States are the Biomedicus Biopump (Medtronic Bio-Medicus, Inc., Eden Prairie, Minn), the Sarns centrifugal pump (3-M Health Care, Ann Arbor, Mich), and the St. Jude Lifestream centrifugal pump (St. Jude Medical, Inc., St. Paul, Minn).

The versatility of centrifugal pumps has allowed them to be clinically implemented in a number of different ways. Extracorporeal membrane oxygenation (ECMO) utilizes a centrifugal pump in combination with a membrane oxygenator to provide complete cardiopulmonary support in the setting of circulatory and respiratory failure. The successful use of ECMO in the pediatric population has been well described.[54,55] The outcomes of ECMO for treatment of cardiac failure in the adult population is more limited. The Extracorporeal Life Support Organization registry reported by Bartlett demonstrates a survival of approximately 40% in over 1600 patients undergoing ECMO for cardiac failure.[56] A large portion of these cases were pediatric patients. Series looking only at adult patients demonstrate lower survival rates.[57] The TandemHeart percutaneous VAD (CardiacAssist, Inc., Pittsburgh, Penn) utilizes a centrifugal pump to pump blood from the left atrium to one or both femoral arteries. The left atrial catheter is placed percutaneously via a transseptal puncture.[58] Thiele and associates reported the results in 18 patients undergoing placement for cardiogenic shock, demonstrating improvements in cardiac index and reductions in pulmonary capillary wedge pressure.[59]

The Impella Recover device (Impella CardioSystems AG, Aachen, Germany) is a miniaturized axial flow pump designed for short-term right, left, or biventricular support. The device is able to generate flows of up to 4 to 5 L/min at rotational speeds of between 28,000 and 32,000 rpm. The device has the advantage of ease of implantation and minimal requirement for anticoagulation. The device can be placed percutaneously and positioned with echocardiographic guidance.[60] Initial clinical experience has been favorable in the setting of postcardiotomy shock and acute heart failure, with some evidence indicating a significant survival benefit in patients receiving the Impella device when compared to IABP placement alone.[61,62]

The Abiomed BVS 5000i (Abiomed Cardiovascular, Inc., Danvers, Mass) is an FDA-approved device for acute postcardiotomy failure. It is a dual-chambered pneumatically driven extracorporeal pump designed for short-term cardiac support. The dual chamber polyurethane blood sacs fill passively, with pneumatically driven ejection. The configuration mimics that of the native atria and ventricles. The device is capable of generating pulsatile flow of up to 6 L/min. The ease of implantation, operation, weaning, cost effectiveness, and widespread availability have made it one of the most commonly used devices in the setting of acute cardiac failure. The indications for use have expanded beyond the postcardiotomy setting to include cardiogenic shock associated with acute infarction, myocarditis, and temporary right ventricular support in association with long-term LVAD implantation.[43,44,63,64] The device has been used extensively in community-based practices, allowing for the transfer of patients to a specialized center for transplantation or more permanent support as previously described.[27,65] Disadvantages include the need for systemic anticoagulation and limited patient mobility. The Abiomed AB5000, also recently approved by the FDA, is the successor to the BVS 5000i system (Fig. 67-1). It consists of a fully automated, vacuum-assisted console with a pneumatically driven blood pump that is placed paracorporeally. It offers the advantage of allowing for patient mobility and rehabilitation and can provide a longer time period of support than its predecessor.

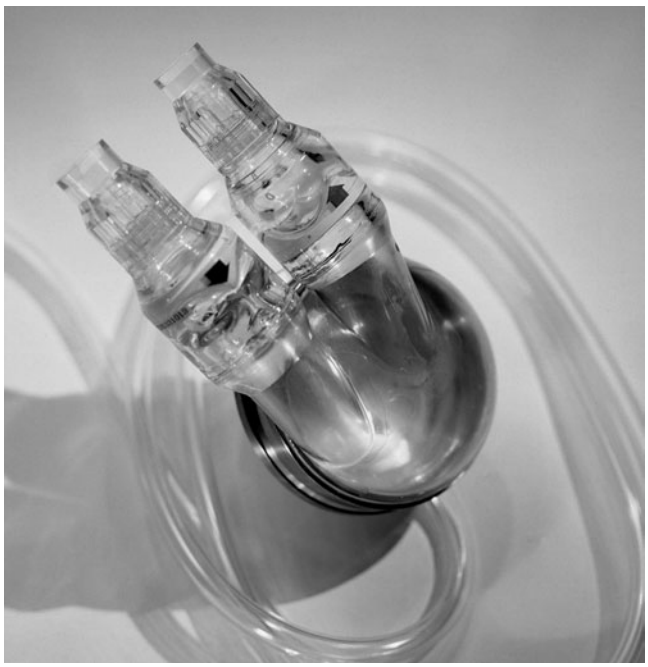

Figure 67-1. The Abiomed AB5000 circulatory support system. *(Courtesy of Abiomed, Inc., used with permission.)*

Early clinical experience with the device is encouraging, although concerns have been raised regarding device-related hemolysis.[66]

Long-Term Mechanical Support

Pulsatile-implantable devices

HEARTMATE XVE: The Heartmate XVE LVAD (Thoratec Corp., Pleasanton, Calif) is FDA approved as a bridge to transplantation and for destination therapy (Fig. 67-2). The original system, developed in 1975, was a pneumatically driven pump. The requirement of a large controller console for the pneumatic unit limited patient mobility and rehabilitative efforts. The newer-generation device is an electrically vented unit with a portable control console and batteries, allowing for greater patient mobility, rehabilitation, and discharge from the hospital.[67]

The pumping chamber is constructed of a titanium alloy and utilizes 25-mm porcine xenograft valves in the inflow and outflow conduits. The device uses pusher plate technology to generate pulsatile flow with a stroke volume of 83 mL and a maximal output of 10 L/min. The LVAD is operated in either fixed mode with a set rate, or in automatic mode, in which the pusher plate is activated when the device senses filling of the blood chamber. In the event of electrical failure of the device, the pusher plate can be driven pneumatically with either a hand pump or the large pneumatic console. The inflow cannula is typically placed in the apex of the left ventricle, with the outflow graft anastomosed to the ascending aorta.[68] The pump is placed either intra-abdominally or in a preperitoneal pocket in the left upper quadrant,

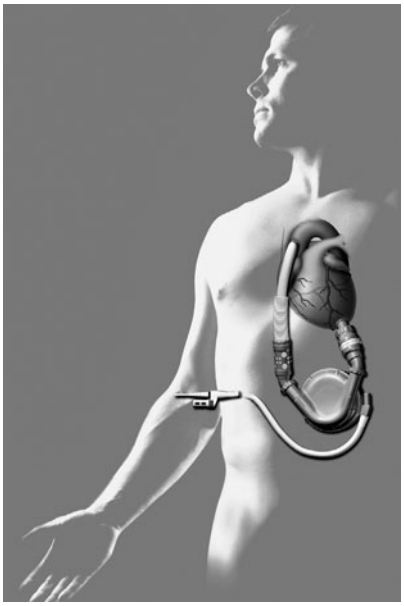

Figure 67-2. The Heartmate left ventricular assist device. *(Courtesy of Thoratec Corp., used with permission.)*

with a driveline tunneled subcutaneously and brought out of the right upper quadrant. Our preference is to create a preperitoneal pocket due to complications associated with intra-abdominal placement.[69] Due to the size and physical characteristics of the Heartmate LVAD, patients undergoing implantation must have a body surface area (BSA) of at least 1.5 m^2.

A unique feature of the device is its sintered titanium and textured polyurethane internal surfaces (Fig. 67-3). This encourages the deposition of circulating cellular elements and the formation of a pseudointima. As a result, the device has a relatively low incidence of thromboembolic events without the need for systemic anticoagulation with warfarin.[70] Patients are maintained on aspirin as an anti-inflammatory agent.

A large amount of clinical experience has been gained with the Heartmate LVAD.[41,68,71] The Thoratec registry is a voluntary database that has collected implantation data from 186 centers worldwide. As of November 2004, 4190 Heartmate LVADs had been implanted (1323 pneumatic and 2867 electric). The average duration of support for patients receiving the Heartmate electrically vented device was 152 days, with support as long as 1854 days being reported.[72]

NOVACOR LEFT VENTRICULAR ASSIST SYSTEM: The Novacor LVAS (World Heart Corp., Oakland, Calif) was first successfully used as a bridge to transplantation in 1984 (Fig. 67-4). It is currently FDA approved for this indication, and has been implanted in over 1700 patients worldwide. Like the Heartmate device, the Novacor LVAS originated as a large console-based system. In 1993, the first portable controller unit with rechargeable batteries was introduced.[73,74]

The device uses dual pusher plates to compress a seamless polyurethane sac, generating pulsatile blood flow of up

Figure 67-3. The textured internal surfaces of the Heartmate left ventricular assist device. *(Courtesy of Thoratec Corp., used with permission.)*

Figure 67-4. The Novacor left ventricular assist system. *(Courtesy of World Heart Corp., used with permission.)*

to 9 L/min. Unidirectional flow is achieved with bioprosthetic valves in both the inflow and outflow conduits. The device can be operated in a fixed mode, an automatic mode, and a synchronized mode. The synchronized mode uses the electrocardiogram signal to coordinate cardiac systole with pump diastole, allowing for maximal device filling. The surgical placement of the device is similar to that of the Heartmate LVAD, with an inflow cannula placed in the left ventricular apex, outflow to the ascending aorta, pump placement in the preperitoneal space of the left upper quadrant, and a percutaneous driveline brought out through the right upper quadrant.

The Novacor system, unlike the Heartmate device, requires systemic anticoagulation with warfarin. Despite systemic anticoagulation, some series have reported thromboembolic rates of over 20%.[75,76] A difficulty, however, in comparing rates of thromboembolism and neurologic events between the Heartmate XVE and Novacor LVAS lies in the variability of definitions used in the literature. Pasque and Rogers used the Heartmate XVE manual definitions of thromboembolic events and applied them to their experience with the Novacor device, finding similar rates of "neurologic dysfunction" (20% for the Novacor versus 27% for the Heartmate) and thromboembolism (10% for the Novacor versus 12% for the Heartmate).[77] The original inflow cannula, constructed of low-porosity polyester (Cooley, Meadox Medical, Oakland, NJ), has been implicated as a source for thromboembolic events. Modifications have included the more recent use of an integral wall reinforced knitted, gelatin-sealed polyester graft (Sulzer Vascutek Ltd., Renfrewshire, Scotland, UK). Portner and colleagues reported on the results of 202 patients receiving the newer inflow conduit (compared to a control group of 280 patients) and found an almost 50% reduction in the incidence of embolic cerebrovascular accidents.[76] Other series have also demonstrated similar results with the use of the Vascutek graft.[78] More recently, expanded polytetrafluoroethylene has been used to construct the inflow conduit (Edwards Lifesciences, Irvine, Calif) with encouraging results.[79]

The Novacor system has demonstrated excellent long-term durability, with over 60% of patients surviving to transplantation.[73,75] Support of more than 4 years without device exchange has been reported.[80] The Investigation of Non Transplant Eligible Patients who are Inotrope Dependent is a nonrandomized trial, currently nearing completion, evaluating the efficacy of the Novacor LVAS for destination therapy.[81]

Figure 67-5. The Thoratec intracorporeal ventricular assist device. *(Courtesy of Thoratec Corp., used with permission.)*

THORATEC INTRACORPOREAL VENTRICULAR ASSIST DEVICE: The Thoratec intracorporeal ventricular assist device (Thoratec Corporation, Pleasanton, Calif) is presently FDA approved for use as a bridge to transplantation and for support in the setting of postcardiotomy shock (Fig. 67-5). The design is based on the success of the Thoratec paracorporeal VAD (described below). Like the paracorporeal system, the intracorporeal VAD offers the advantage of versatility, being able to provide isolated right, left, or biventricular support.

The device housing is constructed of a smooth-surfaced polished titanium alloy. The pumping chamber is a seamless sac made of Thoralon. Unidirectional flow is achieved with the same monostrut occluder disk valves used in the paracorporeal system. Pneumatic compression of an actuation diaphragm achieves pulsatile flow. A small infrared sensor detects whether the sac is full or empty. The device has a stroke volume of 65 mL and is able to generate a maximal flow of about 7.2 L/min. Placement of the housing is either intra-abdominal or preperitoneal, with a percutaneous driveline that exits the skin. As with the paracorporeal system, anticoagulation with heparin and warfarin is required.[82,83]

Clinical data provided by Thoratec on 30 patients undergoing implantation of the device demonstrated a 68% success rate in treatment. Twelve patients were bridged to transplant, 5 patients were bridged to recovery, and 5 patients had ongoing support as of 2003. In this cohort, 63% underwent placement as an LVAD, and 37% for biventricular support. The mean duration of support per patient was 82 days. The size of the device has limited use to a smaller group of patients compared to the larger Heartmate and Novacor LVADs. The mean BSA in these patients was 1.94 m^2, with a range of 1.31 to 2.35 m^2.[84]

Pulsatile-paracorporeal devices

THORATEC PARACORPOREAL VENTRICULAR ASSIST DEVICE: The Thoratec paracorporeal VAD is the result of work done in the 1970s by Pierce and Donachy at Pennsylvania State University (Fig. 67-6). It has been used extensively, with over 2800 implants having been performed worldwide as of November 2004. The device is versatile, offering the option of right, left,

Figure 67-6. The Thoratec paracorporeal ventricular assist device. *(Courtesy of Thoratec Corp., used with permission.)*

or biventricular support. The paracorporeal placement of the pumping chamber allows use in patients with BSAs of $<1.5\ m^2$. The device has been used in a patient weighing only 17 kg with a BSA of $0.73\ m^2$.[84]

The Thoratec paracorporeal VAD consists of a polyurethane blood sac contained within a polycarbonate housing. A large pneumatic console is used to generate pulsatile flow with a maximum stroke volume of 65 mL. Flow rates of up to 7.2 L/min can be achieved. As with the intracorporeal VAD, unidirectional flow is maintained with tilting disk mechanical valves. Since the pumping chamber is placed paracorporeally, less surgical dissection is required at implantation. For left-sided support, inflow cannulas can be placed either in the apex of the left ventricle or in the left atrium, with the outflow graft anastomosed to the ascending aorta. For use as a right VAD, inflow can be achieved either by cannulation of the right atrium or by direct placement into the right ventricle, with outflow into the main pulmonary artery. The device does require systemic anticoagulation with heparin and warfarin. While the dual driver console unit is large and cumbersome, the introduction of the TLC-II portable driver has allowed improved patient mobility and rehabilitation.[85]

As of November of 2004, the voluntary Thoratec registry has reported the use of the paracorporeal VAD system in over 2850 patients, with the longest duration of support being 566 days. In over 1900 patients undergoing implantation for bridge to transplantation, 58% underwent biventricular VAD placement, 35% had left VAD placement, and 7% underwent isolated right VAD placement. Successful bridge to transplantation in various reports has been >60% and is dependent on whether single or biventricular support is required.[85–87]

Axial flow pumps

Axial flow pumps utilize a rotating impeller to provide continuous nonpulsatile blood flow. They typically operate quietly and with less power consumption than the pulsatile LVADs. Due to a decreased number of moving parts and contact bearings, they offer the theoretical advantage of enhanced durability. The smaller size of these devices affords easier implantation and explantation, as well as allowing for support in smaller-sized adults and pediatric patients. Disadvantages of axial flow pumps include the lack of backup mechanisms in the event of device failure, hemolysis secondary to shear forces, and the potential for creating negative intraventricular pressure and subsequent device thrombosis, air embolism, or arrhythmias. Optimization of preload and proper inflow cannula placement are particularly important with axial flow devices to avoid generating negative intraventricular pressure.

At present, the effects of long-term nonpulsatile flow on end-organ function are not entirely known. While differences in the microcirculations of various organs have been demonstrated with nonpulsatile flow, recent evidence seems to suggest that normal end-organ function can be maintained with continuous nonpulsatile axial flow with no adverse effects on morbidity or mortality.[88–91]

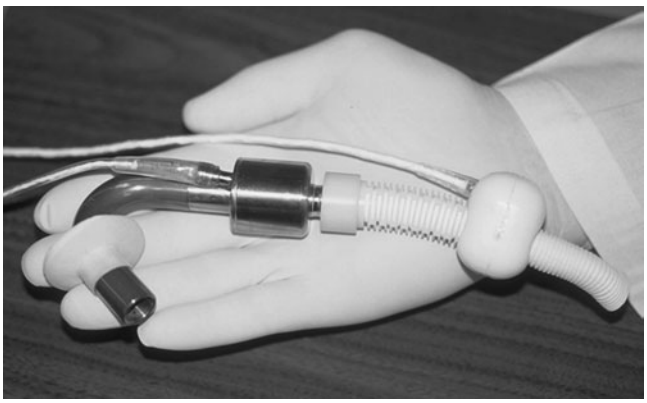

Figure 67-7. The MicroMed DeBakey axial flow pump. *(Courtesy of MicroMed, Inc., used with permission.)*

MICROMED DEBAKEY VENTRICULAR ASSIST DEVICE: The MicroMed DeBakey VAD (MicroMed Cardiovascular Inc., Houston, Tex) was developed in the late 1980s as a collaborative effort between Drs. Michael E. DeBakey and George P. Noon of the Baylor College of Medicine and National Aeronautics and Space Administration engineers (Fig. 67-7). The pump unit, made of titanium, is only 1.2 inches in diameter and 3 inches long and weighs 95 grams. The impeller /inducer is capable of generating flows of up to 10 L/min. Components of the pump include a titanium inflow cannula, a flowmeter, a Dacron outflow graft (Sulzer CarboMedics Inc., Austin, Tex), and a percutaneous cable that connects to a portable control console and battery packs.[92] The inflow cannula is placed in the left ventricular apex, with the outflow graft anastomosed to either the ascending or descending thoracic aorta. Surgical implantation through both a median sternotomy and left thoracotomy have been described.[93] The pump is usually initiated at 7500 rpm and adjusted to maintain average flow rates of between 3.9 and 5.4 L/min. The ultrasonic flow probe on the outflow graft facilitates pump speed adjustment as well as providing an indication of excessive ventricular suctioning. Patients do require systemic anticoagulation with warfarin to maintain an International Normalized Ratio of 2.0 to 2.5.

The MicroMed DeBakey VAD has been implanted in over 300 patients worldwide. Long-term support of over 200 days in 9 patients has been reported.[94] The results of a preliminary clinical trial in 30 patients demonstrated a bridge-to-transplantation rate of 67%. Bleeding was the most commonly observed adverse event, likely related to the need for systemic anticoagulation.[92,95] The portability of the device has allowed patients to rehabilitate at home while awaiting transplant. The device is presently in ongoing clinical trials.

JARVIK 2000: The Jarvik 2000 (Jarvik Heart Inc., New York, NY) was developed by Dr. Robert Jarvik in the late 1980s (Fig. 67-8). The electromagnetically actuated pump is constructed of titanium, measures 2.5 cm in diameter, and weighs 90 g. It has a displacement of 25 mL. Titanium impeller blades are held in place by ceramic bearings. The impeller rotates at speeds of between 8000 and 12,000 rpm

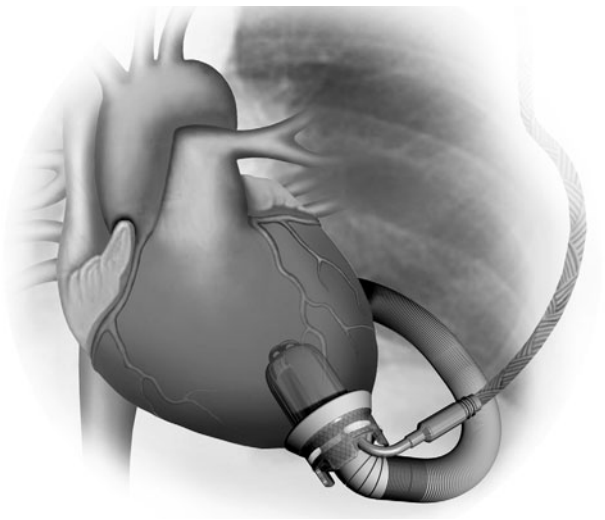

Figure 67-8. The Jarvik 2000 axial flow pump. *(Courtesy of the Texas Heart Institute, used with permission.)*

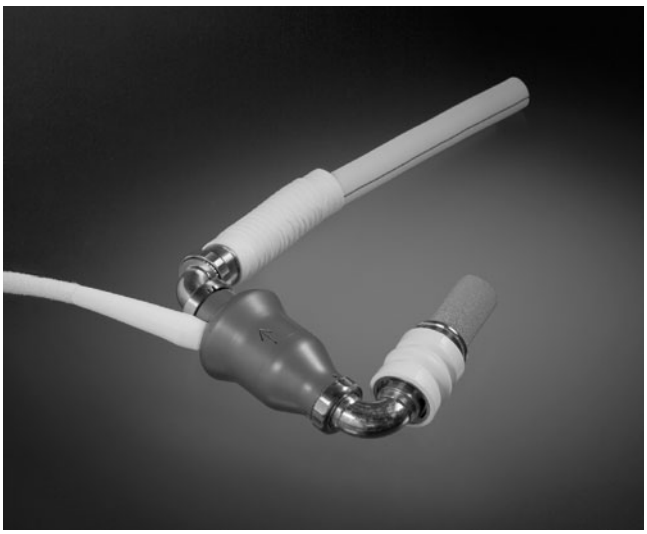

Figure 67-9. The Heartmate II axial flow pump. *(Courtesy of Thoratec Corporation, used with permission.)*

and can generate maximum flows of 7 L/min. A unique feature of this device is that the actual pumping chamber is implanted within the left ventricle. The outflow graft is anastomosed to the descending thoracic aorta. Pump implantation is usually done through a left thoracotomy incision. The pump can be operated via either a fixed-rate analog system or a variable-speed microprocessor-controlled system.[96]

The Jarvik 2000 is available in a few different versions based on the energy systems. There is a percutaneous model, which like other devices has a power line that exits the patient's abdominal wall. There is also a version that is based on skull-mounted pedestals used with cochlear implants, where a titanium pedestal is screwed into the skull with a transcutaneous connector that attaches to the power cord. This vascularity of the skull contributes to a low risk of infection, making this system suitable for long-term support. There is also a completely implantable version that utilizes a transcutaneous energy transfer system.[96]

Siegenthaler and coworkers recently reported on the mechanical reliability of the device. In 102 patients undergoing implantation of the Jarvik 2000 over a 4-year period, there was no implantable component failure. In patients being bridged to transplant, mean support time was 159 days. For destination therapy, mean support time was 551 days, with six patients being supported for >2 years, and the longest being close to 5 years.[97]

HEARTMATE II: The Heartmate II ventricular assist device (Thoratec Corporation, Pleasanton, Calif) is an axial flow device that was developed in the early 1990s through a partnership between the University of Pittsburgh and the Nimbus Company (Fig. 67-9). The device is an axial-flow rotary pump constructed of titanium. The pump can generate flows of up to 10 L/min, and is designed to operate at speeds of between 6000 and 15,000 rpm. Inflow is through the apex of the left ventricle, with an outflow to the ascending aorta. The pump housing is implanted in a small preperitoneal pocket or within the abdominal musculature. A small percutaneous driveline exits the right upper quadrant. The device does require systemic anticoagulation with warfarin. The pump can be operated in both a fixed and an automatic mode.[98]

The device began a multicenter clinic trial in November of 2003. Enrollment in the trial has recently been completed. Pagani and colleagues reported on the initial results of this trial in early 2005. Twenty-three patients underwent implantation, with an increase in mean cardiac index from 2.0 ± 0.5 L/min/m^2 to 3.4 ± 0.5 L/min/m^2 during the first postoperative week. Four patients were successfully bridged to transplant, and 15 patients remained on support, with the longest duration being 318 days.[99]

Totally implantable devices

ARROW LIONHEART LVD-2000: The Arrow LionHeart LVD-2000 (Arrow International, Reading, PA) is a totally implantable pulsatile ventricular assist device designed with the goal of destination therapy for patients in end-stage heart failure. The implantable components of the device include the actual titanium blood pump with inflow and outflow assemblies, motor controller, a compliance chamber, and a transcutaneous energy transmission system. There are no percutaneous lines or connections. The compliance chamber consists of a circular polymer sac and an attached subcutaneous port infusion system. Recharging of the batteries is accomplished through a transcutaneous system with a wand overlying the recharging coil implanted under the skin. Patients may be completely disconnected from the external power supply for only a short period of time. The pump has a stroke volume of 64 mL and generates pulsatile blood flow of up to 8 L/min using pusher-plate technology. Inflow, as with other pulsatile devices, is achieved through the left ventricular apex, with outflow to the ascending aorta. Tilting disk valves in the inflow and outflow assemblies maintain unidirectional flow.[100]

El-Banayosy and associates reported on the results of implantation in six patients. Mean duration of support was 245 days, with the longest being 670 days. Three patients were discharged home. They found no device-related failures or infections.[101] The Arrow LionHeart VAD recently completed European clinical trials. Presently, a new version of the device is undergoing development that has improved battery life and a smaller controller. It will likely undergo clinical trials in the near future.

Total artificial heart

CARDIOWEST TOTAL ARTIFICIAL HEART: The CardioWest Total Artificial Heart (TAH; SynCardia Systems Inc., Tucson, Ariz) is FDA approved for use as a bridge to transplantation in patients with biventricular failure. The device, formerly the Jarvik-7 and Symbion TAH, is a pneumatically driven biventricular assist device that is implanted orthotopically after excision of the native ventricles and cardiac valves. The internal surfaces of the devices are lined with polyurethane, along with a polyurethane diaphragm that is pneumatically displaced. Unidirectional flow is maintained by Medtronic-Hall mechanical valves in the inflow and outflow conduits (Medtronic, Inc., Minneapolis, Minn). The device has a maximum stroke volume of 70 mL and is capable of generating flows of more than 10 L/min. Adequate intrathoracic space is required for device implantation. Patients usually must have a BSA 1.7 m^2 or greater, a cardiothoracic ratio >0.5, an anteroposterior dimension of at least 10 cm, and combined ventricular volumes of >1.5 L. The device does require both antiplatelet therapy and systemic anticoagulation with warfarin. The two pneumatic drivelines, which exit the skin, are connected to a large console controller that limits patient mobility and prevents discharge from the hospital. A more portable controller system is currently under development and has been used in Europe.[9,102–104]

Copeland and coworkers reported the results of a multicenter trial of the TAH as a bridge to transplantation. In 81 patients undergoing implantation of the device, survival to transplant was 79%. One-year survival following device implantation was 70%. The mean time from implantation to either transplantation or death was 79.1 days. Posttransplant survival at 1 and 5 years in patients being bridged with the TAH was comparable to historical United Network for Organ Sharing controls.[102]

ABIOCOR IMPLANTABLE REPLACEMENT HEART: The AbioCor system (Abiomed Cardiovascular Inc., Danvers, Mass) is a totally implantable artificial heart without any percutaneous lines (Fig. 67-10). It is designed for destination therapy. The implantable components of the device are the AbioCor thoracic pumping unit, controller, battery, and transcutaneous energy transfer system. The device is implanted orthotopically once the native heart has been excised, leaving behind atrial cuffs. The two polyurethane pumping chambers have a stroke volume of 60 mL and are capable of providing a cardiac output of up to 8 L/min. A centrifugal pump functions to pressurize a low-viscosity hydraulic fluid, which with a switching valve provides alternating left- and right-sided systole. An atrial flow-balancing chamber is used to adjust for differences in right and left atrial pressures. All blood-contacting surfaces, including the valves of the device, are made of smooth polyurethane. Patients are maintained on systemic anticoagulation with warfarin and antiplatelet therapy with clopidogrel.[105]

Figure 67-10. The AbioCor implantable replacement heart. *(Courtesy of Abiomed, Inc., used with permission.)*

After extensive animal testing at the University of Louisville and the Texas Heart Institute in the late 1990s, the FDA granted approval for a multicenter clinic trial in 2001. Since the device is intended for use as destination therapy, patients in the clinic trial were not transplant eligible. Dowling and associates recently reported the initial clinical experience with the system in seven patients. There were no significant device malfunctions or device-related infections. Thromboembolic complications were seen to result from clot formation on the atrial cage struts, which have been removed for future implants. Three patients were able to make multiple trips outside the hospital, and two patients were discharged. The multicenter clinical trial is presently ongoing.[106]

Newer-generation and future devices

There are presently over 20 new devices either in development or in investigational use. Newer-generation devices try to address the shortcomings of current device technology such as thromboembolic complications, device-related infection, and limited durability. Many third-generation devices make use of magnetic levitation technology, in which a rotating impeller is magnetically suspended within a column of blood, obviating the need for contact-bearing moving parts, providing the theoretical advantage of enhanced durability. Continuous flow pumps are also smaller in size, allowing easier implantation with less surgical trauma, and potentially decreased infectious complications. Advances in

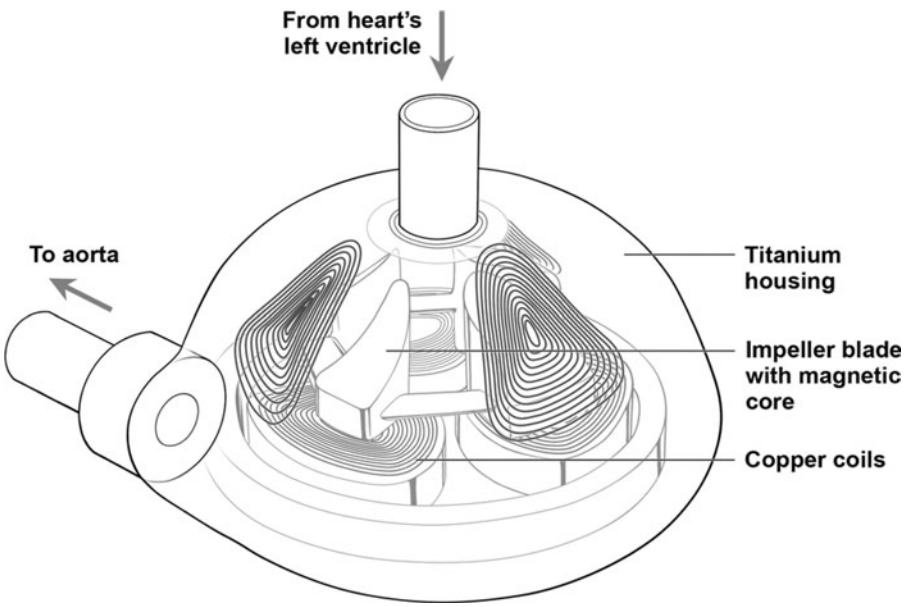

Figure 67-11. The VentrAssist left ventricular assist system. *(Courtesy of Ventracor, used with permission.)*

energy systems have allowed for totally implantable devices without the need for percutaneous lines. Smaller control consoles have afforded greater patient mobility and rehabilitation, as well as allowing patients to be discharged from the hospital. A few of the more recent devices in development and clinical trials will be discussed below.

The Incor left ventricular assist device (Berlin Heart AG, Berlin, Germany) is a magnetically-actuated axial flow pump that weighs 200 g and is 3 cm in diameter. The device's flow is created by an impeller that is held in place by a magnetic bearing. The impeller is not in contact with any other parts and is capable of rotation at 10,000 rpm, producing a flow of up to 7 L/min. Schmid and coworkers reported their initial clinical experience in 15 patients, with 5 patients being successfully bridged to transplant, and one patient being weaned after 171 days of support. Three patients were still supported, and six patients died while on support.[107]

The VentrAssist left ventricular assist system (Ventracor Ltd., Chatswood NSW, Australia) is a centrifugal pump that has a hydrodynamically suspended rotor as its only moving part (Fig. 67-11). The design of the pump maximizes blood flow across all blood-contacting surfaces to avoid stasis and the potential for thrombus formation. The pump weighs about 300 g and measure 2.5 inches in diameter. The device will likely be in clinical trials soon.[108]

WorldHeart (World Heart Corp., Oakland, Calif) has two newer-generation LVADs in development and preclinical testing. The Novacor II is designed to be a totally implantable pump that utilizes pusher plate technology with magnetic actuation to provide pulsatile flow. The WorldHeart rotary ventricular assist device is a magnetically levitated centrifugal pump designed for destination therapy.[109]

Thoratec (Thoratec Corp., Pleasanton, Calif) also is in the process of preclinical evaluation of the Heartmate III. This device is a magnetically suspended centrifugal pump that also uses transcutaneous energy transfer system technology to be totally implantable.[84] Other devices employing magnetic levitation technology include the Terumo DuraHeart (Terumo Heart Inc., Ann Arbor, Mich) and the CorAide blood pump (The Cleveland Clinic Foundation, Cleveland, Ohio).[110]

SURGICAL TECHNIQUE

There are many variations in surgical techniques for left ventricular assist device implantation. In general terms, however, there are a few common steps in the techniques of device implantation. These are (1) mediastinal exposure and creation of the device pocket; (2) outflow graft construction to the ascending aorta; (3) placement of device inflow, usually from the left ventricular apex; (4) de-airing of the device; and (5) device actuation and weaning from cardiopulmonary bypass support. Preoperative preparation includes appropriate correction of coagulopathy with blood product transfusion and vitamin K administration. Preoperative antibiotic prophylaxis covering both gram-positive and gram-negative bacteria is administered and usually continued for 48 to 72 hours postoperatively. Serine protease inhibitors (e.g., aprotinin) are administered prior to skin incision and continued in the perioperative period until mediastinal bleeding has subsided.[111]

A vertical midline incision is made with extension into the abdomen. After standard median sternotomy, a preperitoneal pocket is created in the left upper quadrant.[112] Often the preperitoneal plane is very thin and attenuated, so the posterior rectus sheath is entered and the plane developed. After systemic heparinization, the patient is cannulated for cardiopulmonary bypass. Venous cannulation can be achieved with either a single dual-stage cannula placed in the right atrium, or with standard bicaval cannulation if concomitant procedures are being performed (i.e., tricuspid

valve repair or closure of a patent foramen ovale). Our preference is to cannulate the superior vena cava with a large 31F metal tip right-angle cannula directed into the right atrium. This provides excellent venous drainage while allowing for easy conversion to bicaval cannulation if necessary. The ascending aorta is cannulated distally with consideration for future reoperation for cardiac transplantation.

An effort is made to minimize cardiopulmonary bypass times in this ill group of patients. After cannulation, the device is brought onto the field and positioned in the preperitoneal pocket. The driveline is tunneled percutaneously and brought out of the skin through a counterincision placed in the right upper quadrant. If the hemodynamic status permits, an attempt is made to perform the outflow graft anastomosis off-pump using a partial occluding clamp placed on the ascending aorta. The outflow graft is measured and cut with enough length to allow for a gentle curvature toward the right chest without redundancy that may lead to outflow graft kinking. A longitudinal aortotomy is created and the anastomosis performed using continuous 4-0 polypropylene suture. The anastomosis is reinforced with BioGlue (CryoLife Inc., Kennesaw, Ga).

Cardiopulmonary bypass is initiated and attention is turned to the placement of the left ventricular apical inflow cannula. This is usually done under conditions of normothermia with a beating heart. The presence of left ventricular thrombus may necessitate cardioplegic arrest to prevent systemic embolization. A specialized coring knife is used to create the apical core. Care must be taken to correctly identify the apex of the left ventricle and avoid deviation into the septum. After coring of the apex, care is taken to ensure a clear inflow tract. Any excess trabeculations or myocardium that may impinge on the inflow cannula are excised. Ventricular thrombus is carefully removed. Sutures of 2-0 braided polypropylene reinforced with felt pledgets are then placed around the circumference of the core in a horizontal mattress fashion and passed through the sewing ring of the inflow cuff. The cuff is secured and then attached to the inflow cannula of the device. The heart is allowed to fill with blood and the device is de-aired through a venting hole placed in the outflow graft. Evacuation of air is confirmed with transesophageal echocardiography. The patient is then weaned from cardiopulmonary bypass simultaneously with initiation of the device. After ensuring adequate hemostasis, drains are placed in the mediastinum, pleural spaces, and device pocket. A Gore-tex pericardial membrane (Gore Medical Products, Flagstaff, Ariz) is placed over the anterior mediastinal structures and secured to the pericardial edges to minimize the risk of injury during reoperative median sternotomy. The sternum and soft tissues are then closed in the standard fashion. Particular attention is given to secure abdominal fascial closure to prevent wound dehiscence and subsequent device infection. In certain patients in whom excessive mediastinal bleeding is encountered secondary to coagulopathy, our preference is to pack the mediastinum and perform delayed sternal closure after approximately 24 hours, once bleeding has subsided and the patient has been adequately resuscitated.

POSTOPERATIVE MANAGEMENT

Meticulous postoperative care is critical to successful outcomes in patients undergoing mechanical device implantation. In the immediate perioperative period, proper device function must be ensured to restore and maintain adequate end-organ perfusion. Inadequate device flows may be the result of mechanical problems such as inflow cannula obstruction or malposition, outflow graft kinking, or cardiac tamponade. Phosphodiesterase inhibitors and inhaled nitric oxide are used liberally to support and optimize right ventricular function.[113] Arginine vasopressin has been shown to be effective in treating vasodilatory hypotension in this group of patients.[114] Excessive afterload, particularly with axial flow devices, may impair pump outflow and should be treated accordingly.

Antibiotic prophylaxis is begun preoperatively and is usually continued for 48 to 72 hours postoperatively. The serine protease inhibitor aprotinin is also initiated prior to incision and continued postoperatively until mediastinal bleeding has subsided.[111] Blood product transfusion with platelets, fresh frozen plasma, and cryoprecipitate is given as needed. Once bleeding has subsided, usually by 24 to 36 hours, aspirin and systemic anticoagulation with heparin and warfarin is initiated, depending on the particular device used. Patients are weaned from mechanical ventilatory support as soon as is feasible. Diuretics are administered early in the postoperative course, since many of these patients are in a chronic volume-overloaded state. Perioperative renal insufficiency is usually managed with the early institution of continuous venovenous hemofiltration for optimization of fluid balance. Enteral feedings are resumed early in the postoperative course. Once patients are extubated, attention is focused to physical therapy and rehabilitiation.[115]

COMPLICATIONS

Bleeding

Mediastinal bleeding following left ventricular assist device implantation is relatively common, occurring in some series in as many as 48% of patients.[41,116] This generally requires reoperation early in the postoperative period. Predisposing factors include hepatic congestion and dysfunction related to chronic heart failure, compromised nutritional status, the use of preoperative anticoagulation, extensive surgical dissection, reoperative procedures, prolonged cardiopulmonary bypass, and coagulopathy secondary to interactions between circulating blood elements and the artificial device surfaces.[117]

Due to the requirement of systemic anticoagulation for many devices, as well as the routine use of aspirin as an anti-inflammatory agent, late bleeding and tamponade can occur as well. A high index of suspicion must be maintained in patients with decreased pump flow rates unresponsive to fluid challenge, elevated filling pressures, respiratory distress, or signs of end-organ dysfunction.[118]

The serine protease inhibitor aprotinin has been shown to be of benefit in patients undergoing device implantation. Goldstein and associates reported the retrospective results of 42 patients receiving aprotinin during device implantation compared to a control group of 100 patients. Patients receiving aprotinin had a significant decrease in postoperative blood loss, decreased transfusion requirement, and nearly a 50% reduction in the need for right ventricular assist device placement. Overall perioperative mortality was also reduced in the aprotinin group as well.[111]

Infection

Infection remains a significant source of morbidity and mortality in patients receiving mechanical circulatory support. In the REMATCH trial, the leading cause of death in patients receiving devices was sepsis, accounting for 20 of 52 deaths in this group.[10] A subsequent analysis focusing on infection during the REMATCH trial showed that freedom from sepsis in patients with LVADs was 58% at 1 year and 48% at 2 years. The peak hazard for sepsis occurred early, within 30 days from implantation.[119]

Infections in LVAD patients can affect different components of the device and can vary in severity. These include infections at the driveline exit site, device pocket infections, device endocarditis, and bloodstream infection.[120] Patients can also develop infectious complications at sites remote from the device such as in the respiratory, gastrointestinal, or genitourinary tracts, as well as from indwelling intravenous and central lines. Other patient factors that may increase susceptibility to infection include generalized debilitation and malnutrition, diabetes, renal failure, and immunologic derangements associated with T-cell death seen after device implantation.[121]

A wide range of infection rates has been reported in the literature, partly due to varying definitions of device infections.[41,116] Overall infection rates in patients receiving devices at all sites have been approximately 50%.[120,122] Up to 25% of deaths in LVAD patients are due to systemic sepsis, which occurs in 11 to 26% of patients.[123,124] Bacteria that are able to form a biofilm are common pathogens, including *Staphylococcus*, *Pseudomonas*, *Enterococcus*, and *Candida*.[123,125] While some patients can be treated conservatively with antibiotic-suppressive therapy, others may need surgical drainage of abscesses or fluid collections, débridement, or device exchange. In some cases, the only therapeutic option is device removal and transplantation. Fortunately, device-related infections do not seem to have an adverse impact on transplant outcomes.[126]

Thromboembolism

Thromboembolic events can lead to devastating neurologic and end-organ injury and remain a significant concern in patients undergoing mechanical device placement. Approximately one-third of patients having an LVAD will suffer from such an event.[12] In the REMATCH trial, the rate of neurologic events was 4.35 times higher than in the medically treated group, with 47% of such events being transient.[10] Difficulty in accurately comparing the incidence of thromboembolism among different devices is partly due to inconsistent definitions, as described by Pasque and Rogers.[77] The Heartmate XVE, with its sintered titanium and textured polyurethane internal surfaces, has a relatively low incidence of thromboembolic events without the need for systemic anticoagulation with heparin or warfarin. All device patients are maintained on aspirin, mainly for its anti-inflammatory effect. Most devices presently require anticoagulation with heparin and warfarin to maintain an International Normalized Ratio between 2.5 and 3.5. In addition, depending on the system used, many patients are maintained on antiplatelet therapy with dipyridamole and clopidogrel. Vigilant control of anticoagulation parameters is necessary to balance the risk of thrombus formation with the threat of late mediastinal bleeding.

Right-Sided Heart Failure

Approximately 20% of patients undergoing left ventricular assist device placement will suffer from postoperative right heart failure.[41,127] A recent series from Columbia University examined the incidence of right heart failure in patients with chronic congestive heart failure undergoing LVAD implantation.[128] In 108 patients, right-sided circulatory failure was seen in 42 patients (38.9%), with 14 patients requiring implantation of a right ventricular assist device. Postoperative right ventricular failure has a significant effect on clinical outcomes, leading to increased intensive care unit length of stay, increased 30-day mortality following LVAD implantation, and a lower bridge-to-transplantation rate.[113,128,129]

Right-sided circulatory failure can result from abnormalities both in the right ventricle as well as in the pulmonary vascular bed. Perioperative factors include myocardial stunning, ischemia, infarction, air embolism, and arrhythmias. Changes in ventricular interdependence and septal shifting secondary to mechanical unloading of the left ventricle as described by Santamore and associates can also contribute to impaired right-sided function.[130] In addition, pre-existing right ventricular dysfunction may be unmasked secondary to the augmented preload presented to the right side following LVAD implantation.[113]

Predicting which patients will manifest right-sided failure can be difficult. Several authors have described preoperative risk factors for the development of right ventricular failure. Ochiai and coworkers,[131] in an analysis of 245 patients undergoing LVAD placement, found preoperative circulatory support, female gender, and nonischemic etiology for heart failure as risks for postoperative right ventricular failure requiring right VAD placement. In addition, hemodynamic parameters associated with right VAD use were low mean and diastolic pulmonary arterial pressures, low right ventricular stroke work, and low right ventricular stroke work index, most likely identifying patients with impaired right ventricular contractility. Elevated pulmonary vascular resistance and pulmonary arterial pressures were

not identified as risk factors.[131] Similar findings have been previously reported.[132]

Clinically, the onset of right ventricular failure can be sudden and may occur at the onset of LVAD device initiation. Right-sided failure results in elevations in central venous pressure and impaired filling of the left side, with low device flows and ultimately compromised systemic perfusion. Improvements in medical management of right ventricular failure have resulted in a decreased incidence of right VAD implantation.[133,134] This includes the use of phosphodiesterase inhibitors, inhaled nitric oxide, and aggressive inotropic support of the right ventricle. Blood product transfusion has been shown to have adverse effects on pulmonary vascular resistance.[135] The use of aprotinin has been shown to decrease blood loss, the incidence of right VAD implantation, and perioperative mortality in patients undergoing LVAD placement.[111] When right VAD support is necessary, improved clinical results have been demonstrated by early implantation within 24 hours.[129]

Multisystem Organ Failure

The onset of multisystem organ failure carries a high mortality in patients undergoing device placement, accounting for almost one-third of patient deaths in some series.[124] Patients undergoing VAD implantation have a high incidence of comorbidities, and many manifest significant end-organ dysfunction preoperatively. Some may not recover organ function following device implantation. Other patients may manifest multisystem organ failure as the end result of complications related to device implantation. These include surgical trauma, prolonged cardiopulmonary bypass times, perioperative bleeding, and sepsis.

Device Failure

Device failure is an ever-present concern in patients with mechanical circulatory assistance. Device durability and freedom from device failure are critical factors in establishing mechanical support as a feasible option for providing long-term support and destination therapy. In the REMATCH trial, device failure was the second most common cause of death, after sepsis.[10] While 1-year freedom from device failure and replacement was 87%, this dropped off to 37% by the second year.[10,136] Device failure can occur in any of the components of the system. These include the inflow and outflow conduits, the pumping chamber, or the external components of the system such as the driveline, power source, or controller units. Depending on the mode of failure, urgent reoperation and device replacement may be required. In the event of device failure, some systems have backup support. For instance, in the setting of electrical failure, the Heartmate LVAD can be driven by a pneumatic console. Some newer-generation continuous flow devices, however, lack this provision. In the event of device malfunction, the patients are dependent on their native ventricular function.

Cardiac catheterization as well as transesophageal echocardiography have both been described as useful tools for the diagnosis of device malfunction.[137,138] As clinical experience with individual devices accumulates, modes of failure that are amenable to design change become apparent, allowing for device modification and improvement. Design alterations during and since the conclusion of the REMATCH trial in the Heartmate LVAD include a bend relief to prevent outflow graft kinking, modifications in the inflow assembly to facilitate valve replacement, and smaller size and greater compliance of the percutaneous driveline. Modifications in the controller software allow limitation of pump pressures, thereby reducing stress on bearings, the diaphragm, and the inflow valve.[136] Newer-generation axial and centrifugal flow pumps attempt to address the shortcomings of first-generation devices with smaller pumping chambers and drivelines, transcutaneous energy sources, and the use of magnetic levitation technology to eliminate contact-bearing moving parts, offering the hope of enhanced durability.

Immunologic Effects and Allosensitization

The interaction between prosthetic device surfaces and circulating blood elements has systemic immunologic effects in patients undergoing device implantation. Itescu and John have described the specific cellular changes that occur.[139] First, a number of alterations are seen in T-cell function. These include aberrant T-cell activation and heightened T-cell proliferation, as well as increased apoptotic cell death, and simultaneous defects in T-cell proliferation in response to T-cell–receptor activation. In addition, T cells in LVAD patients demonstrated increased susceptibility to activation-induced cell death. Another aspect of immunologic disturbance that is seen is B-cell hyperreactivity. Alterations in circulating cytokines and cellular milieu are postulated to be responsible for polyclonal B-cell activation. Patients undergoing LVAD placement have a higher frequency of circulating antiphospholipid and anti–human leukocyte antigen antibodies.[121,139]

The overall clinical effect of these changes is twofold. First, patients demonstrate progressive defects in cellular immunity, with a resultant increased risk of infection. Second, B-cell hyperreactivity ultimately leads to allosensitization to human leukocyte antigens. In analysis of a series of 105 patients at Columbia University undergoing cardiac transplantation after being bridged with an LVAD, 66% were sensitized prior to transplant, as opposed to only 6% of non-bridged patients.[140] Untreated allosensitization is associated with prolonged pretransplant waiting times, as well as an increased risk of acute rejection.[140] When sensitization develops, immunomodulation with intravenous immunoglobulin therapy in conjunction with cyclophosphamide has proven to be effective in reducing alloreactivity, and reducing the risk of acute rejection.[139,140]

CLINICAL RESULTS

With limitations in donor availability and prolonged transplant waiting times, mechanical circulatory support has

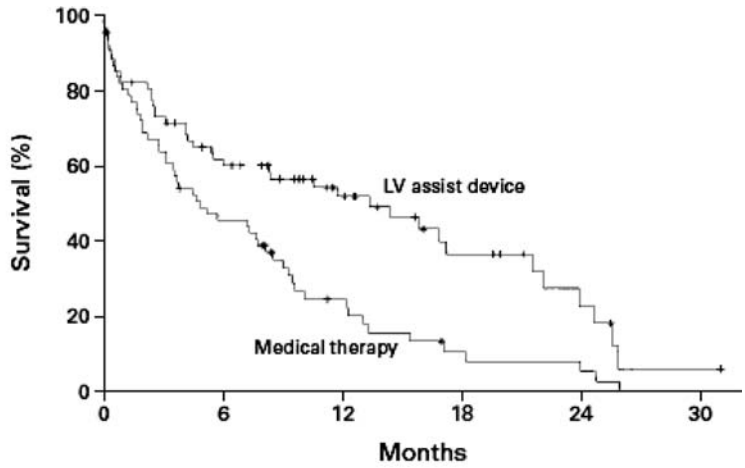

Figure 67-12. Comparison of actuarial survival curves from the REMATCH trial. *(Reproduced with permission from Rose et al.[10])*

emerged as an important tool for both bridging to transplantation and destination therapy, as well as offering a small subset of patients the chance for myocardial recovery.

The multicenter REMATCH trial enrolled 129 patients in end-stage heart failure who were not eligible for transplantation. Patients were randomized to receive either an LVAD (Heartmate VE) or optimal medical therapy. The primary endpoint was death from any cause, with several secondary endpoints such as the incidence of adverse events, days of hospitalization, quality of life, and functional status. When compared to the medically treated group, patients receiving an LVAD had a 48% reduction in the risk of death from any cause (Fig. 67-12). In addition, various quality-of-life and functional status measurements were higher in patients receiving mechanical circulatory support. The limitations of device therapy, however, were highlighted by the increased number of adverse events in the LVAD group. Device patients were more than twice as likely to have an adverse event compared to the medically treated group. The probability of device-related infection was 28% within 3 months after implantation, with the leading cause of death being sepsis. The probability of device failure was 35% at 24 months and represented the second most common cause of death in this group. There was also a significant incidence of bleeding, occurring in 42% of patients by 6 months.[10] Since the conclusion of REMATCH, further analysis of the data by "era" has demonstrated improved survival in device patients enrolled during the second half of the trial.[141] Similar improvements in results for destination therapy have been reported in other series after the REMATCH trial.[142] This is likely a reflection of design enhancements to the device and improvements in patient management. Thus, the REMATCH trial established LVAD therapy as a feasible option for long-term support of patients in end-stage heart failure.

In 2002, the International Society for Heart and Lung Transplantation (ISHLT) began the ISHLT Mechanical Circulatory Support Device database. This voluntary database has collected information on mechanical circulatory support from 60 centers globally. The most recent third annual report in 2005 represents data from 655 patients.[143] The vast majority of patients underwent isolated LVAD placement, approximately 90% of which were pulsatile flow devices. Overall survival was 83% at 1 month and 50% at 1 year. Risk factors for mortality included advanced age and the need for biventricular support. With regard to intent of treatment, 78.3% of patients had device placement as a bridge to transplantation, 12% as destination therapy, and 5.3% as a bridge to recovery. Common adverse events included infection (32.5%), bleeding (27.8%), arrhythmia (24.2%), and renal dysfunction (20.6%). Bridge to transplantation was stratified by age, with 75% of patients <30 years of age transplanted by 1 year. In this group, there was a 13% mortality while on device support. For patients older than 50 years of age, 50% of patients were successfully transplanted, but mortality was considerably higher at 40% while on mechanical support.

Morgan and associates recently reported the bridging-to-transplantation experience at Columbia Presbyterian Hospital.[144] This series of 243 patients spanned a period of 12 years and included three versions of the Thoratec Heartmate device (pneumatic, dual-lead vented electrical, and single-lead vented electrical). Over this time period, improvements were seen in rates of successful bridge to transplantation and in 1-, 3-, and 5-year survival following transplant. The authors attribute this improvement to a combination of factors, including advances in device design, patient selection, surgical technique, and perioperative patient management.

CONCLUSIONS

Mechanical circulatory support has emerged as an important therapeutic option in the treatment of both acute and

chronic heart failure of various etiologies.[145] Active areas of investigation include the effects of mechanical unloading on ventricular remodeling, as well as the potential use of device support in conjunction with other modalities such as gene therapy, pharmacotherapy, and stem cell implantation to promote myocardial recovery. At present, bridge to recovery represents only a small percentage of patients undergoing device placement.[146,147] Limitations of current device technology have fueled intensive research and development efforts to create new devices that offer the hope of improved durability, decreased thromboembolic and infectious complications, and improved quality of life. Decreasing physical size and improved versatility of devices will have important implications for treatment in the pediatric population.[148] Outcomes will likely continue to improve with growing clinical experience and technological advancement.

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CHAPTER 68

Total Artificial Heart

O.H. Frazier • Timothy J. Myers • Igor Gregoric

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States and a significant public health problem in most industrialized nations. Since 1900, it has been the leading cause of death in the United States every year except 1918.[1] In 2002, CVD afflicted 70 million Americans and caused 927,448 deaths. Meanwhile, the number of people with CVD, and especially its advanced forms, has been increasing. There are two main reasons for this. First, while there is still no cure for CVD, palliative therapy has improved to the point that more people are surviving past their initial episodes of CVD to live on with some form of the disease. Second, the average age of the U.S. population is rising as the "baby boom" generation ages.

An increasingly prevalent form of advanced CVD is congestive heart failure (CHF). Almost 4.9 million Americans (approximately 2.4 million men and 2.5 million women) are living with CHF.[1] Its etiology can be ischemic, idiopathic, or viral. More than $36 billion is spent each year on the care of CHF patients, and many therapeutic advances have been made. Nevertheless, between 1979 and 1999 the incidence of CHF increased by 145%. Each year, CHF directly causes 30,000 to 40,000 deaths and indirectly causes another 250,000. As large as the problem is now, its magnitude is expected to worsen as more cardiac patients are able to survive and live longer with their disease and thus increase their chances of developing end-stage CHF.

At present, treatment of advanced CHF takes three forms: medical therapy, surgical therapy, and cardiac replacement.[2] Medical therapy (e.g., intravenous inotropes and vasodilators) relieves symptoms by reducing cardiac work and increasing myocardial contractility. However, while advances in medical therapy have helped improve quality of life for those with heart failure, mortality remains unaffected. Surgical therapy (e.g., revascularization and valve replacement or repair) relieves symptoms of ischemia and valvular dysfunction, but in most cases does not stop the underlying disease process from progressing. When conventional medical and surgical therapies for CHF are exhausted, cardiac replacement (i.e., heart transplantation or implantation of an artificial heart or ventricular assist device) may in some cases become the only therapeutic alternative.

Heart transplantation has evolved into a suitable treatment for advanced CHF. However, it has severe limitations related to patient selection, organ procurement and distribution, and cost-effectiveness. Just over 2000 patients with end-stage heart failure receive heart transplants each year in the United States. However, about 3000 patients are on the active heart transplant waiting list at any given time, and as many as 40,000 more are potential candidates for heart transplantation.[3,4] Heart transplantation for the relatively young (<40 years old) is not very promising because the life expectancy of a donor heart recipient is about 10 years on average and 20 years at most. In 2004, 460 patients on the active waiting list died while awaiting a donor heart. Heart transplantation is also associated with continuous, lifelong, expensive medical therapy.

To help overcome these limitations, engineers and physicians have continued efforts begun over 4 decades ago to develop systems for providing either temporary or permanent mechanical circulatory support (MCS). Originally, such systems were intended to support patients indefinitely because other forms of heart replacement did not appear to be feasible. Temporary MCS has been shown to be a suitable option for some CHF patients who are awaiting heart transplants[5,6] and for others who are not transplant candidates but need support for indefinite periods of time.[7] In recent clinical studies, myocardial function improved sufficiently in some cases to allow removal of the MCS device and avoid heart transplantation.[8,9] Nevertheless, in light of the shortcomings of medical therapy, surgical therapy, and heart transplantation, efforts have continued to develop a total artificial heart (TAH) that would not only save the lives of critically ill CHF patients but also allow them to resume relatively normal lifestyles. Here we review the historical development and current status of TAH technology.

EARLY DEVELOPMENT AND EXPERIENCE

In 1812, LeGallois first proposed the idea of supporting a failing heart with either a permanent or temporary device.[10] In the 1920s, Lindbergh and Carrel discussed and planned an artificial heart.[11] Throughout the 1940s, researchers including Dennis and Gibbon were developing a machine that would bypass the circulation of the heart and lungs to allow open-heart surgery. The modern era of MCS began in 1951 when Dennis first used a heart-lung machine to sustain the circulation while the heart was opened to repair an atrial septal defect.[12] Two years later, Gibbon repeated this procedure.[13] However, high mortality in the first few cases led both Dennis and Gibbon to abandon the use of their heart-lung machines. In 1954, Lillehei began to use cross-circulation (human-to-human perfusion) as a means to support heart and lung function during congenital heart defect repair.[14] However, because of the controversy created by Lillehei's procedure, researchers continued efforts to develop a machine that would allow open-heart surgery.

By 1955, Kirklin at the Mayo Clinic had refined the Mayo-Gibbon machine and the techniques that allowed open-heart surgery.[15] Likewise, DeWall and Lillehei had developed their machine that also allowed for safe open-heart operations.[16] By 1960, Kirklin and Lillehei in Minneapolis and DeBakey and Cooley in Houston had perfected their machines and techniques to the point where heart surgery was becoming routine in Minnesota and Texas. The early developmental work on the use of mechanical circulatory systems by Dennis, Lillehei, DeWall, Gibbon, and Kirklin allowed for many new cardiac operations, including coronary artery bypass, heart transplantation, valve repair, and implantation of a TAH. After refinements of the heart-lung machines, DeBakey and Cooley began to develop many of the surgical techniques that eventually made open-heart surgery routine around the world.

In 1957, Akutsu and Kolff became the first to implant a TAH in vivo.[17] Inserted into the chest of a dog, the pump adequately maintained the circulation for approximately 90 minutes. However, Akutsu and Kolff never applied their TAH technology clinically. In 1964, the National Heart Institute established the Artificial Heart Program to promote the development of the TAH and other cardiac assist devices. In the early 1960s, DeBakey and researchers at Baylor College of Medicine in Houston began developing a TAH. In 1963, DeBakey implanted the first clinical left ventricular assist device (LVAD) into a 42-year-old patient.[18] The pump functioned well, but the patient died of pulmonary complications after 4 days of support. In 1967, DeBakey implanted an LVAD into a 37-year-old patient who presented with symptoms of CHF including easy fatigability and severe dyspnea on slight exertion. This patient also had a history of rheumatic heart disease since age 18 and closed mitral valvulotomy at age 25. The intention was to use the LVAD until sufficient myocardial recovery could be gained. The LVAD supported the patient's circulation for 10 days and was then electively removed. The patient was discharged from the hospital on postoperative day 29 and later resumed normal activity. On follow-up at 18 months after LVAD removal, the patient remained free of CHF symptoms, and a chest x-ray showed a significant reduction in cardiac size.

FIRST TOTAL ARTIFICIAL HEART

The first implantation of a TAH into a human was done by Cooley on April 4, 1969, in a 47-year-old man who could not be weaned from cardiopulmonary bypass (CPB) following left ventricular aneurysmectomy.[19] The intent was to support the patient until a donor heart could be found. The TAH (Fig. 68-1), designed by Liotta, was a pneumatically powered, double-chambered pump with Dacron-lined right and left inflow cuffs and outflow grafts. Wada-Cutter hingeless valves controlled the direction of blood flow through the pump. The TAH itself was connected to a large external power unit, which unfortunately severely restricted patient mobility. The TAH performed adequately for 64 hours until

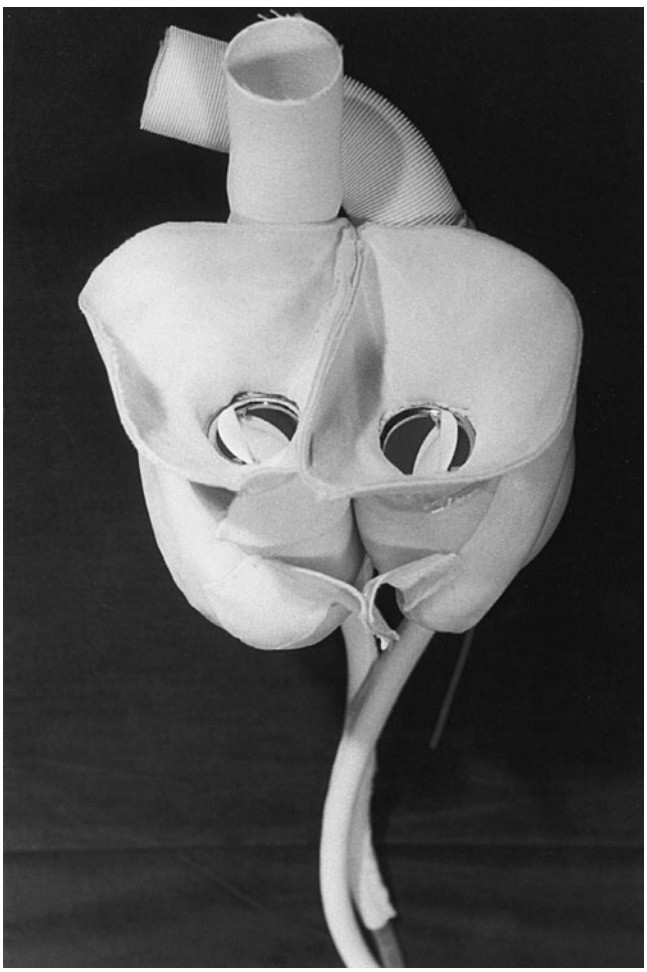

Figure 68-1. The Liotta total artificial heart, the first TAH implanted in a human.

transplantation. The donor heart also functioned well, but the patient died of pseudomonal pneumonia 32 hours after transplantation. Though the Liotta device performed as designed, it was never used clinically again. Nevertheless, this case clearly demonstrated that a TAH could be used safely and effectively in a human as a bridge to transplantation.

AKUTSU-III TOTAL ARTIFICIAL HEART

The second implantation of a TAH in a human was also done by Cooley. On July 23, 1981, Cooley implanted the Akutsu-III TAH into a critically ill 26-year-old man who suffered heart failure after undergoing coronary artery bypass surgery for severe arteriosclerosis. Unable to be weaned from CPB after surgery, the patient was fitted with the TAH in a final effort to sustain his life. The Akutsu-III TAH (Fig. 68-2) consisted of two pneumatically powered, double-chambered pumps featuring reciprocating hemispherical diaphragms.[20] The TAH provided excellent hemodynamics and supported the patient in stable condition for a total of 55 hours until a suitable donor heart was found. The patient finally received a transplant but died of infectious, renal, and pulmonary complications 10 days later. Despite the fatal outcome, this case demonstrated that a TAH could adequately sustain a patient for several days, with no evidence of hemolysis or thromboembolism, until heart transplantation.

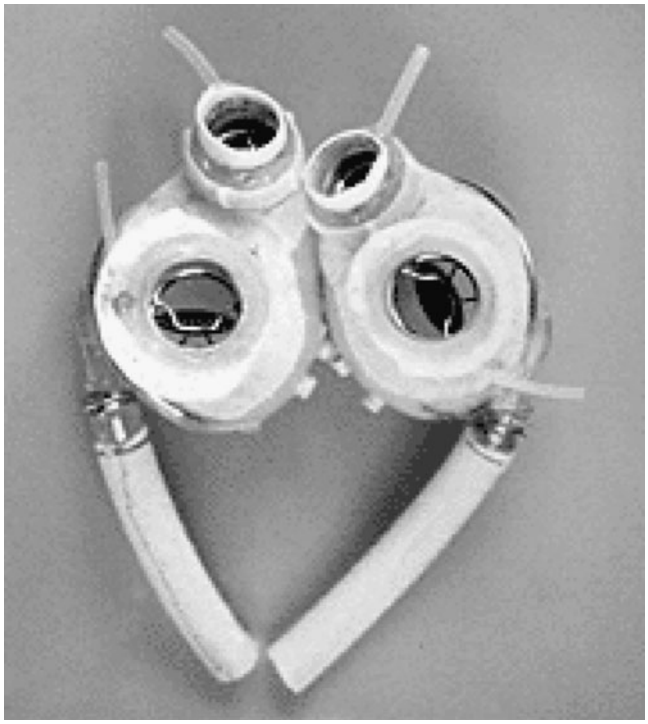

Figure 68-2. The Akutsu-III total artificial heart, the second TAH implanted in a human.

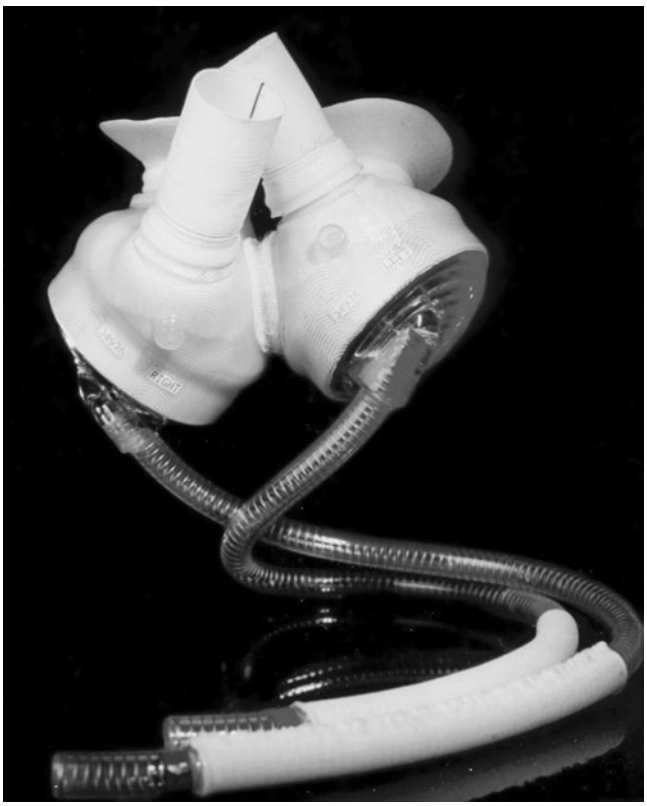

Figure 68-3. The CardioWest total artificial heart (Syncardia Systems, Inc., Tucson, Ariz), formerly the Jarvik-7 and Symbion TAH.

JARVIK-7 TOTAL ARTIFICIAL HEART

In the late 1970s, Kolff and his team at the University of Utah developed the Jarvik-7 TAH. In 1982, DeVries became the first to permanently implant a TAH when he implanted a Jarvik-7 into a dying patient.[21] The Jarvik-7 TAH (Fig. 68-3) was a pneumatically powered, biventricular pulsatile device that replaced the heart.[22,23] The pumps were connected to their respective native atria by synthetic cuffs and connectors. Each pump had chambers for air and blood separated by a smooth, flexible polyurethane diaphragm. The inflow and outflow conduits contained Medtronic-Hall tilting disk valves. The filling of the pumps was aided by vacuum. Pneumatic drivelines, brought out through the chest wall to connect with an external console, shuttled air to the pumps during systole, thereby causing collapse of the pump sac and blood ejection. Pump rate, drive pressure, and systolic duration were monitored and optimized from the external console. The Jarvik-7 had a stroke volume of 70 mL and a normal cardiac output of 6 to 8 L/min (maximum, 15 L/min).

In the initial clinical experience with the Jarvik-7 TAH, a total of five patients were permanently supported for periods ranging from 10 to 620 days. The TAH was able to adequately support circulation, but its large drive console and frequent medical complications limited patient activity. Four

patients were able to make brief trips out of the hospital and to see family and friends. Long-term outcomes, however, were poor. Patients supported by the Jarvik-7 for longer periods suffered several complications including thromboembolism, stroke, infection, and multiorgan failure.

Despite these mixed results, in 1985 the Jarvik-7 (renamed the Symbion) TAH entered clinical trials as a bridge to transplantation. In 1986, Copeland reported the first successful use of this device for this indication.[24] Between 1985 and 1991, approximately 170 patients were supported with the Symbion TAH as a bridge to transplantation.[25] Sixty-six percent underwent successful heart transplantation, a rate similar to those in bridge-to-transplantation studies of left ventricular assist devices. Sepsis and multiple organ failure were the primary causes of death during TAH support.

Although the bridge-to-transplantation study demonstrated that the Jarvik-7 (Symbion) TAH was clinically safe and effective, the U.S. Food and Drug Administration (FDA) withdrew the device's investigational device exemption (IDE) for clinical use in January 1991 because of inadequate compliance with FDA regulations.[26] In January 1993, the investigational device exemption was restored to what was now called the CardioWest TAH, which differed little from the original Jarvik-7. The CardioWest TAH has since been used successfully in the United States, Canada, and France.[27] In a recently completed clinical trial, the survival to transplantation and overall 1-year survival rates were significantly higher for CardioWest recipients (n = 81) than for controls (n = 35) (79% versus 46% and 70% versus 31%, respectively). These results led to market approval of the CardioWest bridge to heart transplantation in 2004.

ABIOCOR TOTAL ARTIFICIAL HEART

On July 2, 2001, as part of an FDA-sponsored phase I clinical trial, surgeons at Jewish Hospital in Louisville, Kentucky, performed the first implantation of the AbioCor TAH in a 59-year-old man suffering from end-stage CHF.[28] The AbioCor totally implantable replacement heart is a self-contained electrohydraulic TAH (Fig. 68-4) that has been developed and tested by ABIOMED, Inc. (Danvers, Mass) and the Texas Heart Institute, with the support of the National Heart,

Figure 68-4. The AbioCor total artificial heart (ABIOMED, Inc., Danvers, Mass).

Table 68–1.

Inclusion and Exclusion Criteria for FDA-Sponsored Phase I Clinical Trial of AbioCor Total Artificial Heart

Inclusion criteria
End-stage heart failure
>70% probability of death within 30 days
Ineligibility for a heart transplant
No other surgical or medical treatment options
Biventricular failure
Exclusion criteria
Significant potential for reversibility of heart failure
Chronic dialysis
Recent cerebrovascular accident
Irreversible liver failure
Blood dyscrasia

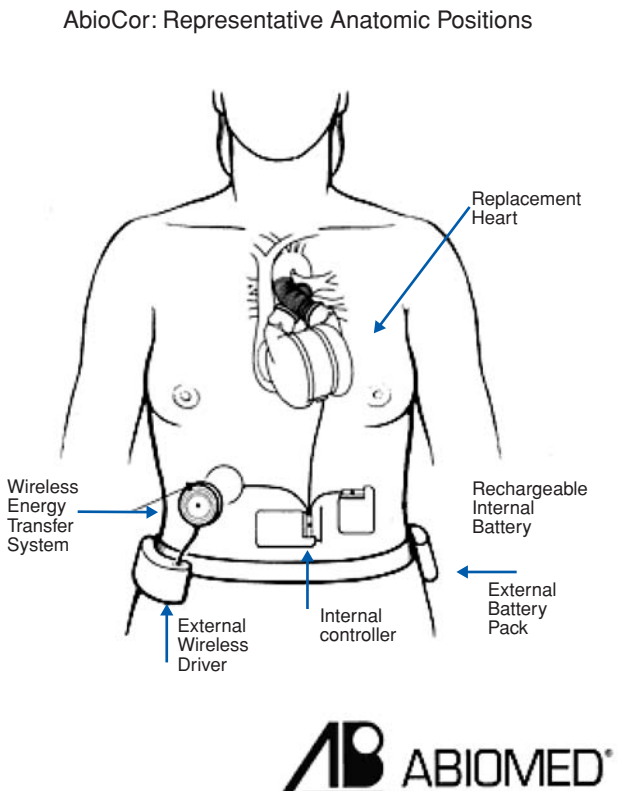

Figure 68-5. The AbioCor system is designed to increase or decrease its pump rate in response to the body's needs. The AbioCor also includes an active monitoring system that provides detailed performance feedback and alarms in the event of irregularities.

Lung, and Blood Institute.[29,30] It is designed to sustain the circulation and extend the lives of patients with end-stage heart failure who have suffered irreversible left and right ventricular failure, for whom surgery or medical therapy is inadequate, and who would otherwise soon die (Table 68-1). The AbioCor is the first TAH to be used clinically that is fully implantable and communicates to external hardware without penetrating the skin. The device utilizes a transcutaneous energy transfer (TET) system and a radiofrequency communication system that allows it to be powered and controlled by signals transmitted across intact skin. A unique feature of the AbioCor is a right-left flow-balancing mechanism that eliminates the need for an external vent or internal compliance chamber.[31]

The internal components of the AbioCor system consist of a thoracic unit, internal TET coil, controller, and battery.[32] The thoracic unit (pump) weighs about 2 pounds and consists of two artificial ventricles, four valves, and an innovative motor-driven hydraulic pumping system (Fig. 68-5). The pump's motor rotates at 6000 to 8000 rpm, which allows sufficient hydraulic fluid pressure to compress the diaphragm around the blood chamber and eject blood. A miniaturized electronics package implanted in the patient's abdomen monitors and controls the pump rate, right-left balance, and motor speed. An internal rechargeable battery, also implanted within the abdomen, provides emergency or back-up power. The internal battery is continually recharged via the TET system and can provide up to 30 minutes of untethered operation.

The AbioCor's external components include a computer console, an external TET coil, and external battery packs. The external computer communicates via the radiofrequency communication system with the abdominally implanted controller, which controls the pump. The external TET coil provides the pump with power from the console or from the external battery packs. The external battery packs can power the AbioCor TAH for 2 to 4 hours.

In the Phase I feasibility trial, 14 patients received the AbioCor as destination therapy (Table 68-2). Thromboembolism was a significant adverse event in this group of patients, and there were two pump failures. However, compared with the known rates of infection for implantable systems with percutaneous drivelines, device-related infections in this trial were relatively rare. The longest surviving patient was supported for 512 days, most of whom lived at home with a good quality of life (Fig. 68-6). A smaller AbioCor TAH is undergoing preclinical testing and is to begin clinical trials in 2006.

COMPLICATIONS

Use of a TAH is associated with serious complications. The most frequent complications are infection, severe postoperative bleeding, and thromboembolism.[33–36] Potentially serious but less frequent complications are renal, hepatic, pulmonary,

Table 68–2.

Summary of Initial Clinical Experience with the AbioCor Total Artificial Heart*

Patient no.	Implantation date	No. of days supported	Age (y)	Institution and city	Outcome
1	July 2, 2001	151	58	Jewish Hospital, Louisville, Ky	Died
2	September 13, 2001	512	70	Jewish Hospital, Louisville, Ky	Died
3	September 26, 2001	142	68	Texas Heart Institute/St. Luke's Episcopal Hospital, Houston, Tex	Died
4	October 17, 2001	56	74	University of California, Los Angeles, Los Angeles, Calif	Died
5	November 5, 2001	293	51	MCP Hahnemann University Hospital, Philadelphia, Pa	Died
6	November 27, 2001	0	79	Texas Heart Institute/St. Luke's Episcopal Hospital, Houston, Tex	Died
7	April 10, 2002	0	61	Jewish Hospital, Louisville, Ky	Died
8	January 7, 2003	100	79	Jewish Hospital, Louisville, Ky	Died
9	January 22, 2003	53	65	Jewish Hospital, Louisville, Ky	Died
10	February 24, 2003	115	69	Texas Heart Institute/St. Luke's Episcopal Hospital, Houston, Tex	Died
11	May 1, 2003	100	64	Texas Heart Institute/St. Luke's Episcopal Hospital, Houston, Tex	Died
12	February 20, 2004	86	63	Texas Heart Institute/St. Luke's Episcopal Hospital, Houston, Tex	Died
13	May 3, 2004	146	72	Jewish Hospital, Louisville, Ky	Died
14	May 24, 2004	164	72	Jewish Hospital, Louisville, Ky	Died

**As of July 5, 2005.*

and neurologic dysfunction and complications due to technical problems.[33,37] Complicating factors include patient selection, device size, implantation timing and location, the need for extensive surgery at implantation, and the reliability of support equipment.

Life-threatening infections have been the most important complication for patients being supported permanently by a TAH.[38] In the Jarvik-7 experience, all patients supported for many months developed serious infections that eventually contributed to their deaths.[22,39] Patients supported by a TAH for shorter periods while awaiting heart transplantation had infection rates of 30 to 40%.[34–38] During the 1980s, driveline and mediastinal infections in TAH-supported patients were frequent and severe, regardless of the duration of support. However, in the more recent bridge-to-transplantation experience with the CardioWest TAH, the infection rate was no more than 20%.[40,41]

Patients supported with a TAH, regardless of the intended use, are very susceptible to infection. Predisposing factors include the tissue trauma associated with surgical implantation; contamination of the implanted device; depression of the body's immune defenses; the large amount of foreign material present on the surface of the device; and use of the drivelines, tubes, catheters, and other devices that are necessary for the care of these patients. Infections can occur at any point during TAH support. Once an internal component of the TAH system is infectiously colonized, treatment is difficult and often ineffective. Infections are more likely to occur in the early postoperative period, especially in the most critically ill patients, as a result of (1) device

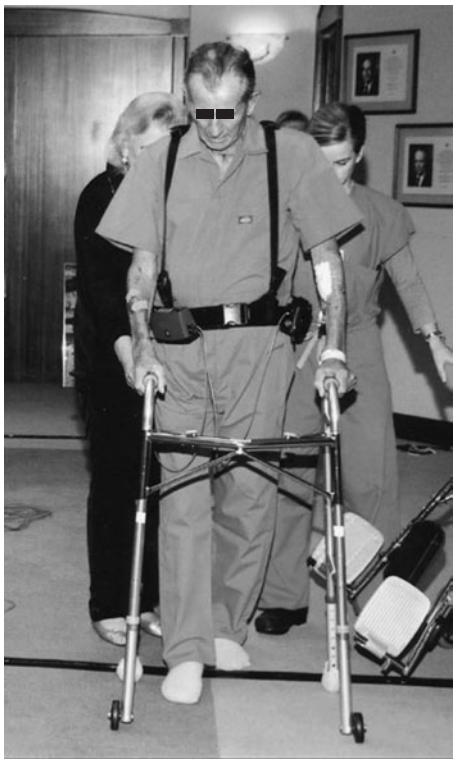

Figure 68-6. The third patient to receive the AbioCor TAH. This patient was supported by the AbioCor for 144 days and underwent physical rehabilitation, but ultimately died of thromboembolic complications.

contamination during the course of care and (2) postoperative bleeding due to intensive care procedures and exposure during reoperation. Meticulous care and numerous infection prevention measures are vital in all TAH patients.

Postoperative bleeding is a frequent and serious complication of TAH implantation. It generally occurs in 40 to 50% of TAH or ventricular assist device recipients.[33] In the more recent CardioWest experience, the rate was approximately 25%. Contributing factors include severe CHF and associated hepatic dysfunction, the extensive surgery and lengthy CPB time required for implantation, and the necessity for postoperative anticoagulation therapy. Severe CHF often leads to hepatic dysfunction and subsequent derangement of the coagulation system. Patients with severe CHF are often receiving continuous preoperative anticoagulant or antiplatelet therapy, the effects of which are often difficult to reverse before TAH implantation. The extensive surgery and lengthy CPB time required for implantation can lead to severe depletion of clotting factors. The necessity for postoperative anticoagulation therapy requires that a proper balance be established between preventing thrombosis and allowing blood to clot, through the careful management of hemostasis and anticoagulant therapy.

Thrombosis within the TAH is of particular concern. Five of the first six Jarvik-7 recipients suffered thromboembolic events. However, the frequency of thromboembolism has decreased significantly since that initial experience and is now an estimated 10 to 15%.[33,34,42] Preventive measures are primarily targeted at precisely monitoring the thrombotic and fibrinolytic systems, maintaining sufficient flow through the device to avoid stasis, and providing adequate anticoagulation and antiplatelet therapy. Generally, heparin and warfarin are used as antithrombotic therapy to achieve a prothrombin time, activated thromboplastin time, or International Normalized Ratio two to three times greater than the baseline or normal value. Aspirin or dipyridamole or both are also used.

There is a complex though poorly understood interrelationship between infection, bleeding, and thromboembolism. Thrombus formation may lead to the development of infection, and bacterial colonization may lead to thrombus formation. Bacteria are often seen in thrombi found in cardiovascular devices.[43] Bacteria embedded in a thrombus are protected from circulating antibiotics and leukocytes. Bacteria, endotoxins, and inflammatory cells may contribute to thrombus formation by their effect on platelet aggregation.[44] Bacterial endotoxins can cause platelet aggregation, endothelial injury, and increased endothelial thromboplastin activity. Excessive bleeding most often results in reoperation, which increases the patient's exposure to contamination. Also, blood transfusions and intravascular monitoring for these critically ill patients are more extensive and result in frequent exposure to the external environment. Infection, bleeding, and thromboembolism can contribute individually and collectively to the development of multiple organ failure, one of the most frequent causes of death in TAH recipients.

Other important problems and issues related to TAH implantation are device malfunction, poor fit or size mismatch between TAH and patient, social and ethical issues, mobility, and nutrition. Device malfunction leading to catastrophic failure of the TAH or ventricular assist device is rare. Most technical issues have involved external components and have been readily resolved. Fit and size mismatch remain a problem. All TAH models used to date have been relatively large and only fit adequately into patients with a body surface area greater than 1.7 m^2. Because the cost of TAH technology is fairly high and most candidates for TAH implantation are in their sixth to seventh decade of life, many groups question whether society should bear the cost of developing this technology. Until recently, the external components of the TAH equipment have been large and cumbersome, thus limiting patient mobility, exercise, and rehabilitation. More recent designs of the TAH allow for much more mobility.

COMMENT

Since the 1950s, when the heart-lung bypass machine was developed, many advances have been made in the surgical treatment of CVD. Many surgical procedures considered impossible just 40 years ago are today considered routine. A

classic example is heart transplantation. However, TAH technology has not evolved at the same pace. Although the first human heart transplantation and first human TAH implantation occurred within 2 years of each other, TAH implantation is still neither routine nor widely available. However, two TAHs are undergoing clinical trials at present in the United States. The CardioWest (formerly the Jarvik-7) TAH, which is the more widely used of the two, is now approved for use as a bridge to transplantation. The AbioCor TAH is still in the early stages of clinical testing and is likely years away from approval as an alternative to heart transplantation. However, should its unique TET system and flow-balancing mechanism prove to be reliable for extended periods of time, the AbioCor may become a widely used alternative to heart transplantation for those patients who have no other treatment options.

There are many obstacles to overcome before any TAH is widely accepted. Infection, bleeding, thromboembolism, and biocompatibility issues are serious problems that affect nearly all implantable cardiovascular devices including TAHs. Improved biomaterials, better prevention, and more effective antibiotic and anticoagulant medications may help overcome these problems. Acceptance by the public, by some critics in the health professions, and by third-party payors may be slow. Quality in manufacturing is needed to ensure reliability of TAH components. Addressing these problems will help bring the TAH more quickly into routine clinical use.

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CHAPTER 69

Nontransplant Surgical Options for Heart Failure

Martinus T. Spoor • Steven F. Bolling

Congestive heart failure (CHF) has become a major worldwide public health problem. In our ever-aging population, medical advances that have extended our average life expectancy have also left more people living with chronic cardiac disease than ever before. In the United States alone there are nearly 4.9 million suffering with heart failure, yet of the 500,000 new patients diagnosed each year, less than 3000 are offered transplantation due to limitations of age, comorbid conditions, and donor availability. Despite the significant improvements in medical management, CHF patients are repeatedly readmitted for inpatient care and the vast majority will die within 3 years of diagnosis.[1]

The successful and reproducible long-term results with orthotopic heart transplantation (OHT) have made it the treatment of choice for patients with medically refractory endstage heart failure.[2] Unfortunately, the obvious limitations to OHT include the need for immunosuppression and the severe shortage of donor organs. This past decade has seen the annual number of transplants performed worldwide plateau at less than 4000.[3] This lack of donor availability has thus necessitated that rigorous selection criteria be applied to potential recipients in order to optimize the utility of these precious organs, indicated only for patients with endstage cardiomyopathy in whom all other modes of therapy have been exhausted. Access to OHT has thus been restricted to those without comorbid medical conditions and relatively restricted to those younger than age 65. This leaves the vast majority of CHF patients seeking other options.

Despite the technological strides being made toward total implantability, the role for mechanical support presently remains primarily as a bridge to transplantation or for temporary support. Though there have been a number of clearly successful cases of ventricular assist device (VAD) use as a bridge to recovery, its long-term efficacy for this purpose or its use as a long-term therapy for chronic heart failure remains to be fully evaluated by multicenter clinical trials.[4–9] Though assist device technology may be on the verge of being implemented as a destination therapy for CHF, its current primary indication as a bridge to transplantation results in the restriction of its use to patients fulfilling candidacy for OHT. These confines, and the high cost associated with these devices, have yet to make the VAD an unrestricted surgical solution for the management of most CHF patients.

This clinical dilemma has provided the impetus for surgeons to develop new alternatives for the treatment of heart failure. As OHT and VAD use is more stringently applied, techniques to restore myocardial perfusion, eliminate valvular regurgitation, and restore ventricular geometry have emerged as the first-line surgical approach to heart failure. In response to the growing need for the proficient application and critical appraisal of the expanding menu of surgical options, the new subspecialty of heart failure surgery has emerged. The following will briefly review established nontransplant surgical modalities for heart failure such as coronary revascularization, geometric mitral reconstruction, and geometric ventricular reconstruction. Alternative options such as partial left ventriculectomy and cardiomyoplasty as well as some innovative devices currently being evaluated for clinical application will also be discussed.

CORONARY REVASCULARIZATION

We have known for nearly 20 years that revascularizing patients with left ventricular dysfunction can result in upwards of a 25% improvement in long-term survival.[10,11] Early enthusiasm was tempered by reports of high operative mortality in patients with a low ejection fraction (EF). Since then, as success with the medical and surgical management of heart failure and transplantation grew, so did the interest in applying this experience to patients with ischemic

cardiomyopathy. Successful revascularization can now be performed on patients with an EF less than 30% with hospital mortalities as low as 5%.[12–14]

The premise behind the improvements in EF, long-term survival, and quality of life of these patients following coronary artery bypass grafting (CABG) is believed to be due to postoperative myocyte recruitment. Restoration of perfusion resuscitates dormant viable myocardium and serves to protect the previously functioning portions of the ventricle from further ischemic insults, arrhythmias, and infarction.

In order to minimize morbidity, a multidisciplinary approach to the preoperative management of heart failure is essential. Patients ideally suited for CABG are those who are medically optimized, with or without angina, who have good distal coronary targets, functional hibernating myocardium identified preoperatively, and no evidence of right ventricular dysfunction.[15] As experience in managing these patients increases, many surgeons have operated on patients with ejection fractions less than 10%, those requiring reoperation, and those with moderate elevations in pulmonary artery pressure. Nevertheless, patients with clear documentation of poor right ventricular EF, clinical right-sided congestive symptoms, or fixed pulmonary hypertension above 60 mm Hg systolic should be approached cautiously, because these patients may in fact be better suited for transplantation.

The process of preoperative investigation should coincide with optimizing the patient's medical management. This should entail an aggressive regimen of diuretic and vasodilator therapy to minimize ventricular afterload and normalize the patient's circulating volume. For patients with severe heart failure, a brief period of inotropic therapy for ventricular resuscitation may be necessary to optimize their medical management. Inability to be weaned from this support is often indicative of severe myocardial injury and poor overall prognosis with any surgical therapy other than mechanical ventricular assistance or transplantation.

Preoperative investigations should begin with transthoracic echocardiography to grossly evaluate ventricular function and identify any underlying valvular pathology. Baseline screening physiologic studies of oxygen consumption, pulmonary function, and cardiopulmonary endurance are recommended. Identification of reversible ischemia by means of a nuclear study can be helpful; however, for patients with angina, many centers will proceed directly to coronary angiography. Though angina may be indicative of living ventricular muscle, perhaps the most important correlate of successful surgical recovery is the quantification of myocardial viability. Not only is a determination of myocardial contractile reserve essential to ensure that the patient can be safely separated from cardiopulmonary bypass, this information is predictive of ventricular recovery and long-term survival after operation. Though thallium-201 perfusion scans may distinguish myocytes with membrane integrity from scar, positron emission tomography scanning and dobutamine stress echocardiography permit the preoperative identification of myocardial viability and the prediction of postoperative function.[16–18]

The fundamental premise behind a successful operation is to attain an expeditiously performed and yet complete revascularization. As the failing myocardium is particularly intolerant to further episodes of ischemia, careful consideration should be given to the quality of the distal vessels and the ease with which good anastomoses can be achieved. Operative time expended grafting small or extensively diseased vessels, or performing additional techniques such as endarterectomy, may be counterproductive. Since the price to pay for incomplete revascularization or transient ischemia may be severe, off-pump techniques may not be ideally suited for these patients unless performed flawlessly.

Multiple groups have been uniformly successful in demonstrating improvements in survival, ventricular function, and functional status with coronary revascularization in patients with ischemic cardiomyopathy with ejection fractions less than 25%.[19–21]

The 5-year survival with transplantation ranges from 62 to 82%, whereas with medical therapy alone, it is less than 20%. Most series report survival following CABG for ischemic cardiomyopathy ranging from 85 to 88% at 1 year, 75 to 82% at 2 years, 68 to 80% at 3 years, and 60 to 80% at 5 years. Operative mortality has been reported from 3 to 12%, with the main predictor of increased risk being urgency of operation. When compared to medical therapy, revascularized patients have significant improvements in quality of life. Most series consistently report considerable enhancements in patient mobility, peak oxygen consumption, and functional status. The average preoperative New York Heart Association (NYHA) class of 3.5 reportedly drops to 1.5 after revascularization. Postoperatively, there are substantial reductions in readmissions for CHF and many patients return to work.

It is encouraging to note that the long-term survival of CHF patients following CABG is equivalent to transplantation in many series. The superior survival of CABG over transplant in the first 2 years postoperatively may be due to early attrition from rejection or infection in the latter group. Although there has been little reported on patients with ejection fractions under 10%, from the above data, one could infer that these patients would have a similarly better outcome than their nonrevascularized counterparts. As experience with heart failure surgery expands, refinements in preoperative and operative management of CABG patients will no doubt be reflected in the uniformity of future long-term results.

GEOMETRIC MITRAL RECONSTRUCTION

Functional mitral regurgitation (MR) is a significant complication of endstage cardiomyopathy and it may affect almost all heart failure patients as a preterminal or terminal event. Its presence in these patients is associated with progressive ventricular dilatation, an escalation of CHF symptomatology, and significant reductions in long-term survival, which is estimated to be between only 6 and 24 months.[22]

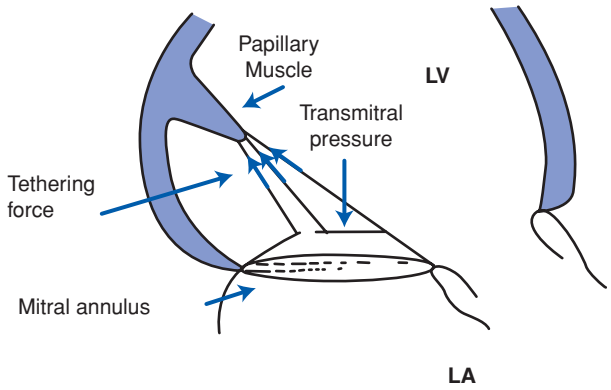

Figure 69-1. Various forces exerted on mitral valve leaflets are provided by the mitral valve apparatus, papillary muscles, and important three-dimensional relationships in the ventricle itself of all of the associated structures. Geometric mitral regurgitation results from a combination of annular dilatation, papillary muscle displacement, increased leaflet tethering forces, and weakened leaflet closing forces.

A firm understanding of the functional anatomy of the mitral valve is fundamental to the management of MR in heart failure. The mitral valve apparatus consists of the annulus, leaflets, chordae tendineae, and papillary muscles, as well as the entire left ventricle. Thus, the maintenance of chordal, annular, and subvalvular continuity is essential for the preservation of mitral geometric relationships and overall ventricular function. As the ventricle fails, the progressive dilatation of the left ventricle gives rise to MR, which begets more MR and further ventricular dilatation (Fig. 69-1). With postinfarction remodeling and lateral wall dysfunction, similar processes combine to result in ischemic mitral regurgitation (Fig. 69-2). Left uncorrected, the end result of progressive MR and global ventricular remodeling is similar regardless of the etiology of cardiomyopathy. Incomplete leaflet coaptation, loss of the zone of coaptation, and regurgitation develop secondary to alterations in the annular-ventricular apparatus and ventricular geometry.[23,24] Thus, reconstruction of this geometric abnormality serves to not only restore valvular competency, but also improve ventricular function.[25–28]

Historically, the surgical approach to MR was mitral valve replacement, yet little was understood of the interdependence of ventricular function and annulus-papillary muscle continuity.[29] Consequently, patients with low EF who underwent mitral valve replacement with removal of the subvalvular apparatus had prohibitively high mortality rates.[30] In an attempt to explain these outcomes, the concept of a beneficial "pop-off" effect of mitral regurgitation was conceived. This idea erroneously proposed that mitral incompetence provided low-pressure relief during systolic ejection from the failing ventricle, and that removal of this effect through mitral replacement was responsible for deterioration of ventricular function. Consequently, mitral valve replacement in patients with heart failure was discouraged. More recent studies documenting the importance of

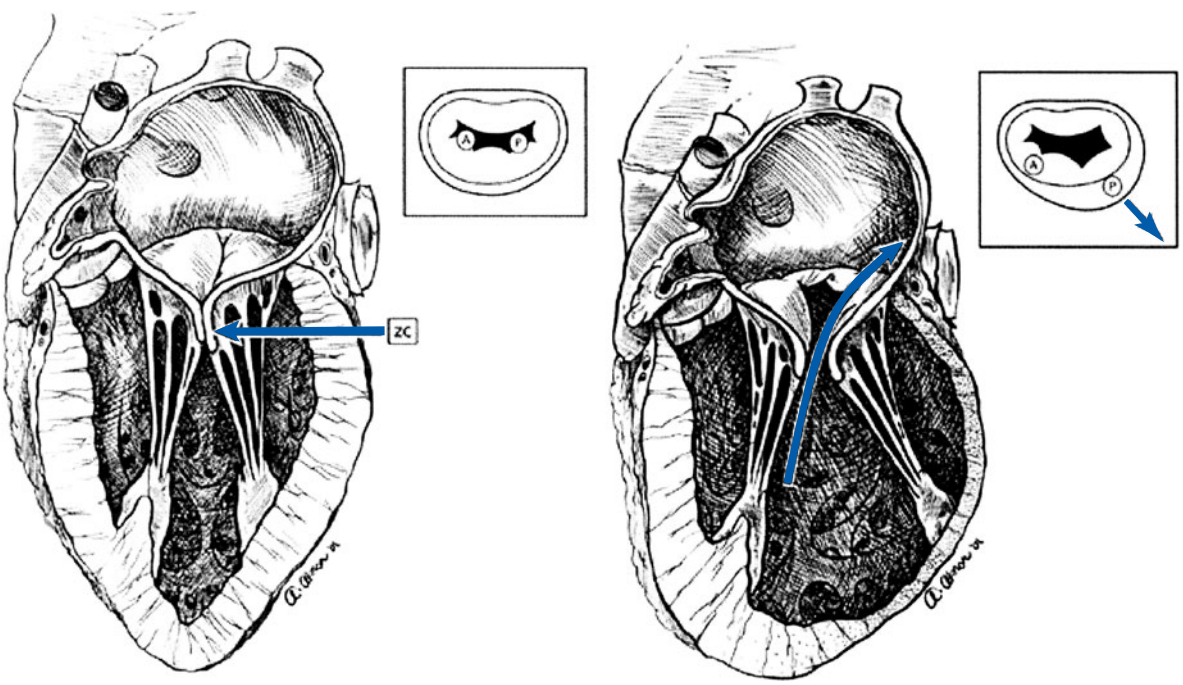

Figure 69-2. In ischemic cardiomyopathy, changes within the left ventricle may be asymmetrical and still lead to functional mitral regurgitation. With ischemic damage and thinning of the ventricular wall, there is lateral tethering, displacement of the papillary muscle, and loss of the zone of coaptation (ZC), resulting in an eccentric jet of mitral regurgitation. This illustrates the concept that ischemic mitral regurgitation results from lateral wall dysfunction that if left untreated, will progress to global left ventricular dysfunction and severe heart failure.

maintaining subvalvular integrity to preserve postoperative left ventricular function have led to surgical techniques that have been applicable to patients with heart failure.[31] Accordingly, preservation of the mitral valve apparatus in mitral surgery has been demonstrated to enhance ventricular geometry, decrease wall stress, and improve systolic and diastolic function.[32] Therefore, maintenance of chordal, annular, and subvalvular continuity is essential for the preservation of optimal mitral geometry and overall ventricular function. Furthermore, preservation of both the leaflet integrity as well as the dynamic function of the mitral apparatus with mitral repair has unmistakable functional benefits.

In treating heart failure patients, the most significant determinant of leaflet coaptation and MR is the diameter of the mitral valve annulus. The left ventricular dimension is of less importance in functional MR, as the lengths of the chordae and papillary muscles are similar in myopathic hearts regardless of the presence of MR. Observations with medically managed patients with severe heart failure and MR reveal that decreasing filling pressure and systemic vascular resistance lead to reductions in the dynamic MR associated with their heart failure.[33] This is attributed to a reduction in mitral orifice area relating to decreased left ventricular volume and decreased annular distention. This complex relationship between mitral annular area and leaflet coaptation may thus explain why an undersized "valvular" repair may help a "ventricular" problem. This restoration of the mitral apparatus and ventricle forms the premise behind geometric mitral reconstruction (GMR) for the treatment of heart failure (Fig. 69-3).

At the University of Michigan from 1992 to 2004, over 289 patients with EF ≤30% received an undersized complete mitral annuloplasty ring as their mitral valve replacement procedure. Of these, 170 patients had a flexible complete ring while the remaining patients received a nonflexible undersized complete ring. In follow-up, 16 flexible ring patients (9.4%) required a repeat procedure for significant recurrent geometric MR and CHF (10 replacements, 3 re-repairs, and 3 transplants). The average time to reoperation was 2.4 years. In contrast, 119 patients with an EF ≤30% received a mitral valve replacement using an undersized nonflexible complete ring. Only 3 nonflexible patients required a repeat operation, 1 a mitral valve replacement and 2 patients required a transplant. The time to reoperation was 4.0 years. There was a significant difference in reoperation rates for recurrent MR between the two groups ($p = 0.012$). There were no differences between groups in terms of age, ring size used, preoperative EF, left ventricular size, MR grade, or NYHA class.[34] All patients were in NYHA class III or IV heart failure despite receiving maximal medical therapy. On immediate postoperative echocardiograms, the mean transmitral gradient was 3 ± 1 mm Hg (range 2 to 6 mm Hg). The overall operative mortality has been under 5%. There have been 27 late deaths: 12 from sudden ventricular arrhythmias, 9 from progression of CHF but without MR, 3 related to complications from other operative procedures, 2 that progressed to transplantation, and 1 suicide. The 1-, 2-, 3-, and 5-year actuarial survivals following GMR are 82%, 71%, 68%, and 57% respectively.

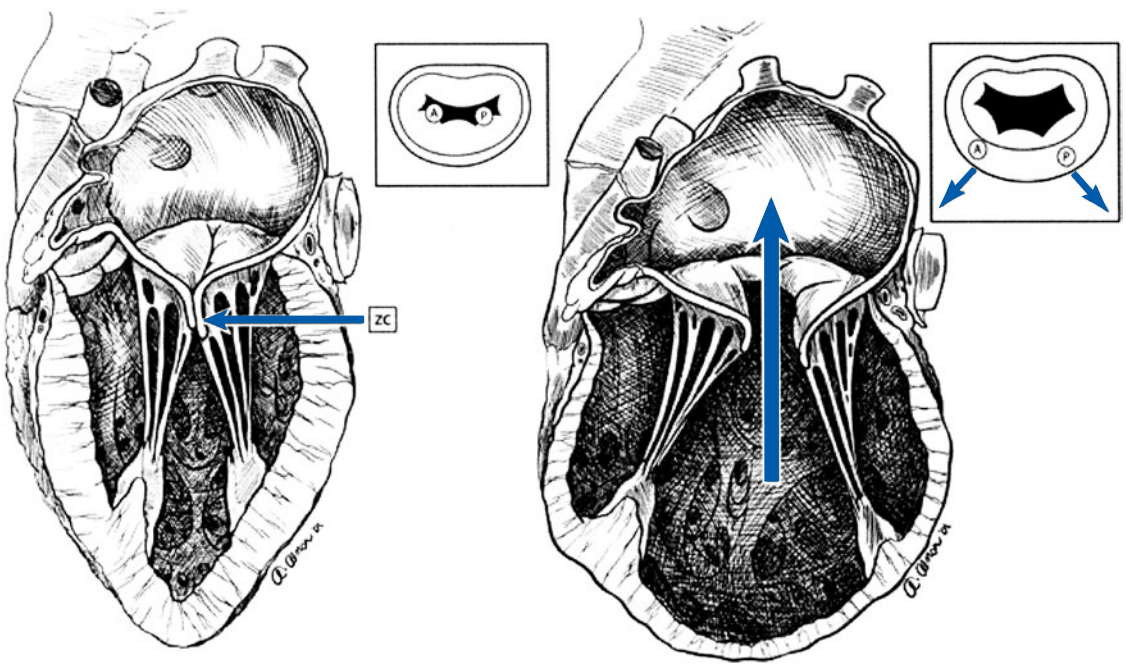

Figure 69-3. In non-ischemic cardiomyopathy note the geometric changes that occur from the normal to the failing left ventricle. With the ventricular and annular dilatation of heart failure, the mitral leaflets cannot adequately cover the enlarged mitral orifice, resulting in the loss of the zone of coaptation (ZC). Geometric mitral regurgitation results from a combination of annular dilatation, papillary muscle displacement, increased leaflet tethering forces, and weakened leaflet closing forces.

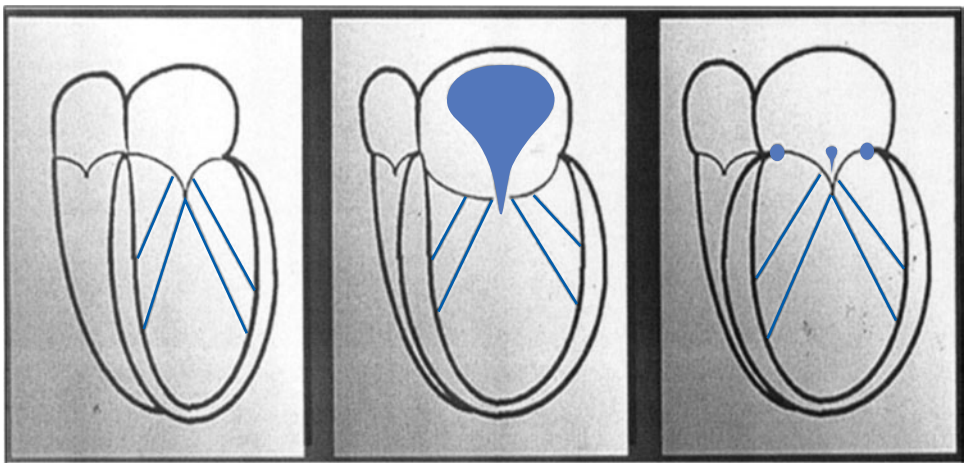

Figure 69-4. Geometric mitral reconstruction for heart failure. Successful augmentation of the zone of coaptation and prevention of recurrent MR can be achieved with placement of an undersized circumferential annuloplasty ring performed with multiple annular sutures. Note the changes in the relationship of the papillary muscles in the left ventricle in the new geometry following mitral repair.

At 24-month assessment, mean EF increased to 26% and all patients were in NYHA class I or II. NYHA symptom scores were reduced from 3.2 ± 0.2 preoperatively to 1.8 1642 ± 0.4 postoperatively. These improvements paralleled subjective functional improvements reported by all patients. Echocardiographically, there were marked improvements in regurgitant fraction, end-diastolic volume, cardiac output, and sphericity index Although significant undersizing of the mitral annulus was employed to overcorrect for the zone of coaptation (Fig. 69-4), no systolic anterior motion of the anterior leaflet or mitral stenosis was noted in these patients.

The technique of undersizing in mitral reconstruction avoids systolic anterior motion in these myopathic patients, likely due to widening of the aorto-mitral angle in these hearts with increased left ventricular size. Furthermore, acute remodeling of the base of the heart with this reparative technique may also reestablish the somewhat normal geometry and ellipsoid shape of the left ventricle. As evidenced by the decreased sphericity index and left ventricular volumes seen in these patients, the geometric restoration from mitral reconstruction not only effectively corrects MR, but also achieves surgical unloading of the ventricle.

Many centers have reported similar consistent findings following GMR.[35–39] With outcomes equating to those of transplant while avoiding immunosuppression, this straightforward reparative operation performed in conjunction with medical management may be offered to all patients with MR and cardiomyopathy as a first-line therapy.

GEOMETRIC VENTRICULAR RECONSTRUCTION

Myocardial revascularization and GMR reliably improve ventricular function. However, further surgical techniques have been developed that attempt to augment left ventricular function through a reduction of end-diastolic wall tension following the principles of the law of Laplace. Since ventricular wall tension is directly proportional to left ventricular radius and pressure and inversely proportional to wall thickness, any intervention to optimize this relationship would be beneficial. As heart failure progresses, so does the progressive thinning and dilatation of the left ventricle, thus leading to increasing wall stress and further dilatation. This remodeling process may result in regional left ventricular dysfunction, as occurs following segmental myocardial infarction, or global left ventricular dysfunction, which may arise from either ischemic or nonischemic etiologies. The concept of reducing wall stress through the surgical restoration of left ventricular cavity size and geometry remains the guiding principle behind many innovative techniques including those developed for the isolation of left ventricular aneurysms and nonfunctioning ventricular segments.

After an acute myocardial infarction, the noncontractile myocardium undergoes thinning and fibrous replacement often following the segmental distribution of the arterial occlusion. This nonfunctional left ventricular segment may remain akinetic or transform into a dyskinetic aneurysm, depending on factors such as age and regional collateral circulation. Though such postinfarct pathologic remodeling may occur in any area of the heart, the most common clinically relevant region that manifests is the anteroapical segment of the left ventricle. The resulting loss of contractile function in the affected segment results in global increases in left ventricular wall tension and myocardial oxygen consumption, in turn leading to compensatory left ventricular dilatation in accordance with the law of Laplace. These geometric ventricular changes may also result in loss of the zone of coaptation and MR following infarction, as discussed earlier. Moreover, when a dyskinetic region expands and becomes aneurysmal, cardiac work is further increased due to the paradoxical systolic motion of the thinned segment. These pathologic alterations often result in CHF. The principle of surgical restoration of left ventricular geometry involves the isolation of these nonfunctional areas and a subsequent reduction in left ventricular volumes. This concept has been clearly

illustrated by Dor and others, who have revealed significant improvement in heart failure after endoventricular patch exclusion of dyskinetic or akinetic ventricular segments.[40–43]

The preoperative selection and preparation for left ventricular reconstruction should follow the identical medical optimization discussed earlier. In addition to viability assessment, echocardiography, and contrast ventriculography, cardiac MRI and left ventricle–gated nuclear imaging have proved valuable tools for pre- and postoperative volume estimation and anatomic assessment of the left ventricular wall and septum. The pre- and intraoperative decision on when to perform left ventricular reconstruction should be based on the function, viability, and thinning of the segment, as well as the location of viability-targeted concomitant coronary grafting. Benefits obtained from repairing dyskinetic thin aneurysmal defects are well established.[40,42] More recently, however, preliminary reports have revealed encouraging results with endoventricular repair of nondilated akinetic segments when combined with CABG. These findings have spawned the multicenter Surgical Treatment of Ischemic Heart Failure (STICH) trial to evaluate its long-term functional benefit.

The operative principles of left ventricular reconstruction involve optimal myocardial preservation, septal exclusion of the nonfunctioning segment with an endoventricular patch, and closure of the excluded ventricular myocardium. To improve the visual and tactile identification of the nonfunctioning segment, the ventricular repair is often performed on the perfused beating unvented heart decompressed with cardiopulmonary bypass. Entry should be at least 1 to 2 cm to the left of the anterior descending coronary artery to avoid the septum. The thinned segment often will pucker when the left ventricle is decompressed, thus marking the initial access point. A point knife is used to gain entry to permit complete decompression and endocardial visualization under direct vision as the incision is further developed. This allows for the safe removal of any left ventricular thrombus if present, as well as for the visual and tactile identification of the septum and demarcation zone between functioning and nonfunctioning myocardium. A circumferential monofilament suture or "Fontan stitch" is then placed within this zone and tied as advocated by Dor. The resulting reduced size of the defect is then patched with bovine pericardium and the residual myocardial defect is buttressed closed with strips of bovine pericardium or felt. Though concomitant GMR and CABG can be performed before or after left ventricular reconstruction, it is often advocated before, so as to allow for improved myocardial recovery and reperfusion following removal of the aortic cross-clamp.

Results from left ventricular reconstruction have been favorable and consistent between groups regardless of whether endoventricular circular patch plasty or a modified linear patch closure technique is utilized. Significant reductions in left ventricular end-systolic volume index and improvements in EF, NYHA class, and long-term survival have resulted. It is being regularly performed with hospital mortalities of under 8% and with a 12-month freedom from readmission for CHF of over 80%.[40,42–46] Therefore, geometric left ventricular reconstruction by endoventricular exclusion of nonfunctional segments should be placed alongside high-risk CABG and GMR as a first-line surgical option for heart failure.

PARTIAL LEFT VENTRICULECTOMY

Batista has furthered the concept of surgical ventricular remodeling to optimize wall tension in dilated ventricles with the contention that all mammalian hearts should share the same mass-diameter ratio regardless of size. He proposes that all hearts not complying with this relationship should have a segment of the left ventricular wall excised in order to diminish mural tension and improve myocardial oxygen consumption in accordance with the law of Laplace.[47,48] This interesting concept was initially presented as a case report of a 34-year-old patient who underwent a partial left ventriculectomy (PLV) that reportedly increased the EF from 17 to 44% at 2 months postoperatively. Batista performed over 150 such procedures predominantly on patients with Chagas disease and dilated cardiomyopathy. Though this experience stimulated much interest, unfortunately no meaningful follow-up data or statistical analyses have ever been made available from this series.

To further evaluate the potential benefits of PLV, the Cleveland Clinic performed 62 such cases on patients with idiopathic dilated cardiomyopathy awaiting transplant. The ventriculectomy involved resection of the lateral wall of the left ventricle in the circumflex coronary artery distribution to the base of the papillary muscles with closure between two strips of felt or bovine pericardium. This was one of the largest North American series, reporting a 3.5% operative mortality with 7 late deaths and a 1-year actuarial survival of 82%. However, of the total 62 patients, 24 (39%) were considered short-term treatment failures: 11 required left VAD support, 6 were listed for transplantation again, and 7 non-left-VAD patients died.[48] Moreover, a further 30% attrition rate at 2 years following PLV has been reported.[49,50] These results may be superior to no surgical treatment, but they fall short of those obtained by other surgical options for heart failure. As a result, PLV has fallen into disfavor in North America. However, in the Asian-Pacific region, where transplantation is not widely available, efforts by Suma and associates to improve selection criteria and introduce echo-guided surgical decision making have resulted in PLV persisting as a viable option for heart failure in this part of the world.[51]

In attempting to elucidate the mechanism behind the relative success of PLV, it is quite interesting to note that over 95% of the cases performed in the Cleveland Clinic experience also involved a mitral reconstruction. Therefore, it becomes difficult to discern the role mitral repair plays in the overall utility of PLV, since patients undergoing mitral reconstruction alone also attain normalization of the left ventricular mass-to-volume ratio, but without the excision of viable myocardium.[26] Furthermore, experimental models of heart failure have revealed that correction of the MR alone permits left ventricular remodeling that may be rapid and complete, with resulting regurgitant fractions of less than 30%.[52]

Though the concept of instantly remodeling the left ventricle through PLV is mechanically appealing, discarding functioning myocardium is not. Patients with ischemic cardiomyopathy with a dyskinetic aneurysmal segment have undergone successful remodeling with an endoventricular patch repair. Patients with dilated cardiomyopathy and MR have undergone mitral reconstruction thereby altering the angulation of the base of the heart and promoting favorable left ventricular geometry and remodeling. Thus, at this time, when similar if not superior results can be obtained by methods that preserve myocardial integrity, the application of PLV to patients with endstage heart failure should be approached with an element of caution.

DYNAMIC CARDIOMYOPLASTY

Another alternative method to surgically optimize Laplace's law is dynamic cardiomyoplasty (DCMP) using the patient's own skeletal muscle wrapped around the heart to help reduce wall stress and provide limited cardiac assistance. The latissimus dorsi muscle is wrapped around the failing heart, and by means of an implantable cardiomyostimulator, the muscle is stimulated to contract in synchrony with cardiac systole.

Starting in 1985, Medtronic Inc. began coordinating a multicenter Food and Drug Administration trial to evaluate the cardiomyostimulator. Pooled observations after DCMP reveal a paucity of positive quantitative hemodynamic or survival data, yet paradoxically, patients report over 30% functional improvement when compared to medical therapy alone.[53,54]

Though DCMP is now only rarely performed in North America, the recently available LD Pace myostimulator out of Russia has allowed this procedure to continue to be available in that country as well as throughout various centers in Europe, Asia, and the Caribbean.

Investigations into the mechanisms of DCMP have generated spinoffs in the fields of myoblast transplantation and remodeling surgery. Studies revealed that the wrap actually contributes to significant reductions in myocardial wall stress.[55] In effect, this conceptually protects myocytes from overt functional stresses and thereby prevents the adaptive progressive dilatation of heart failure. Working in favor of the law of Laplace, this girdling effect of DCMP was seen with unstimulated adynamic cardiomyoplasty. Original experiments comparing adynamic cardiomyoplasty to synthetic material revealed that this beneficial girdling effect even occurs when a passive constraint of prosthetic mesh fabric is applied to the ventricles, and they have spawned the development of novel biomedical devices currently under clinical investigation.[56]

EMERGING BIOMEDICAL DEVICES FOR HEART FAILURE

The Acorn Cardiac Support Device (ACSD; Acorn Medical, Minneapolis, Minn) is a polyester mesh fabric that attempts to reduce ventricular wall stress by providing external support. Much like DCMP, the ACSD is placed around the ventricles from posterior to anterior, using stay sutures as well as an anterior fabric seam for snug tailoring to the patient's heart.

Taking advantage of the girdling effect, the purpose of this device is to passively support the failing ventricles and prevent further dilatation. Preclinical data have shown decreased left ventricular volumes and improvements in regional wall motion, EF, and other functional parameters without any evidence of constrictive physiology.[57] Histologic animal studies have also demonstrated decreased myocyte hypertrophy and interstitial fibrosis, as well as improvements in several biochemical markers of failure.[58,59] A phase I and II clinical trial has been completed to assess the safety and the early remodeling ability of the ACSD when used on heart failure patients with or without concomitant cardiac procedures. While not currently approved by the Food and Drug Administration for general use, the device continues to remain under current investigation. Preliminary experience reveals that the ACSD is easily applied, and may even be performed without the necessity of cardiopulmonary bypass.

The Myocor Myosplint (Myocor Medical, St. Paul, Minn) is a second device developed to reduce ventricular wall stress by directly altering cardiac geometry. Working on the premise of optimizing the law of Laplace, it involves the placement of transventricular tension bands through the right ventricular and left ventricular walls that have the unique ability to be individually tightened in order to achieve a 20% reduction in wall stress. Preclinical animal data have shown improvements in end-diastolic volume, end-systolic volume, and EF. These experiments reveal that the Myocor device becomes readily incorporated within a fibrous capsule that has been free of thrombus formation. A phase I clinical trial is underway to assess device safety in patients prior to cardiectomy at the time of transplant. Preliminary data reveal that the device can be readily deployed without harm to other cardiac structures. Further chronic studies are required to address the efficacy of this unique device.

The Geoform mitral valve annuloplasty ring (Edwards Lifesciences, Irvine, Calif) has a three-dimensional shape that attempts to combine the previously discussed principles of mitral valve repair and geometric remodeling of the left ventricle into the next generation of mitral valve rings (Figs. 69-5 and 69-6). This ring attempts to change and promote remodeling of the left ventricle through alterations in the mitral valve apparatus. The basic anatomic problem in dilated left ventricles, whether from ischemia or not, is the tendency of the posterior mitral valve annulus to fall away from the annular plane, which further promotes increased mitral regurgitation and increased left ventricular wall stress. Restoring the zone of coaptation of the mitral valve using this ring in the normal plane has two combined effects, of correcting the mitral regurgitation and changing the shape of the left ventricle (Fig. 69-7). Based on the elegant and pioneering efforts of Alfieri's group, the new geometry of the

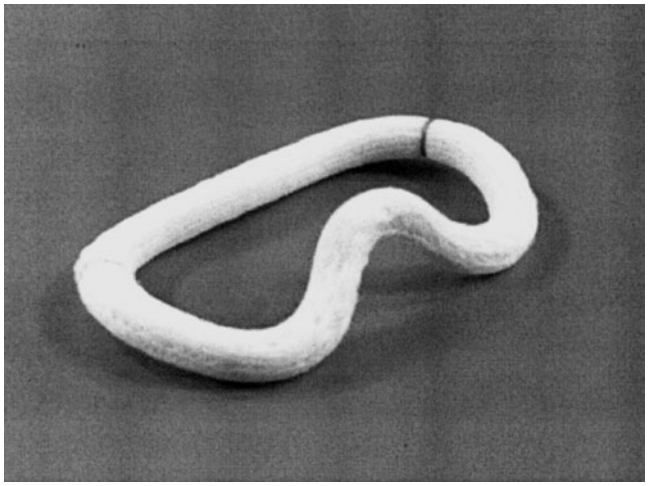

Figure 69-5. Oblique view of the Geoform mitral annuloplasty ring. Note the posterior ring design element which reverses the adverse changes in the posterior mitral annulus associated with geometric mitral regurgitation.

ventricle following this procedure has lower wall stress, which should promote further beneficial changes in the ventricle over time as the volume overload is relieved following correction of the mitral regurgitation[60] (Fig. 69-8). The Geoform ring is currently approved for clinical use with multiple implants performed at several centers worldwide.

PERCUTANEOUS MITRAL VALVE REPAIR

The Edwards Milano II mitral clip (Edwards Lifesciences, Irvine, Calif) and Evalve Mitraclip system (Evalve Inc., Menlo Park, Calif) use a catheter-based approach to deliver a clip to both the anterior and posterior mitral valve leaflets using the principles of mitral repair pioneered by Dr. Otavio Alfieri. Percutaneous catheters are introduced via the femoral vein and cross the atrial septum to enter the left

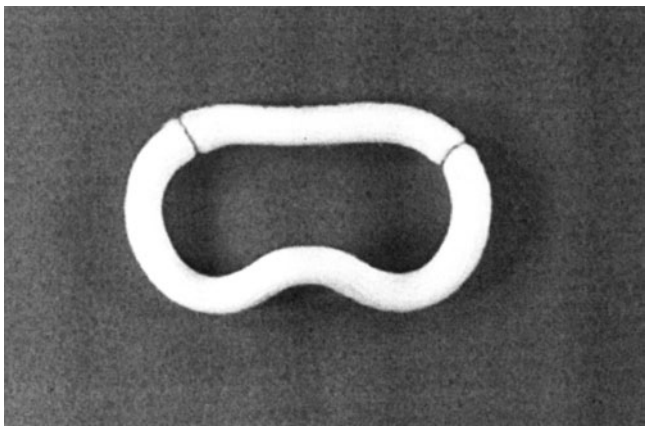

Figure 69-6. Superior view of the Geoform mitral annuloplasty ring. The three-dimensional cross-sectional area is not restrictive to atrial blood flow.

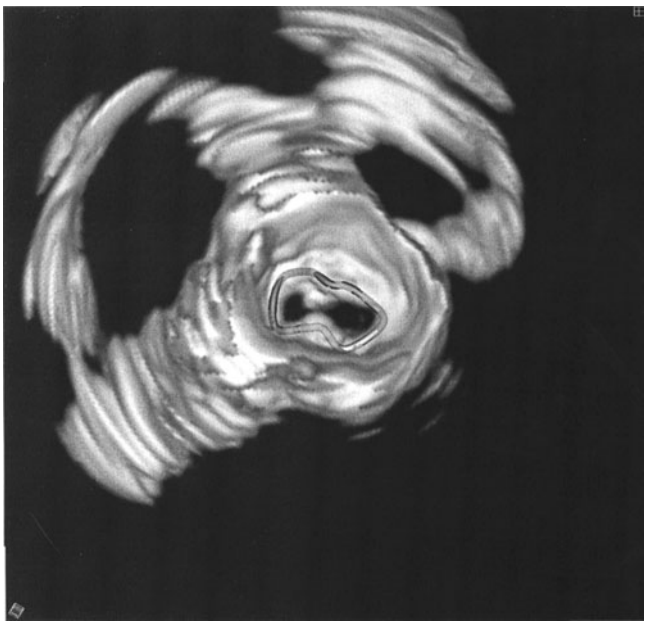

Figure 69-7. Postoperative three-dimensional echocardiography of a mitral repair performed using the Geoform mitral annuloplasty ring. Note the apposition of the central areas of the anterior and posterior mitral valve leaflets which help to establish a zone of coaptation and abolish mitral regurgitation.

atrium similar to a percutaneous mitral balloon annuloplasty approach. A catheter-based clip is then used to create a permanent coaptation point between the leading free edges of the anterior and posterior mitral leaflets. This technology is in the investigational stage with the Evalve clip currently being evaluated in the phase II EVEREST trial.

The Viacor percutaneous mitral annuloplasty system (Viacor Inc., Wilmington, Mass), Edwards Viking percutaneous mitral annuloplasty system (Viking, Edwards Lifesciences Inc.,

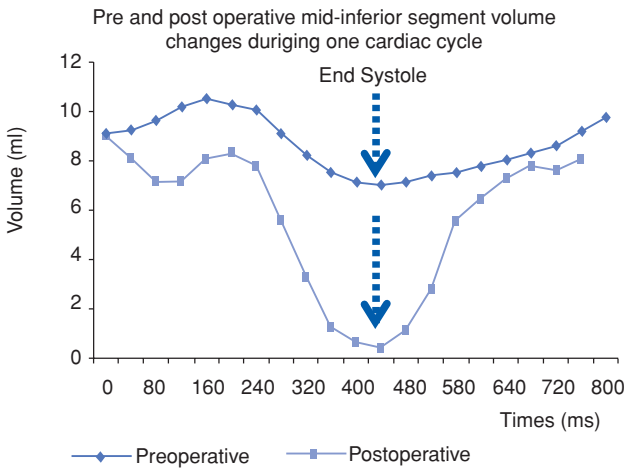

Figure 69-8. Left ventricular volume changes obtained on postoperative day 5 following geometric mitral valve repair. Increases in regional EF in the infero-basal wall are shown which are the opposite of the decreased EF expected following MVR based on historical teaching. (*Courtesy of Nadia Nathan, MD.*)

Irvine, Calif), and Carillon mitral contour system (Cardiac Dimensions, Kirkland, Wash) all use an emerging technology approach to mitral annuloplasty using a catheter-based approach to the mitral valve. Using percutaneous catheters, a permanent nitinol strut is placed into the coronary sinus that wraps around the posterior annulus of the mitral valve and attempts to indirectly influence the action of the posterior mitral valve leaflet similarly to a partial ring annuloplasty by reducing the anterior-posterior dimension of the mitral annulus. The devices are presently under investigational study and are not currently approved for routine use.

CONCLUSIONS

As surgical therapies for heart failure rapidly evolve, the need for their critical appraisal is essential so that they may be offered to the growing population of CHF patients in a prompt yet effective manner. Transplantation continues to offer selected patients reliable long-term survival in a reproducible fashion, and it thus remains the gold standard surgical therapy for heart failure. Though in time we may see mechanical assist devices play a more prevalent role in myocardial recovery or destination therapy, currently their main utility is as a bridge to transplantation. With the growing disparity between donor availability and heart failure patients, experience is mounting with effective nontransplant surgical solutions.

The results of the more conventional techniques of CABG, geometric mitral reconstruction, and ventricular reconstruction, when combined with the optimal medical management of heart failure may now be on a par with transplantation. Therefore, these modalities now form the new first-line surgical therapy for heart failure when applicable. Patients with primary ischemic cardiomyopathy with favorable anatomy may be effectively managed with revascularization alone or in combination with left ventricular reconstruction. Myopathic patients with MR, regardless of etiology, may be effectively managed with mitral reconstruction. With the superior results of these approaches, the use of other techniques such as PLV and DCMP should be reserved as viable alternative surgical options for heart failure. The prudent and effective application of the growing menu of surgical strategies for heart failure enables the scarcely available donor hearts to be efficiently used for patients with truly no other surgical or medical alternatives. Along with the utility of emerging biomedical devices, each of these unique modalities has enhanced the clinically effective armamentarium of the modern surgeon treating patients with heart failure.

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CHAPTER 70

Tissue Engineering for Cardiac Valve Surgery

John E. Mayer

Tissue engineering is a developing science, which brings together engineering and biology in an attempt to develop replacement tissues beginning with their individual cellular components. The impetus for our work on tissue engineered cardiovascular structures derives from the need to replace cardiovascular tissues that failed to develop normally during embryogenesis or have become dysfunctional as a consequence of disease, as well as from the fact that currently available replacement structures have significant limitations. In the cardiovascular sphere, the structures most often affected, excluding atherosclerotic coronary disease, are the cardiac valves and the great vessels. Diseases of the heart valves and large "conduit" arteries account for approximately 60,000 cardiac surgical procedures each year in the United States, but all of the currently available replacement devices have significant limitations.[1,2] Ideally, any valve or artery substitute would function in similar fashion to the normal valve or artery to allow blood to pass through it without narrowing or leakage, but would also have the following characteristics: (1) durability, (2) growth potential (for infants and children), (3) compatibility with blood so that thrombus would not form on its surface and activation of inflammatory cascades would not occur, and (4) resistance to infection. None of the currently available devices constructed from either prosthetic or biologic materials meet these criteria. Prosthetic heart valves are very durable, but they require anticoagulation to reduce the risk of thrombosis and thromboembolism.[1,2] Notwithstanding anticoagulation, the incidence of thromboembolic complications is not zero.[1,2] Biologic valves, whether they are of allograft or heterograft origin, remain subject to structural deterioration after implantation.[2–4] Neither prosthetic nor biologic valves have any growth potential, and this limitation represents a major source of morbidity for pediatric patients who must undergo multiple reoperations to replace valves and/or valved conduits as the patients grow. The tissue engineering approach to overcome these shortcomings offers the possibility of creating replacement cardiovascular structures from cells and scaffolds with the result that the tissue-engineered construct is a living structure with the capacity for growth, repair, and remodeling similar to normal tissues. This chapter summarizes some of the progress that has been made in tissue engineering research as it relates to cardiac valves and conduit arteries, and to then outline the areas where additional efforts must be focused in order to make cardiovascular tissue engineering a clinical reality.

Much of the strength and flexibility in normal tissues is due to specialized proteins and polysaccharide-protein complexes (extracellular matrix) that are produced by the cells in the tissue.[5,6] For cardiac valves, the biomechanical demands are particularly high, as there are approximately 40 million openings and closures of the valves per year. The normal valve presents minimal resistance to opening and no pressure gradient during systolic forward flow. In diastole this same structure must close promptly and completely to prevent valvular regurgitation, and must resist pressure differences between the diastolic arterial or pulmonary artery pressure and the ventricular diastolic pressure. The extracellular matrix of the normal semilunar heart valve is not homogeneous,[5] and the arrangement of the extracellular matrix seems uniquely designed to provide a high degree of flexibility during systole but a high degree of strength to resist the diastolic pressure load.[5] In order for a tissue-engineered cardiac valve to function effectively, it seems intuitively obvious that extracellular matrix production, composition, and remodeling processes are critical, and should result in a structure that is similar to the native valve. The determinants of extracellular matrix composition in a given tissue are incompletely understood, but are determined to some extent by the types of cells in the tissue, by the interactions among these cell types, by a variety of cytokine signals that the cells receive, and by the biomechanical signals that the cells receive.[5]

One potential source of insights for the development of a tissue-engineered heart valve (TEHV) is the process by which the normal valve develops from the embryonic to the mature adult form. A recent publication by Aikawa and colleagues[7] demonstrates that the normal semilunar valve undergoes significant in vivo maturational changes during development, which include changes in the extracellular matrix composition, collagen fiber alignment, and cellularity, and the development of a nonhomogeneous layered architecture. The mature semilunar valve structure with a more dense layer of collagen on the valve surface facing the sinus of Valsalva, (fibrosa layer) a middle layer of glycosaminoglycans, (spongiosa) and an elastin-rich layer facing the ventricular cavity and the flow from the ventricle to the great artery (ventricularis) seems uniquely designed to allow optimal semilunar valve function.[6] However, fetal semilunar valves and even those obtained from children are more cellular and do not have a fully mature valve structure.[7] Thus the semilunar valves undergo significant maturation in vivo under continuous biomechanical and other signaling conditions, and studies of tissue-engineered pulmonary valves from our laboratory have shown a similar evolution in histologic appearance, extracellular matrix composition, and organization of the collagen fibers in the extracellular matrix.[8] The signals and genetic changes controlling the early embryonic development of mammalian semilunar valves have recently been reviewed by Armstrong and Bischoff,[9] and it has become evident that the genetic mechanisms and signaling pathways are quite complex and tightly controlled, and are not completely understood at this point. The insights gained from an understanding of normal semilunar valve development is of potential application to the development of TEHVs, although it seems that the complexities of normal valve development will be difficult to replicate completely.

In our laboratory at the Children's Hospital, Boston and in the laboratories of other investigators, attempts to create TEHVs have been made over the last decade with varying degrees of success,[10–18] constructing these valves from a variety of cell types and scaffolding materials. Most of the in vivo studies have been carried out in the lower-pressure pulmonary circulation, which is more forgiving of an imperfectly functioning valve construct. The longest successful in vivo implant from our laboratory is 8 months, but the optimal process for engineering of a tissue-engineered pulmonary valve remains incompletely defined. If a tissue-engineering approach to the creation of a heart valve substitute is to be successful, several basic questions must be addressed: (1) What cell type or combination of cell types is necessary to allow the production and maintenance of an appropriate extracellular matrix? (2) To what extent can cellular phenotype be altered or "engineered" to replicate cells found in the normal valve? (3) How can these cells be spatially organized during the development of the tissue-engineered structures until sufficient extracellular matrix is produced by the cells in the construct? (4) What biochemical signals are necessary during the development of these structures to ensure proper extracellular matrix production? (5) What mechanical signals are necessary for the optimal tissue development? (6) Should a tissue-engineered valve construct be completely developed and "mature" prior to implantation, or can there be further "maturation" of a tissue-engineered construct in vivo after implantation in a fashion similar to the age-related maturational changes in the normal valve?[7] Progress has been made in addressing each of these questions, and this progress will be reviewed.

CELL TYPE OR TYPES FOR TISSUE-ENGINEERED HEART VALVES

A considerable effort has been made to explore the optimal cell source (or sources) for tissue-engineering applications. From a conceptual standpoint, the cells for a TEHV can be derived from fully differentiated cells with the capability to synthesize collagen, elastin, and glycosaminoglycans or from less committed, pluripotent stem cells with the potential to differentiate into multiple cell types. A second-order decision regarding cell source is the choice of autologous versus allograft cells. This choice will have significant implications if the tissue-engineering approach is to become a clinical reality. In order to avoid any confounding effects of immune rejection in our laboratory, we have based all of our research on the use of autologous cell lines, and it is our intuition at this time that if a tissue-engineering approach to development of a cardiac valve is to be successful, then it will likely involve the use of autologous cells, unless a nonantigenic cell source is identified or selective immune tolerance can be established. The ultimate choice of cell type(s) will likely reflect a complex interplay between what is favored in terms of basic cell biology, what tissues are readily available for harvest in the individual patients, and what is clinically acceptable to both patient and physician.

Considerable early success in fabricating a TEHV was achieved in our laboratory using myofibroblasts and endothelial cells derived from the systemic arteries of immature animals.[10–14] These cells were chosen by virtue of their anatomic location within the arterial limb of the cardiovascular system and their known ability to synthesize structural extracellular matrix components such as collagen and elastin. A comparison of myofibroblasts from the wall of the ascending aorta with those from discarded segments of saphenous vein revealed that the latter cells exhibit superior collagen formation and mechanical strength when cultured on biodegradable polyurethane scaffolds.[19] We were able to construct TEHVs based on these cells from the systemic blood vessels that functioned for periods of up to 4 months in vivo.[10,12] However, enhanced collagen formation may be a double-edged sword. The rapid formation of new tissue in the early culture period could give rise to uncontrolled proliferation and synthesis of matrix elements, leading to decreased flexibility and potential tissue shrinkage. Early studies with dermal fibroblasts showed that leaflets constructed from these cells did develop tissue contraction,

which limited the ability of these leaflets to coapt with other leaflets effectively.[21] In addition, mature cells may present a problem of senescence in long-term cell cultures in vitro, which limits the ability to produce sufficient numbers of cells to seed a TEHV construct. Finally, the prospect of harvesting segments of artery from an otherwise normal peripheral circulation in order to obtain cells for a TEHV represents a somewhat unattractive solution clinically, and therefore led to the search for alternative cell sources.

The search for a more clinically palatable source of cells led us to investigate the use of stem cells for tissue-engineering applications. Our initial experience was gained with autologous endothelial progenitor cells (EPCs) that were isolated from the circulating blood of lambs and then seeded onto decellularized arterial segments.[20] These seeded arterial grafts were then implanted as an interposition graft in the carotid artery of the donor lamb.[20] These grafts remained patent and functional for up to 130 days.[20] Cebotari and colleagues have recently reported an initial experience with seeding EPCs onto homograft valves followed by implantation into two children.[39] In our subsequent studies, Sutherland and associates used ovine bone marrow mesenchymal cells to seed a biodegradable scaffold formed into a three-leaflet valve within a conduit[19] (Fig. 70-1). These valved conduits were implanted to replace the pulmonary valve for periods up to 8 months and functioned well hemodynamically. An echocardiographic image of the valve in open position in vivo is shown in Fig. 70-2. Importantly, these valve leaflets underwent a "maturational" process after implantation[18] similar to our earlier findings using myofibroblasts and endothelial cells from systemic arteries,[12] and in both sets of experiments a layered histologic appearance developed during the time after implantation. Other investigators have also used bone marrow as a cell source for tissue-engineered cardiovascular structures. Matsumura and associates have shown that bone marrow cells labeled with green fluorescent protein can be seeded onto a copolymer of lactic acid and ε-caprolactone and found that these seeded cells contribute to the histogenesis of a tissue-engineered vascular graft. Their tissue-engineered vascular grafts remained patent and at explant the constructs contained green fluorescent protein–labeled cells which expressed both endothelial-specific and smooth muscle cell–specific markers.[21] The group at Tokyo Women's Medical College has also carried out implants of tissue-engineered vascular grafts in children undergoing repair of certain types of congenital heart disease using a similar technique with encouraging early results.[23]

Figure 70-1. The tissue-engineered substitute pulmonary valve viewed from below prior to implantation.

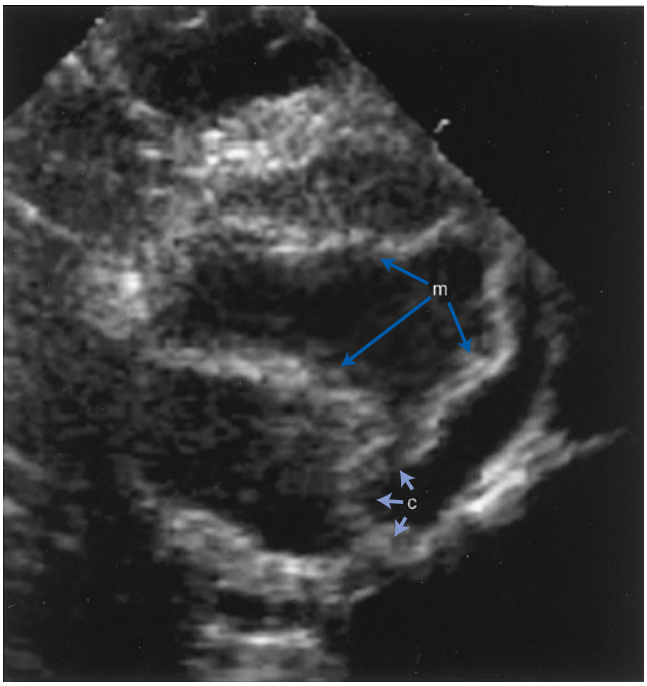

Figure 70-2. Short-axis echocardiogram of a substitute pulmonary valve in late systole showing the leaflet free margins (m) and absence of reverse bending at the commissures (c).

To further complicate the issue of choice of cell type, there is now evidence that stem cells with proliferative and regenerative capacities reside in many tissues. These stem cells are now believed to be capable of not only acting locally in the tissues in which they reside, but they may also be recruited out of the circulation and enlisted in the regeneration of diverse tissues at distal sites.[24] These stem cells are thought to be highly plastic and amenable to change if placed in an appropriate microenvironment.[24] In a recent review Rafii and Lyden have concluded that there is emerging evidence that bone marrow–derived endothelial, hematopoietic stem and progenitor cells can also contribute to tissue vascularization during both embryonic and postnatal physiological processes.[25] Visconti and coworkers have made the intriguing observation that cardiac valve interstitial cells in mice appear to originate in the bone marrow and to be of

hematopoietic origin.[26] Others, however, have cast doubt on whether bone marrow stem cells can migrate to damaged heart muscle and repopulate areas of myocardial infarction,[27] and therefore the ability to repopulate a tissue with circulating stem or progenitor cells remains in some question. The early unfavorable experience with the SynerGraft decellularized heterograft valved conduits, which were implanted in children as right ventricle–to–pulmonary artery conduits with the expectation that they would be repopulated by circulating cells from the bloodstream or by ingrowth from adjacent normal tissue has raised questions about the clinical applicability of these concepts about repopulation of decellularized grafts.[28] However, this progenitor ("adult stem cell") cell population represents an attractive source of cells for application of the tissue-engineering approach to development of cardiac valves because they can be obtained relatively less invasively and because these cells may have the capacity to assume a more appropriate phenotype.

ENGINEERING OF CELLULAR PHENOTYPE

Among the more interesting observations on mesenchymal stem cells is that the phenotype of these cells seems to be dependent on the local environment in which they come to reside.[29] However, the factors in these local environments that control differentiation into various phenotypes remain unknown.[29] For EPCs, there is evidence that these cells have the ability to transdifferentiate in response to various signals in a tissue-engineering environment. Dvorin and colleagues have shown that transforming growth factor (TGF)-β_1 can induce EPCs to express α-smooth muscle actin (α-SMA) after these cells had been seeded onto a tissue engineering scaffold of polyglycolic acid (PGA)/poly-4-hydroxybutyrate copolymer.[30] This α-SMA expression is not characteristic of endothelial cells or EPCs, and its expression suggests that the EPCs have undergone a phenotypic change into a cell type resembling cardiac valve interstitial cells. Human aortic valve endothelial cells, but not vascular endothelial cells, respond to TGF-β_1 in a similar fashion, suggesting that EPCs may be an appropriate cell type to serve as valve endothelium.[30] It is noteworthy that endothelial transdifferentiation to a mesenchymal phenotype is a critical step during the normal embryonic development of cardiac valves, and Dvorin and associates have speculated that the ability to recapitulate some normal steps in embryonic valve development is relevant to the choice of cell types for tissue engineering of cardiac valves.[30] More recent studies by Sales and coworkers in our laboratory have shown that exposure of EPCs to TGF-β_1 while being grown on tissue-engineering scaffolds not only begin to express α-SMA, but also demonstrated increased production of laminin, fibronectin, tropoelastin, and collagen when compared to EPCs seeded on the same scaffold without TGF-β_1.[38]

An additional issue for cell selection for a TEHV is whether better results will be obtained by seeding the scaffold with more than one cell type and whether the different cell types are seeded at the same time or sequentially. In our initial studies, both endothelial cells and vascular smooth muscle cells were seeded sequentially[10] onto a PGA scaffold with favorable results. In subsequent in vitro studies, we observed an interaction between human EPCs and vascular smooth muscle cells when these cells were co-seeded onto PGA/poly-L-lactic acid (PLLA) scaffolds such that microvascular tube formation was observed when these two cell types were co-seeded versus when EPCs alone were seeded onto the same scaffold material.[31] The potential for interactions among cells of differing origin and phenotype adds another dimension of complexity to the tissue-engineering process. It is quite clear that normal embryologic development of semilunar valves involves important interactions between cells of different embryologic origins and between cells and the extracellular matrix surrounding them.[9] It has seemed reasonable to us to conclude that similar interactions could play an important role in the evolution of a TEHV.

STRUCTURAL ORGANIZATION SCAFFOLD

Although it is has been possible to grow individual types of cells in culture for some time, it is more difficult to induce these cells to assemble or organize into the more complex structural arrangements that are found in normal tissues or to produce normal extracellular matrix components in an organized fashion. For this reason, most attempts to create tissue-engineered structures have started with a scaffold onto which cells are "seeded." Any scaffold for tissue engineering applications must be biocompatible and allow cells to adhere and proliferate. Thus the chemistry of the scaffold itself and the scaffold degradation products must be nontoxic at the outset. If the tissue-engineered construct is to have any growth potential, then ultimately the scaffold must either degrade or be able to be remodeled. A fundamental difference in the various tissue-engineering strategies in different laboratories has centered on this choice of scaffold materials. One option is to use decellularized biologic tissues with the extracellular matrix remaining after the decellularization process serving as the scaffold for cellular attachment and structural organization. The alternative approach is to use synthetic biodegradable polymer matrices to provide these scaffold functions with the anticipation that the cells in the tissue-engineered construct will produce their own extracellular matrix and that the synthetic scaffold will be degraded and eliminated. The disadvantages of decellularized grafts include the relative shortage of available homografts and potential immunogenicity problems that may arise from the use of decellularized xenogeneic tissues. Perhaps more importantly, the density of residual extracellular matrix that is attractive from a structural integrity and early post-implant functional perspective may prevent the penetration of seeded cells into the interstices of the matrix. Furthermore, given the complex and poorly understood interactions between the cellular cytoskeleton and the extracellular

matrix in normal tissues, it may be naïve to expect cells seeded onto decellularized tissues to assume those same relationships with matrix that may be altered by the decellularization process or may differ in subtle ways from species to species. There has been some experience gained in cardiac valve tissue engineering using small intestinal submucosa as the scaffold.[16] In our laboratory, we have constructed trileaflet valved conduits and seeded them with EPCs. After these conduits were implanted in an ovine model, there was satisfactory short-term function, but there was no penetration of any cells into the substance of the small intestinal submucosal scaffold.

Our primary laboratory efforts to develop heart valves and large arteries have utilized the alternative approach of seeding cells onto biodegradable polymer scaffolds that temporarily provide the macroscopic structure and the mechanical stability that are necessary for "tissues" to develop from their individual cellular components. Ideally, these polymer scaffolds then degrade during the time that the cells in the developing "tissue" are producing normal structural proteins and are becoming organized and oriented to replicate normal tissue structure. Initially, the biodegradable scaffolds that we used were based on materials already in clinical use, including PGA and PLLA. Each of these materials has differing characteristics, including the length of time to degrade the polymer and the rate at which polymer degradation and loss of strength occur. PGA was introduced into clinical practice as a biodegradable suture material and marketed under the trade name Dexon (U.S. Surgical, Norwalk, Conn). The ability to extrude PGA into fibers permits it to be fabricated into nonwoven sheets with an open porous structure. Pore size has been shown to be important in the choice of scaffold material for tissue engineering liver for a variety of cell types,[32] and it is likely that pore size will also be important for cardiovascular structures. An open pore structure seems to facilitate both cell delivery and subsequent cell proliferation by allowing free access to suspended cells, free diffusion of nutrients and dissolved gases, and removal of waste products of metabolism. These spatial properties combined with a consistent and relatively rapid loss of polymer mass relative to other biodegradable materials have made PGA an attractive choice for tissue engineering. One disadvantage that we have observed is that there is a more rapid loss of strength than polymer mass as the polymer degrades by hydrolysis, and this property limits the amount of time that PGA-based tissue-engineered constructs can be kept in aqueous culture before implantation. This shortcoming of PGA was offset to some degree by impregnating PGA with the thermoplastic polymer poly-4-hydroxybutyrate (P4HB), which allowed flat sheets of scaffolding to be assembled into a trileaflet structure by a series of two or more wraps around a cylindrical mandrel and using heat welding to create a tubular conduit containing a trileaflet valve.[12]

Despite promising early results using the PGA/P4HB composite, in subsequent studies we experienced some problems with the use of this material, particularly continued problems with loss of structural integrity with longer periods of time in an aqueous tissue culture environment. As the rate of loss of strength increases, there is an increased requirement for the cells in the tissue-engineered construct to produce extracellular matrix at an earlier time point prior to implantation. There were problems with suture retention and actual tearing of the wall of the conduit in some of our experiments with valved conduits developed from PGA/P4HB scaffolds. For these reasons, Sutherland and associates in our laboratory adopted a scaffold composed of a mixture of PGA and PLLA.[18] PLLA is the α methyl substituted form of PGA, and it was initially developed for the biodegradable suture market. This polymer hydrolyzes at a much slower rate than PGA, and the initial tensile strength of PLLA is less than that of PGA. This composite material was able to be fabricated into a valved conduit with a three-leaflet valve that functioned quite well at the time of implantation, and then over periods of up to 8 months after implantation, and had significantly improved surgical strength and handling characteristics.[18] The importance of scaffold degradation time was demonstrated in experiments reported by Stock and colleagues from our laboratory,[34] in which the use of polyhydroxy-octanoate as scaffolding material was associated with excessive tissue buildup and leaflet retraction.[34]

These PGA and PLLA scaffolds for cardiac valves have one additional disadvantage, and that is they are significantly stiffer than a normal valve leaflet and only gradually become less stiff with time.[12,18,33] As a consequence of this finding but also because of evidence that mechanical signals influence cellular behavior, a new more elastomeric polymer was designed for tissue-engineered heart valve application by Wang and colleagues at the Massachusetts Institute of Technology. This polymer is a rapidly degrading elastic polymer based on sebacic acid.[35] Preliminary experiments have shown that this polymer will support cell attachment and proliferation, but much additional experimental work will be necessary to determine if this material will be suitable as a scaffold for a tissue-engineered heart valve. However, the availability of this more elastic polymer will allow further studies of the effects of mechanical scaffold properties on the development of a TEHV.

In addition to the influence of the chemical, degradation, and mechanical properties of the scaffold material, there is preliminary evidence that the fabrication techniques can affect the mechanical behavior of the scaffold and may be of importance to the development of tissue-engineered constructs. Engelmayr and associates have shown that dimensions of the pores within a scaffold can guide engineered tissue cellular and collagen orientation in two-dimensional systems,[36] and it seems reasonable to anticipate that similar phenomena will occur in three-dimensional systems. To date, it has been difficult to explore the impact of scaffold fiber orientation on the development of tissue-engineered cardiac valves since the methods needed to fabricate these scaffold materials into more organized structures than films or nonwoven meshes have been limited. A promising fabrication technique that has recently been evaluated for tissue-engineering applications is electrospinning, which

allows the macromechanical characteristics of scaffold materials to be controlled so that they mimic those of a native semilunar valve leaflet.[37] As this and other fabrication methods evolve, it seems likely that further exploration of the effects of scaffold mechanical behavior at the macroscopic level on developing tissue-engineered structures will be necessary.

CYTOKINE SIGNALS

Based on extensive experience with culturing a variety of cell lines, TEHVs have been grown in media containing fetal bovine serum, which is known to contain multiple factors that promote cell proliferation in vitro. To the extent that cytokines can alter cell phenotype, these signals may provide additional opportunities for engineering the environment to guide the development of a tissue-engineered heart valve. The findings that TGF-β_1 could induce endothelial progenitor cells to produce α-SMA[31] and alter the types and amounts of extracellular matrix being produced,[38] are examples of the potential ability to use cytokine signals to affect cell phenotype and protein synthesis. Few studies have been undertaken to explore this approach to engineering the environment in which a tissue-engineered construct takes place. In future engineering of valve tissues, one might envision localizing growth factors within the developing tissue-engineering construct to guide behavior at the microstructural level, particularly in regard to control of the types and amounts of extracellular matrix.

BIOMECHANICAL SIGNALS

Several lines of in vitro and in vivo evidence indicate that both tissue-engineered and normal valve leaflets respond to mechanical signals with changes at the cellular and extracellular matrix levels. In the natural "experiment" provided by the Ross procedure, in which a pulmonary valve from the low-pressure pulmonary circulation is transplanted into the aortic position and subjected to systemic pressure, significant changes in the phenotype of valvular interstitial cells have been observed, including an increase in the activity of matrix remodeling proteins.[9] In experiments from our laboratory reported by Hoerstrup and colleagues,[12] the ability of mechanical flow and pressure signals in vitro were shown to increase the production of collagen in tissue-engineered semilunar valves. Lee and associates have shown that in cultures of vascular smooth muscle cells exposed to tightly controlled mechanical strains, mRNA and protein levels for versican, biglycan, and perlecan increased, while those for decorin decreased. Also hyaluronan-versican aggregation was enhanced following deformation.[40] Engelmayr and coworkers have also shown that vascular smooth muscle cells seeded onto biodegradable scaffolds and then subjected to flexure increased the production of collagen and vimentin, and had increased tissue stiffness.[33] In subsequent studies on bone marrow stem cells, Engelmayr and associates have found that combined flow and flexure signals result in increased collagen concentration and tissue stiffness.[41] These natural and laboratory experiments demonstrate that biomechanical signals clearly alter cellular behavior and therefore engineering of the in vitro mechanical environment, and offer an additional method to guide the development of tissue-engineered cardiac valves.

IN VIVO MATURATION

The experiments from our laboratory reported by Hoerstrup[12] and subsequently by Rabkin[8] indicate that there is an ongoing evolution of tissue-engineered heart valves after implantation into the circulation. This evolution occurs at the macroscopic level with thinning of the tissue-engineered leaflets, as well as at the histologic level with development of distinct layers in the valve leaflet.[12] Picrosirius red staining indicated that there was a progressive evolution of the orientation of the collagen in the tissue-engineered valve with increasing time in the in vivo environment. There was an evolution of cellular phenotype with decreased expression of SMemb, αSMA, and MMP-13, and increased expression of vimentin, a process which is consistent with an evolution from an "activated" state of these valve cells to a more inactive state. Importantly, the microscopic structure of the valve leaflets evolved from a relatively homogeneous appearance to a layered structure with increased collagen on the sinus side of the leaflet and elastin formation on the ventricular side of the leaflet. The mechanisms by which this in vivo evolution of structure and cellular activity occurs remain completely unexplored, but these observations suggest that a tissue-engineered valve may not have to be a "finished product" at the time of implantation into the circulation.

In summary, the tissue-engineering approach to the development of a living heart valve structure represents an exciting new direction for heart valve research. Numerous refinements of the current approaches will likely be necessary, including the optimization of the scaffold materials, cell types, in vitro biochemical and mechanical conditions, and the development of reproducible valve development processes. The observation of in vivo maturation and/or evolution of these tissue-engineered constructs introduces an additional variable that will complicate regulatory efforts to ensure patient safety. It seems likely that initial clinical experience will be gained in the low-pressure pulmonary circulation since valve failure in this position is likely to be well tolerated based on years of clinical experience in patients with tetralogy of Fallot treated with transannular patches. The challenges for application in the systemic circulation will be much greater, as the consequences of valve failure will be much more likely to be catastrophic.

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CHAPTER 71

Stem Cell–Induced Regeneration of Myocardium

Robert P. Gallegos • R. Morton Bolman, III

INTRODUCTION TO CELLULAR THERAPY

Cardiovascular disease remains the leading cause of death in industrialized nations despite major advances over the past 60 years in medical and surgical therapy. Largely this relates to the growing worldwide epidemic of congestive heart failure (CHF) currently affecting ~15 million patients and which carries a 5-year mortality of 50%.[1] Heart failure—severe ventricular dysfunction—has numerous etiologies but is most often seen as a result of ischemic cardiomyopathy. The hallmark of end-stage CHF is cardiomyocyte loss unmatched by myocyte regeneration following myocardial infarction (MI). Early rapid revascularization—be it with pharmacotherapy, stenting, or surgery—may potentially improve myocardial blood flow with resultant improvement in the function of remaining viable myocardium. However, current therapeutics cannot regenerate myocytes lost to necrosis. As a result, complete cardiovascular functional restoration remains unattainable with the currently available conventional therapies.

Myocardial regeneration—the replacement of lost myocytes—is seen in organisms such as the newt and zebra fish. In higher mammals, dogma has dictated the impossibility of such myocyte regeneration, as the heart was viewed as a terminally differentiated organ. This lack of regeneration prompted interest in organ transplantation as a means of complete replacement of the failing organ. The successful development and implementation of heart transplantation by Barnard and Shumway has greatly improved the clinical outcome for patients diagnosed with end-stage CHF.[2] Unfortunately, several constraints associated with the origin of the donor heart limit the potential for broad application of transplantation in the affected CHF population. The most significant limitation remains the limited availability of donor organs (Fig. 71-1).[3] Complications of immune rejection and immunosuppression also limit the long-term benefits of heart transplantation. Efforts to eliminate the limitations of organ transplantation with the use of mechanical left ventricular assist devices (bridge to transplantation or destination therapy) have similarly been thwarted by finite device durability or device-related complications.[4]

The need for a broadly applicable causally directed therapeutic option that would complement the function of remaining healthy myocardium has prompted significant interest in cell-based regeneration (Fig. 71-2).[5] Much of the excitement in cell-based therapy lies in the premise that repairing the injured heart will overcome the inherent limitations for the broad application of both organ transplantation and mechanical assist devices. The use of native cardiac myocytes (an obvious choice for cell-based cardiac regeneration) was felt to be impossible, as the mammalian heart was believed to be terminally differentiated. However, recent findings revealing resident stem cells within the heart have challenged this accepted dogma.[6,7] Nevertheless, the use of cardiac stem cells for tissue regeneration currently is not feasible, secondary to technical limitations in isolation and expansion.

Despite significant limitations, the inherent potential in cell-based therapies has incited the search for additional sources of stem cells and methods of restoring cardiac function.[8–10] The potential that noncardiac stem cells, such as those from bone marrow or even other organs, could engraft in injured regions of myocardium was first recognized in the evaluation of myocardial biopsies taken from gender-mismatched heart transplant recipients.[11,12] In these male patients, biopsies taken from hearts derived from female donors were found to contain nucleated cells clearly of male origin, containing both the male chromosome and cell markers consistent with cardiac phenotype. Although the exact origin of these new male cells has been debated, several key points were identified. First, injured myocardium through some unknown mechanism attracts stem cells. Second, these stem cells can engraft into regions of injured myocardium. Finally, these engrafted stem cells, of noncardiac origin, appear to

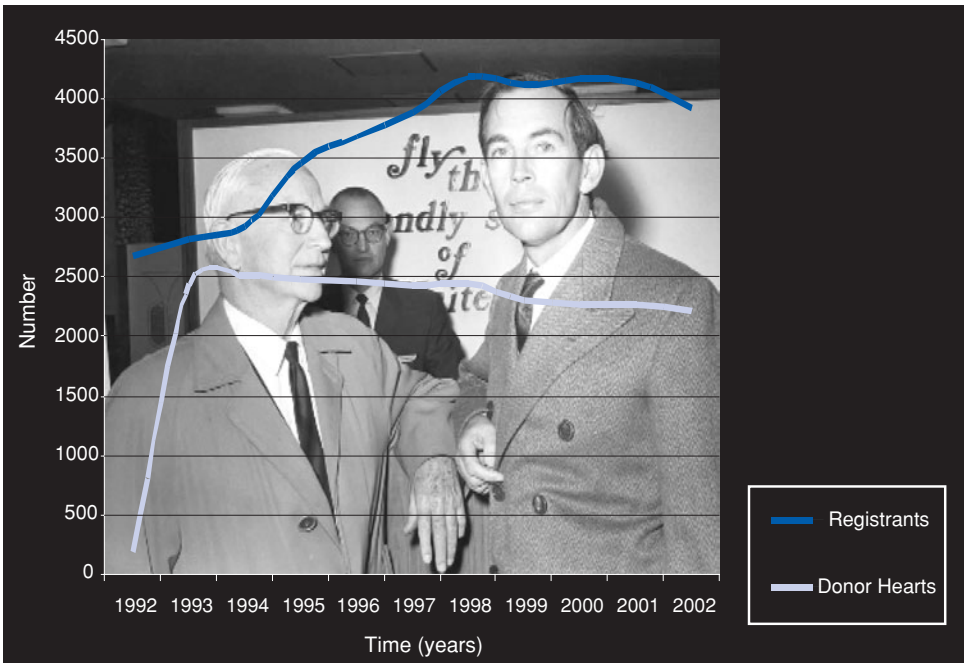

Figure 71-1. Imbalance between donor and recipient ratio. (*R. P. Gallegos; data from United Network for Organ Sharing.* Photo inlay: Dr. Owen Wangenstein (left) with Dr. Christiaan Barnard (right), who performed the first human heart transplant in the world.)

be capable of differentiation into cardiac myocytes that integrate with the surrounding native myocardium.

Cardiovascular disease remains a formidable clinical challenge for which no absolute solution is currently available. Cellular-based tissue regeneration may be of significant importance but remains to be developed further before its true potential may be realized. The following discussion will review the development of cell-based therapy from animal models to current clinical trials.

The Ideal Cell Type

The potential therapeutic benefit offered by cell-based therapies has spurred numerous investigators to search for the ideal stem cell population. This stem cell would effectively engraft and integrate into regions of damaged myocardium and restore cardiac function without improper differentiation into other contaminating cell types. This would require not only neomyogenesis, but also accompanying neoangiogenesis, either as direct or indirect consequence of the implanted cell.

Many cell types with the potential to repair the injured heart have been considered, including differentiated (e.g., fetal myocytes and satellite muscle cells) and undifferentiated primordial cell lines (e.g., embryonic or adult stem cells). Primordial cell lines, or stem cells, that might be utilized for cell-based therapy were first developed from embryonic tissue.[13,14] Embryonic stem (ES) cells are pluripotential (i.e., capable of functional plasticity with the ability to differentiate into all cell types found in the fetus and placenta in vitro). Once established, the cell lines can be propagated in cultures to provide a continuous source of material for transplantation. In fact, ES line–derived cells have shown the ability to form myocytes that generate stable cardiac engraftment.[15] Unfortunately, extensive experimentation in vivo is still necessary to properly direct the formation of integrated, functional cardiac tissue at the site of injury without improper differentiation to form teratomas or other noncardiac cell types. In addition, numerous obstacles that plagued organ transplantation will also likely prevent the widespread use of ES cell therapy. These issues are directly related to the origin of the cell line. First is the issue of allogenicity, which might confer a small potential for rejection, thereby requiring lifelong immunosuppression. But more importantly, the lack of general availability of embryonic stem cells, not dissimilar to the lack of donor hearts, may be most limiting. Current ethical obstacles surrounding the use of embryonic tissue and the current governmental ban on the development of new cell lines will limit the availability of tissue for transplantation.[16–21] New discoveries that have allowed the cloning of ES cells may alleviate this limitation,[22,23] but realization of this potential will await further investigation. Consequently, to utilize stem cell transplantation in a clinical setting, stem cells derived from other sources require investigation.

Stem cells have been demonstrated to be present within various organ tissues in the adult.[24–27] Recent interest has been focused on these cell lines, and the term adult stem cell has been used to differentiate these from ES cell lines. Adult stem cell lines, on exposure to specific signal molecules, have demonstrated the capability of generating myocytes in vitro.[28,29] In addition, the ability to induce in

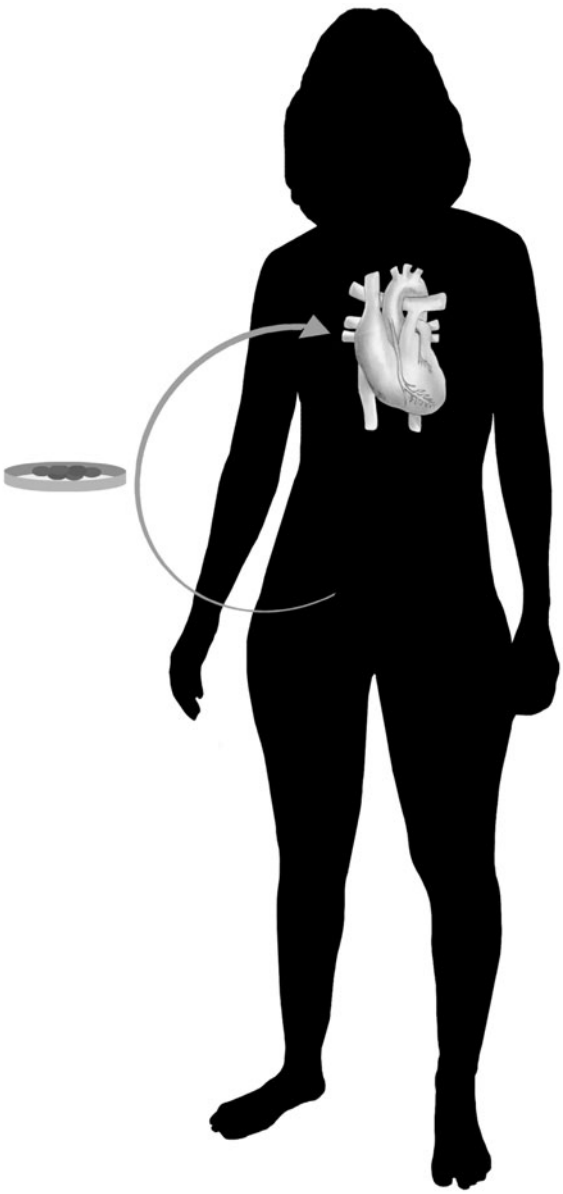

Figure 71-2. Cellular therapy model. Diagram illustrates the use of autologous cells for myocardial repair. Stem cells removed from the body are expanded in culture and then injected into the damaged organ to repair the injured tissue. (*Illustration by Kathy B. Nichols Medical Art, 2006.*)

vivo transformation of bone marrow–derived mesenchymal stem cells into myocytes in the rat has been reported.[30,31] Rather than forcing differentiation to take place in vitro prior to transplantation, it appears that stem cell transplantation, in itself, is a sufficient trigger for differentiation. The implicit assumption made is that the desired native tissue offers to the stem cell an environment rich in the signals of differentiation. Hence adult stem cells may be viewed as the primordial building blocks for selective regeneration of injured myocardium.

Multipotent tissue-specific cells that have already committed to a distinct lineage, such as hematopoietic stem cells, mesenchymal stem cells, and endothelial progenitor cells, have also produced encouraging results when used for cell-based cardiac regeneration therapy.[10] However, to date, the use of these cells often results in incomplete engraftment and a failure to restore cardiac function over time.[32]

Stem Cell Delivery Methods

Multiple methods for stem cell delivery have been investigated, including direct myocardial injection, peripheral transfusion, and/or stem cell mobilization.[33] No current study to date is available to elucidate which approach is superior, though only endocardial and epicardial injections would likely be relevant to cardiac surgeons. Both transfusion and mobilization of resident stem cells offer the least invasive means of stem cell delivery. However, this requires the availability of effective homing signals to direct the correct location for engraftment while preventing the potential for adverse engraftment in other regions (e.g., promoting tumor growth). This impediment is avoided by using direct myocardial injections, either surgically or via interventional catheter techniques (Fig. 71-3). Direct epicardial myocardial injection can be consistently completed intraoperatively during concomitant procedures (e.g., coronary arterial bypass, arrhythmia surgery, mechanical assist device implantation, and valve operations) or via minimally invasive approaches for isolated cell therapy. Direct endocardial injection will likely be accomplished by using commercially available radiographic stem cell injection catheters (Fig. 71-4). Currently, we believe that multiple stem cell injections may be required to achieve full therapeutic myocardial regeneration. As a result, the use of stem cell injection catheters may become the standard of practice following initial open chest cell injection therapy. In addition, the use of advanced imaging techniques (magnetic resonance imaging [MRI] and electromechanical catheters) will likely be used to allow for real-time image-guided smart injection (in a manner akin to guidance of "smart" bombs) at areas of identified myocardial damage. Further investigation is required to identify the best delivery method, number of cells, and treatment regimen. It is likely this information will be gleaned from ongoing clinical trials (Table 71-1) and animal experimentation.

Animal Models for Stem Cell Research

Regardless of the cell type used in cell-based therapy, it is clear that animal models will play a critical role in the translational research that will be necessary to advance this theory out of the lab and into clinical practice. Multiple animal species from rodents to humans have now been used for the study of cell-based therapy. Although many anticipate that cellular therapy will be a panacea for multiple forms of cardiovascular disease, few disease models have actually been rigorously investigated. Much of the early basic and clinical research has been conducted in acute ischemia models. However, while effective treatment options for acute ischemia do exist (thrombolytics, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft

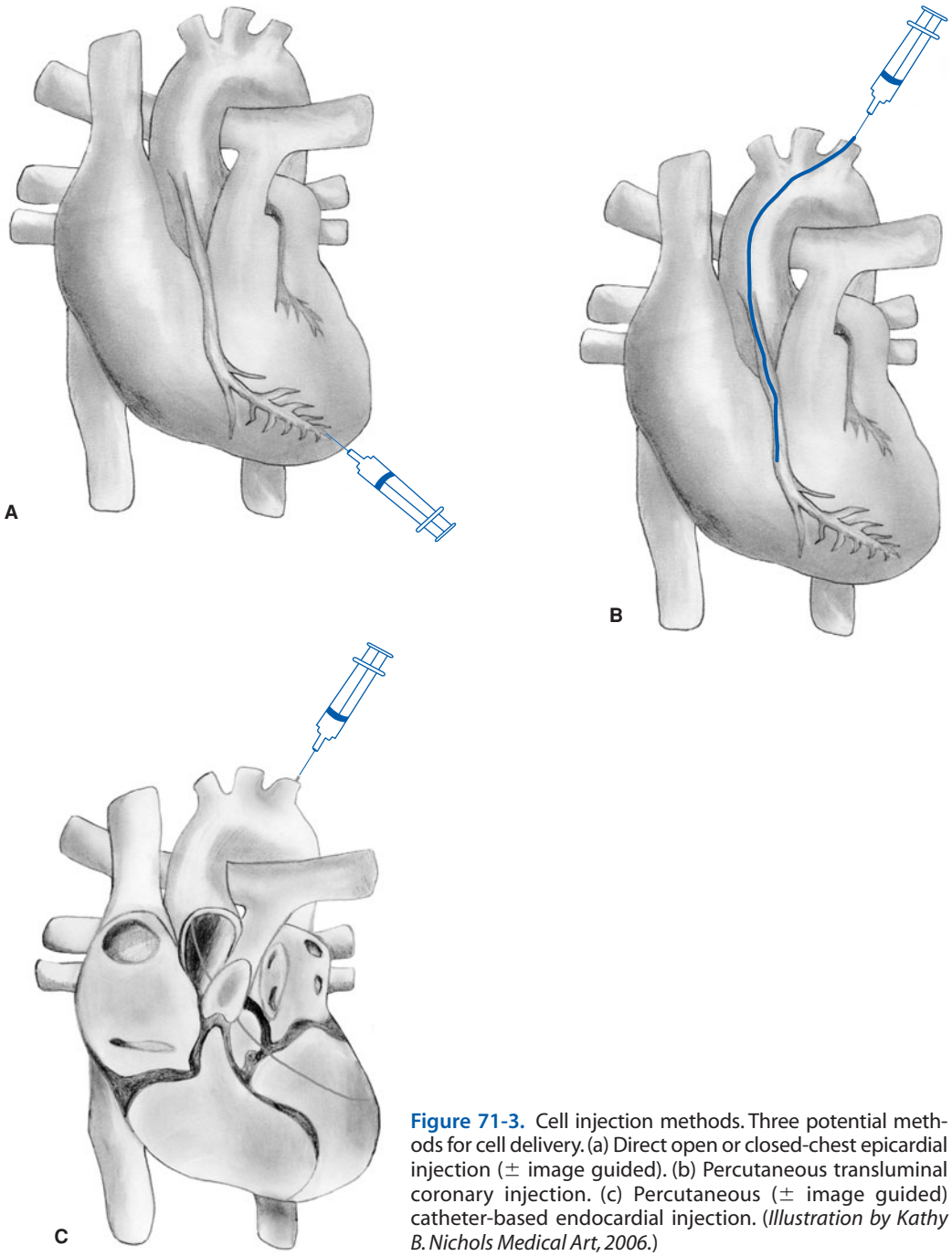

Figure 71-3. Cell injection methods. Three potential methods for cell delivery. (a) Direct open or closed-chest epicardial injection (± image guided). (b) Percutaneous transluminal coronary injection. (c) Percutaneous (± image guided) catheter-based endocardial injection. (*Illustration by Kathy B. Nichols Medical Art, 2006.*)

[CABG]), only limited options are available for chronic myocardial ischemia. This observation strongly suggests that further development of the chronic cardiovascular disease models using cell-based therapy is warranted. This observation has clearly been recognized, as numerous investigators are now incorporating cellular therapy in combination with mechanical assist device insertion.

As with most research, the experimental hypothesis will remain fundamental in choosing the correct animal model. However, the availability of appropriate stem cell lines in the desired species will add additional limitations in the field of cellular cardiovascular therapy. Full characterization of the cell lines is critical to allow for safety evaluation and is advantageous in correctly ascribing functional changes to the appropriate precursor cell. The multiple types of stem cells available for the rodent have made small-animal models effective for investigations of stem cell engraftments. However, significant differences in myocar-

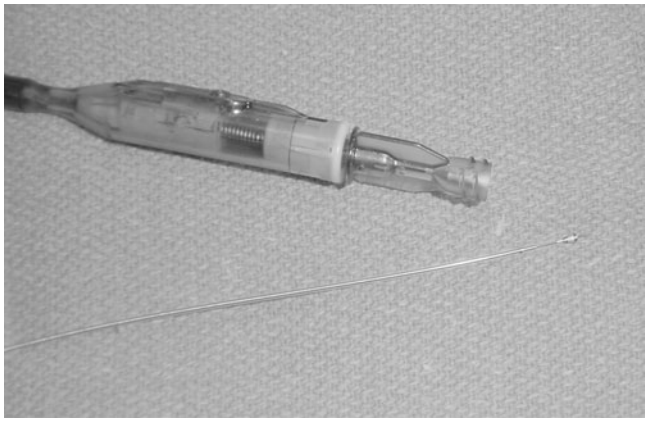

Figure 71-4. Stem cell injection catheter. (*Courtesy Boston Scientific and R. P. Gallegos.*)

dial anatomy and physiology raise serious concerns that findings may not be directly translatable to humans. Ultimately, large-animal models that better approximate the diseased human heart will be required to fully assess stem cell engraftment, differentiation, and/or functional improvement. In general, large-animal models are considered better suited for assessment of myocardial function via angiography, echocardiography, or MRI; however, the limited availability of appropriate stem cell lines for use in these models has prevented the widespread use of large-animal models.

Stem Cell Engraftment

The ability to track the implanted cell is critical not only to assess the potential of engraftment, but also for later determination of differentiation and incorporation into the native tissue. Multiple cell-labeling techniques are under investigation, including the use of viral gene transduction (e.g., green fluorescent gene and lacZ), incorporation of dyes, and the use of metallic microparticles.[34,35] Gene insertion can be fairly easily accomplished, allowing for fluorescence microscopy or quantitative polymerase chain reaction identification of the stem cell. However, the exact insertion site into the DNA of the cell cannot currently be well controlled, introducing the possibility for non-expression of the gene or potential disruption of normal cellular transcription and translation processes. The use of dyes incorporated into the cells by pinocytosis has been reported (e.g., 4,6-diamino-2-phenylindole; DAPI). The primary disadvantage of this technique has been the potential for dye incorporation into native cells in vivo. The use of metallic microparticles has received recent attention, in that such particles may allow for real-time identification of cells by MRI imaging and later pathologically by staining. However, information about the potential disruption of cellular function and possible uptake in vivo by native cells has yet to be fully elucidated.

Several clinical trials utilizing various cell types and disease models have now been completed (see Table 71-1). Unfortunately, these studies have been limited by the recovery of insufficient postimplantation tissue. This limitation is a direct result of study design—cell-based therapy in patients undergoing revascularization. Few patients having received cell therapy have experienced adverse events resulting in death. As a result, no tissue has been available for autopsy evaluation. Future studies involving end-stage CHF patients utilizing mechanical assist device implantation as a bridge to transplantation may alleviate this limitation.[36] In these patients, myocardial samples will be taken pre–cell implantation at the time of mechanical device insertion or cell injection. Similarly, post–cell-treated myocardium will be available at the time of device explantation or orthotopic heart transplantation.

Functional Assessment of Stem Cell Therapy

Numerous researchers have dedicated their efforts to demonstrating improvement in cardiac function following cell-based therapy. Each author has utilized their preferred method of assessing cardiac function. Regardless of the specific method used by any given investigator (pressure measurements, ultrasonic microcrystal placement, echocardiography, or MRI), all have been able to conclude that cell therapy positively impacts some element of cardiac function. However, long-term follow-up studies directly comparing cardiac assessment techniques specifically for the assessment of cell-based therapy do not currently exist in the literature. Therefore, no conclusions may currently be drawn regarding the superiority of any individual technique of cardiac assessment. It is the authors' opinion that cardiac MRI offers the greatest ability to follow long-term patient outcome. MRI allows for a noninvasive serial assessment of cardiac perfusion, contractility (global and regional), wall motion, infarct size, and chamber size. In addition, the use of real-time MRI may allow for precise delivery of cells using MR-safe injection catheters currently in development.[37] Finally, the use of metallic microparticles, as mentioned above, may allow for cell tracking following cell injection.[34,35] Drawbacks to MRI of course do exist, including the inability to scan patients with newly implanted pacemaker leads and other prohibitive patient contraindications to MRI. More research and further refinements in measurement techniques will likely offer additional strategies that will ultimately be universally applicable.

Mechanism of Myocardial Repair Following Cell Therapy

The concept of myocardial cellular therapy was originally conceived based on the example set by the success of whole organ transplantation—replace what has been lost. However, with the need for whole organ transplantation far exceeding the organs available for donation (see Fig. 71-1),

Table 71–1.

Cell Therapy Clinical Trials, 2001–2005

	Cell source	Delivery	(n)	(Months)	Inclusion criteria	Outcome
Hamano et al[92]	Mononuclear BMCs	IM injection/CABG	5	12	Old MI; no revascularization	↑ perfusion (3/5 pts)
Stamm et al[83]	AC133 bone marrow cells	IM injection/CABG	12	3–9	MI >10 d and <3 mo	↑ EF (4/6 pts), perfusion (5/6 pts)
Strauer et al[80]	Mononuclear BMCs	IC infusion/PTCA	10	3	5–9 days post-MI	↓ Infarct region size ↑ Wall motion/perfusion
Assmus et al[82]	Mononuclear BMCs cultured blood–derived EPCs	IC infusion/PTCA	20	4	<3 days post-MI	↑ LVEF, EDV, perfusion, contractile function
Tse et al[84]	Mononuclear BMCs	Percutaneous IM injection electromechanical mapping	8	3	Severe ischemic heart disease	↓ Anginal symptoms ↑ Perfusion, contractile function
Perin et al[89]	Mononuclear BMCs	Percutaneous IM injection electromechanical mapping	14	2	CHF	↑ LVEF, perfusion, contractile function
Wollert et al[90]	BMCs	IC infusion/PTCA	30	6	<5 days post-MI	↑ LVEF and contractile function
Chen et al[91]	BMSCs	IC infusion 18 days post-PTCA	34	3–6	10 days post-MI	↑ Perfusion, ventricular EDV/ESV, wall movement, and LVEF
Menasche et al[93]	Skeletal myoblasts	IM injection/CABG	10	10.9	CHF	↑ LVEF, contractile function
Menasche et al[93]	Skeletal myoblasts	IM injection/CABG 3 months	12	10.9	Old MI; ischemic CAD	↑ LVEF, contractile function
Pagani et al[87]	Skeletal myoblasts	IM injection/LVAD implant	5	2.25–6.3	Ischemic cardiomyopathy; refractory CHF	Development of myotubes in scarred MI
Smits et al[88]	Skeletal myoblasts	Percutaneous IM injection/ electromechanical mapping	5	6	Ischemic heart failure	↑ LVEF, wall thickening
Kang et al[78]	Peripheral blood SC IV G-CSF	IC infusion after PTCA	10	6	Acute MI (>48 hours) or old MI	↑ in-stent restenosis after G-CSF

↓ = decreased; ↑ = increased; BMC = bone marrow cell; BMSC = bone marrow stem cell; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; EDV = end-diastolic volume: EF = ejection fraction; EPC, endothelial progenitor cell; ESV = end-systolic volume; G-CSF = granulocyte colony-stimulating factor; IC = intracoronary; IM, intramuscular; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; pts = patients.

the goal of cell-based therapy is to restore cardiac function by the replacement of only the sections of dead myocardium. Here the replacement of lost myocytes would be accomplished by the implantation of a population of readily available cells that integrate into the existing matrix and provide synchronized contractile activity.[38] To date, both animal and human studies have been reported demonstrating improvement in various parameters of heart function in support of this goal. However, the means by which cellular transplantation has provided this benefit to cardiac function remains unclear and hotly debated.[39] A significant problem in understanding the mechanism is undoubtedly related to the limited ability to track implanted cells. No universally reliable technique has thus far allowed tracking of implanted cells, particularly in human trials. Furthermore, as mentioned previously, limited tissue has been available for engraftment studies.

The implantation of adult and fetal cardiomyocytes has been attempted experimentally, with limited success. In these instances, cellular replacement would require only engraftment and integration into the conglomerate contractile apparatus to potentially repair the damaged myocardium. This is not the case for naïve stem cells, which have been intently used for myocardial cell transplantation. In this scenario, implanted stem cells (e.g., embryonic, bone marrow, or skeletal stem cells) would require not only engraftment and integration, but also, most importantly, transdifferentiation into cardiomyocytes. Chiu proposed the notion that transdifferentiation could result from some unknown signaling process commenced by exposure to the local milieu present in the region of injured myocardium.[40,41] This concept does have some support from studies following cardiac transplantation in sex-mismatched pairs where the presence of integrated cardiomyocytes of recipient origin has been identified, presumably following engraftment of circulating stem cells or resident stem cells.[11,12] The importance of the local milieu was highly suggestive, if one considers that the number of engrafted recipient cells increased with the greater incidence of donor organ rejection. This observation emphasized the requirement for myocardial injury as a strong factor involved in the recruitment and engraftment of stem cells.

Several in vitro and in vivo studies exist in the literature that support the hypothesis of the transdifferentiation of stem cells into cardiomyocytes.[28,31,42] At the bench, various forms of bone marrow–derived stem cells (e.g., hematopoietic stem cells, bone marrow mesenchymal stem cells, and multipotent adult progenitor cells) have been successfully induced into a cardiomyocyte phenotype.[43–45] Animal studies using injected cultured stem cells or mobilized stem cells (induced by stem cell factor treatment) have demonstrated rapid regeneration of myocardium, the first being reported by Orlic and colleagues.[31,42,46] In this seminal effort, the expression of cardiomyocyte-specific genes in labeled implanted stem cells was strongly suggestive for integration of the implanted cells with the host myocardium and supported the potential for synchronous contraction. Since the publication of this report, numerous preclinical and clinical trials have demonstrated myocardial repair and regeneration.

Unfortunately, the number of engrafted cells following injection is typically insufficient to account for the degree of improvement in myocardial function. Furthermore, the mere presence of cardiomyocyte-specific gene products alone is insufficient evidence that the transplanted cells actually regenerate myocardium that electromechanically integrates with host myocardium. Finally, the concept of transdifferentiation itself has been called into question. Opponents point to reports demonstrating stem cell fusion with native parenchymal cells, producing a hybrid cell containing both stem cell and myocyte-specific markers, accounting for prior observation of supposed "neomyogensis."[47–49] Additional negative evidence has recently been offered by recent independent reports where the transdifferentiation of bone marrow stem cells into cardiomyocytes did not occur after implantation.[50–52] The credence of current evidence does not fully support the concept of stem cell transdifferentiation, although sufficient evidence does not exist to dispel this concept. In addition, it is not clear that the observed improvement in cardiac function is the direct consequence of electromechanical integration of the implanted cell. This is certainly the case with skeletal myoblast therapy, in which cell injection results in the formation of isolated skeletal myotubes within the scar. Although the myotubes remain electrically and functionally isolated from the host myocardium, both preclinical and clinical trials have provided documented improvement in cardiac function.[51,53–55]

Alternative Mechanisms of Repair

The lack of absolute evidence to support transdifferentiation of implanted cells into myocytes as the sole mechanism, or even one of the mechanisms, for the observed functional improvement in cardiac function has spawned ongoing interest in both preclinical and clinical research. Regardless of the direct contribution of the injected cells to myocyte mass, it is clear that cellular transplantation results in neomyogenesis, neoangiogenesis, and alterations in ventricular remodeling.[40,56–60]

Recent work has suggested that the mechanisms of cellular therapy may involve cytokines and growth factor–mediated endogenous stem cell mobilization, improved homing of stem cells to sites of injury, and induction of antiapoptotic pathways.[61,62] All mechanisms may contribute to an overall increase in functional myocardial mass salvage in the area of injury. Release of these factors may occur systemically or locally at the site of injury both from and as a result of cellular transplantation. In addition, some have theorized that observed cell fusion could be responsible for the release of factors. Research involving infusion of pharmacologic agents with anti-apoptotic properties (e.g., ursodeoxycholic acid [bear bile]) suggests improvement in survival of ischemically damaged cardiomyocytes, supporting this mechanism. The exact contribution of these mechanisms to the overall effect of cellular therapy remains to be elucidated.

Induction of neovascularization, a crucial component of cellular therapy, is mediated by both cytokine release and potentially by direct cellular contribution of endothelial progenitors, as has been observed following bone marrow stem cell therapy.[10,63,64] Increased angiogenesis provides not only the potential for improved perfusion in the region of myocardial injury, but may also prevent myocyte apoptosis and maladaptive remodeling of the myocardial matrix.[40,57,63,65] Overall, neovascularization could improve cardiac function by preventing cell loss and ventricular dilatation while also recruiting hibernating myocardium. Both preclinical and clinical studies using bone marrow–derived stem cell injections following MI support this theory, with documented increased capillary density in conjunction with an improvement of myocardial contractility.[66,67]

In addition to improved myocardial perfusion, cellular therapy appears to be an integral factor in the preservation of the integrity of the extracellular matrix (ECM) following myocardial injury. Myocyte loss results not only from the initial acute ischemic injury, but also from degradation and maladaptive remodeling of the ECM. As a result, disruption of the matrix network impairs support for heart cells, leading to further cell loss and ventricular dilatation, ultimately culminating in CHF.[57,68,69] Cellular transplantation may prevent ECM degradation or may induce the restoration of the ECM, or a combination of both scenarios. This may result from direct secretion of new matrix elements by the injected cells or by secretion of cytokines that result in activation of the biochemical cascades ultimately responsible for ECM stabilization.[53,70–72] In any event, stabilization of the ECM provides structural support for host heart cells, limiting infarct expansion and improving regional ventricular compliance and function.[57,73–75] Numerous reports offer evidence of a beneficial effect following cellular therapy on the ECM, not only in the infarct zone but also in regions of normal myocardium.[57] Functional improvement has been reported following the injection of various types of cells, in spite of a lack of a complete understanding of the true mechanism by which stem cells improve cardiac function. Certainly much more additional investigation at the bench side and bed side is required before the true mechanism is elucidated.

CLINICAL TRIALS IN CELLULAR THERAPY

Scattered individual case reports of patients receiving "cell injections" rapidly appeared in the literature following positive reports in preclinical animal studies.[76–78] This rapid transition of bench-side research into the clinical realm was felt to be justified based on the need for a broadly applicable approach to counteract the ever-increasing incidence of CHF following MI. Though numerous authors reported significant improvement in cardiac function, most of these case studies were severely limited, being confounded by concomitant revascularization and poor characterization of the injected cells. Furthermore, follow-up periods were short and conclusions regarding improvement in cardiac function were based on a variety of clinical nonstandardized end points.

Despite the questionable validity of these preliminary case reports, interest in cellular therapy has steadily increased. The first results from an organized human cellular therapy trial were reported by Menasche and colleagues.[79] Since its publication in 2001, 13 trials involving over 170 enrolled patients have been reported (see Table 71-1) and are discussed in the remainder of this section. As with the animal trials that proceeded, various cell delivery methods, cell types, disease states, and cardiac function assessment methods were utilized in these preliminary phase I feasibility trials (Table 71-2).[78,80–93] Again, all trials supported the feasibility of cell therapy, indicating a positive impact on cardiac function after cell implantation.

Despite the positive conclusions, the strength of many of the authors' conclusions has been questioned due to the potential confounders associated with concomitant revascularization and by the absence of appropriate randomized, double-blind, placebo-controlled experimental protocols. In addition, the potential for serious adverse sustained tachycardia (primarily with skeletal myoblasts) raised significant safety concerns. Although preliminary trials are encouraging, the technique remains in its infancy with little known of the true mechanism associated with improved cardiac function. Significant research is still required to ultimately elucidate the mechanisms of repair and overall long-term results of cell therapy. Clinical trials will undoubtedly assist with

Table 71–2.

Summary of Cell Therapy Clinical Trial Models

Cell delivery method	Cell type	Disease state
Direct epicardial injection	Skeletal myoblasts	Acute myocardial infarction
Percutaneous endocardial intramyocardial injection ± image or NOGA-catheter–guided	Peripheral blood stem cells	Chronic congestive heart failure
Intracoronary infusion with angioplasty	Bone marrow stem cells	

**NOGA Cardiac Guidance System, Biosense Webster, Inc., Diamond Bar, California.*

this endeavor and will answer additional important questions that include (but are not limited to) the identification of the appropriate candidates for cell therapy, and to assess for the appropriate cell type, number, and route of delivery. Only then will the expected benefits and potential side effects be thoroughly appreciated.

Skeletal Myoblast Trials

Skeletal myoblasts (SMs) are primordial cells that are precursors to skeletal myocytes. These cells can be obtained readily by small biopsy of peripheral skeletal muscle and can be expanded by in vitro culture to obtain an adequate number of cells for use in cellular therapy.[94] The first patients to be involved in human cellular therapy trials received direct epicardial SM injections following MI. In this pivotal trial, Menasche and associates injected autologous SMs into a segment of non-revascularizable, nonviable infarcted myocardium in 10 patients with ischemic heart failure who were undergoing planned CABG.[93] At the end of the 11-month follow-up period, all patients demonstrated an improvement in the New York Heart Association functional class and left ventricular ejection fraction (LVEF) with an associated increased viability of the grafted scar. No immediate perioperative deaths were reported, with only one late death occurring secondary to stroke more than a year after transplant. Most concerning was the development of sustained ventricular tachycardia in four patients. These results were supported by Herreros and coworkers, demonstrating similar improvements in cardiac function by 3 months following injection in 12 patients undergoing CABG after MI.[85] Here only 1 of 12 patients developed a nonsustained ventricular tachycardia. Both trials suffered significantly from the inability to rigorously evaluate the cell-treated region, as little tissue was available for pathologic review.

This problem was ameliorated by Pagani and associates who injected SMs in five patients undergoing left ventricular assist device (LVAD) implantation for severe ischemic cardiomyopathy and refractory heart failure.[87] Following explantation of the hearts, histologic evaluation demonstrated the formation of viable islands of muscle grafts in the scarred myocardial tissue where SM injection was performed. Again, 3 of 5 patients experienced documented ventricular tachyarrhythmias. Nonsurgical catheter-based percutaneous injection of SMs have also been successfully accomplished in humans. Using this technique, mapping of damaged regions of myocardium can be performed, allowing for precisely guided injection of cells using stem cell injection catheters. Smits and colleagues treated five patients with ischemic CHF after MI in this fashion, injecting SMs using a catheter-based endocardial approach.[88] On follow-up 6 months after treatment, imaging demonstrated improved myocardial wall thickening within the injection region and an overall improvement in LVEF. As seen with the open surgical technique, 1 of 5 patients developed nonsustained ventricular tachycardia, reflecting that the cell injection and not technique was likely responsible for the dysrhythmia. In summary, these early feasibility trials in humans supported the potential efficacy of SM-based cellular therapy. Importantly, the LVAD trial conducted by Pagani identified the ideal initial candidates for future trials. Critical histologic data not previously obtainable with outpatient death are possible now for the entire heart following heart transplantation rather than relying on small tissue biopsies. The trials have not yet provided data supportive of any apparent obvious superiority of one delivery method over another. Most concerning, the trials also raised serious safety concerns with regard to the induction of severe ventricular arrhythmias, necessitating the use of antiarrhythmics or automated implantable defibrillators.

Blood- and Bone Marrow–Derived Stem Cell Trials

Shortly after the reports of success with SM injection, bone marrow– and blood-derived stem cells were explored as a new potential cell source. The first group trial was reported by Hamano and colleagues, who performed autologous mononuclear bone marrow cell injection in 5 patients undergoing CABG.[81] One year following cell injection, 3 of 5 patients demonstrated improved perfusion in the region of injury. Benefit to cardiac function was suggested by Strauer and Assmus and their coworkers (Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction; TOPCARE-AMI), who performed separate nonrandomized trials of autologous cell injection with concomitant percutaneous transluminal coronary angioplasty for recent acute ST-elevation myocardial infarction (MI).[80,82] Strauer infused autologous bone marrow mononuclear cells (n = 10 patients), while Assmus evaluated the use of either autologous circulating blood-derived or bone marrow–derived progenitor cells (n = 20 patients). All patients were evaluated 3 to 4 months post–cell infusion and were compared with matched historical control patients. Cell infusion was associated with a reduction in infarct size and left ventricular end-systolic volume, and was coupled with an improvement in myocardial perfusion and contractility (global and regional). The TOPCARE-AMI trial offered additional conclusions regarding the need for exact stem cell characterization. In this trial, serial contrast-enhanced MRI and ex vivo migratory capacity assay of the implanted cells confirmed that implantation of cells with high migratory capacity was associated with higher beneficial effects on infarct size and left ventricular remodeling.[95] Importantly, no death was directly attributed to cell injection. No significant morbidity attributable to arrhythmia was reported.

The use of bone marrow– and blood-derived stem cells has also been explored in patients with chronic cardiac disease. Tse and colleagues offered cell therapy to eight patients with stable refractory angina.[84] Patients in this trial received autologous bone marrow mononuclear

cells via percutaneous catheter-based myocardial injections guided by electromechanical mapping. Consistent with the trials completed in the acute MI series, patients demonstrated increased myocardial perfusion and contractility, and reported reduced anginal episodes and nitroglycerin usage by 3-months' follow-up. No adverse events were reported, suggesting a higher degree of relative safety compared with SM injection. However, this conclusion was questioned by Perin and associates, who conducted a similar trial, treating patients (n = 14) with severe chronic ischemic heart failure with autologous mononuclear cells.[89] Cell injection resulted in improved cardiac function at the 4-month evaluation consistent with prior studies; however, one fatality was attributed to sudden cardiac death.

Unlike SMs, blood- and bone marrow– derived stem cells can be mobilized using drug infusion with stem cell colony-stimulating factors. Kang and coworkers randomized patients (n = 27) with MI who underwent percutaneous transluminal coronary intervention into three experimental groups to determine if there was any benefit to granulocyte colony-stimulating factor with or without intracoronary infusion of peripheral blood stem cells compared to the control percutaneous coronary intervention group.[78] At the 6-month follow-up, a high rate of in-stent restenosis was observed in patients who received granulocyte colony-stimulating factor.

Success achieved with initial trials was encouraging and ultimately led to the first true randomized controlled trial examining the safety and efficacy of cell therapy for acute ST-elevation MI, completed by Wollert and colleagues.[90] Patients (n = 60) included in the BOOST trial (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) were randomized to primary percutaneous intervention with or without intracoronary infusion of autologous bone marrow cells. At the 6-month follow-up, no adverse events were reported. All patients were followed with cardiac MRI, which demonstrated significant improvement in LVEF in the cell treatment group (from 50 to 56.7%) compared to the control group (from 51.3 to 52%). To further explore the conclusions drawn from the BOOST trial, Chen and colleagues randomized patients (n = 69) undergoing primary percutaneous coronary intervention after acute MI to receive intracoronary infusion of autologous bone marrow–derived mesenchymal stem cells or cell-free saline injection.[91] At the 3-month follow-up, patients having received cell therapy were noted to have a greater improvement in LVEF, myocardial perfusion, and wall motion relative to the saline-treated group.

The initial available data involving blood- and bone marrow–derived stem cell therapy are encouraging and should pave the way for larger phase II/III trials aimed at assessing when, how, and to whom cells should be delivered after MI. These future trials will address safety concerns including postimplantation incidence of severe ventricular arrhythmias, though current studies would suggest this to be less concerning with these types of stem cells.

FUTURE DIRECTIONS

Significant translation of bench research in cellular therapy into clinical trials has occurred, offering the cardiovascular physician a new weapon in the armamentarium for prevention and treatment of myocardial injury. Numerous reports in both preclinical and clinical studies demonstrate that cellular therapy is safe and may be efficacious as a treatment option to treat both acute and chronic myocardial injury. Although specific safety concerns remain related to induction of clinically relevant ventricular arrhythmias, preliminary clinical trials suggest that cellular therapy may be routinely engaged for the treatment of myocardial injury with the ultimate goal of prevention of end-stage cardiac failure. Several questions remain to be evaluated, including identification of the ideal cell type or types, the exact cell dose, timing and number of treatments, and most importantly, careful determination of each of these variables as they relate to specific disease states. Certainly both the type (acute versus chronic) and severity of disease will dictate the overall treatment protocol. Additional research is required not only in clinical trials, but also at the bench side to determine the exact mechanism by which cellular therapy improves cardiac function. Cellular therapy likely induces neoangiogenesis, neomyogenesis, anti-apoptotic pathways, and stabilization of the ECM—all contributing to improved cardiac function. Once the specific mechanisms are identified, either the use of purified cytokines or genetic manipulation of the injected cells may add further efficacy while providing an increase in safety by minimizing or eliminating the use of cellular injection itself.

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